Follow-up after curative treatment of colorectal cancer - The COLOFOL trial

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The COLOFOL trial

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PERNILLA HANSDOTTER is a colorectal surgeon at the Department of Surgery, Skåne University Hospital in Malmö. Her thesis is about follow-up after curative treatment for colorectal cancer, to study the pattern, incidence, sites and risk factors for recurrence and to evaluate the impact of metastases treatment and follow-up strategy on survival.

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Follow-up after curative treatment of colorectal cancer

The COLOFOL trial

Pernilla Hansdotter

LUND UNIVERSITY

DOCTORAL DISSERTATION

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Abstract:

Background: Colorectal cancer is the second most common cause of cancer-related mortality worldwide, mainly due to metastasizing disease. Metachronous metastases develop in 20-25% of the cases Although an increasing proportion of metastases now are treated with curative intent the optimal design of a follow-up program after surgery of colorectal cancer with curative intent is yet to be established.

Aims: To study the pattern, incidence, sites and risk factors for recurrence in colorectal cancer and to evaluate the impact of metastases treatment and follow-up strategy on survival.

I. An evaluation of the COLOFOL trial, its generalizability.

II. To evaluate the form of detection, pattern and incidence, treatment and its intention, risk factors, and survival of the patients with recurrence within 5 years after treatment for CRC. Including evaluation of any re-recurrence.

III. To evaluate treatment and survival of patients with recurrence to the liver.

IV. To evaluate treatment and survival of patients with recurrence to the lungs.

Methods: The work is based on the COLOFOL-trial population, a prospective randomized multicenter trial of 2509 patients radically treated for colorectal cancer stage II-III between 2006-2010. The patients were randomized to either low- or high-frequency follow-up programs, comparing overall and cancer specific mortality depending on follow-up regimen. In all patients who developed recurrences within 5 years, in Denmark and Sweden, the medical files were scrutinized, and date, type of recurrence, and treatment were registered. Mortality was checked through the population registries.

Results: Study 1: Drop-out analysis: No difference in age or sex distribution was observed between randomized and nonrandomized eligible patients, but minor differences were noted in tumour location and stage distribution

Study 2-4: Retrospective studies of the 471 (19.3%) patients who developed recurrences. The total 5-year overall survival rate after detection was 32.0 %, 58.6% in the group treated with curative intent and 7.7% in the palliatively treated group; Curative treatment was possible in 52% of the 235 patients with liver recurrences, with 5-year OS of 58%

Study 4: Curative treatment was possible in 37% of the 165 patients with lung recurrences, with a 5-year OS of 72% if surgery and chemotherapy was combined.

Importance: The results show the pattern, risk factors and timeline for recurrences in the modern era and that a very high proportion of patients can be curatively treated with high survival rates with multimodal treatment based on assessment in multi-disciplinary boards

Key words: follow-up, colorectal cancer, recurrence, treatment of recurrence, survival

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To my mother and father

Omnia mirari etiam tritissima.
Linné

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Original papers

This thesis is based on the following papers, in the text referred to by their Roman numerals

I. Hansdotter Andersson P, Wille-Jørgensen P, Horváth-Puhó E, Høirup Petersen S, Martling A, Toft Sørensen H, Syk I. The COLOFOL trial : study design and comparison of the study population with the source cancer population. Clinical Epidemiology 2016 Jan 28 ;8 :15-21. doi: 10.2147/CLEP.S92661

II. Hansdotter P, Scherman P, Petersen SH, Mikalonis M, Holmberg E, Rizell M, Naredi P, Syk I. Patterns and resectability of colorectal cancer recurrences : outcome study within the COLOFOL trial. BJS open. 2021 Jul 6;5(4):zrab067. doi: 10.1093/bjsopen/zrab067

III. Scherman P, Hansdotter P, Holmberg E, Petersen S, Rizell M, Naredi P, Syk I. High resection rates of colorectal liver metastases after standardized follow-up and multimodal management : An outcome study within the COLOFOL trial. HPB. 2023 March 08. doi : 10.1016/j.hpb.2023.03.003

IV. Hansdotter P, Scherman P, Nikberg M, Petersen SH, Holmberg E, Rizell M, Naredi P, Syk I. Treatment and survival of patients with metachronous colorectal lung metastases. J Surg Oncol. 2023 ; 1-9, Jan 6. doi: 10.1002/jso.27188

Abbreviations

ACS	Adenoma Cancer Sequence
AI	Artificial Intelligence
APC	Adenomatous Polyposis Coli
ASA	American Society of Anesthesiologist
BSC	Best Supportive Care
CEA	Carcino Embryonic Antigen
CI	Confidence Interval
CIN	Chromosomal Instable Neoplasia
CRC	ColoRectal Cancer
CT	Computed Tomography
CTCs	Circulating Tumour Cells
ctDNA	circulating tumour DNA
FAP	Familial Adenomatous Polyposis
FIT	Fecal Immunochemical Test
HIPEC	Hyperthermic IntraPEritoneal Chemotherapy
HNPCC	Hereditary NonPolyposis Colorrectal Cancer
LNR	Lymph node ratio
MDK	MultiDisciplinär Konferens
MTB	Multidisciplinary Tumour Board
MRI	Magnetic Resonance Imaging
OS	Overall Survival
RCT	Randomized Controlled Trial
SCRCR	Swedish ColoRectal Cancer Registry
TNM	Tumour Node Metastases
UICC	Union for International Cancer Control

List of Papers

Paper I

Hansdotter Andersson P, Wille-Jørgensen P, Horváth-Puhó E, Petersen S.H, Martling A, Toft Sørensen H, Syk I. The COLOFOL trial : study design and comparison of the study population with the source cancer population. Clinical Epidemiology 2016:8 15–21

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Paper IV

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Populärvetenskaplig sammanfattning

Kolorektal cancer är den tredje vanligaste cancerformen, efter lung- och bröstcancer, i världen.[1] Mer än 1,9 miljoner människor får diagnosen varje år, med nästan 1 miljon dödsfall pga sjukdomen. I Sverige diagnostiseras nu mer än 7000 personer årligen. Det är i huvudsak den äldre generationens sjukdom, men de senaste decennierna har allt fler yngre, dvs under 50 år, drabbats.[2, 3] Orsaken till detta är okänd men troligen är det miljöfaktorer som inverkar. Det är skillnad mellan industriellt utvecklade länder, med en högre förekomst av cancern, jämfört med mindre utvecklade länder. Skillnaden är ffa förklarad på grund av olika kostvanor.

Möjligheten till bot och överlevnad har stadigt ökat över tid, pga bättre diagnostik, screeningprogram samt behandlingsmöjligheter både kirurgiskt och onkologiskt, samt kombinationer av dessa. Nästan 70% av de som får besked om kolorektal cancer kan idag opereras, med eller utan för- och/eller efterbehandling onkologiskt. Detta bidrar till att den relativa 5-årsöverlevnaden har ökat till en bra bit över hälften av de som fått diagnosen.

Kolorektal cancer är den näst största orsaken till cancerrelaterad död. Detta framför allt pga dottertumörer, sk metastaser. Dessa kan upptäckas i samband med diagnosen och är ibland inte tillgängliga för botande behandling. Eller att de upptäcks efter en initialt potentiellt botande behandling, så kallade recidiv. För att upptäcka dessa metastaser i efterförloppet, följs patienterna upp enligt särskilda scheman efter den primära tumörbehandlingen, för att om möjligt upptäcka recidiven i så god tid att de kan behandlas. Trots detta finns det inget generellt etablerat schema för hur patienterna ska följas upp, eller hur recidiven bäst ska behandlas.

I Sverige följs patienterna, vanligtvis, i minst tre år efter potentiellt botande behandling av kolorektal cancer. Patienterna planeras enligt lokalt utarbetade uppföljningsprogram för skiktröntgen, CT, av lungor och buk, samt blodprov, CEA, den cancer-markör som framför allt används för den här cancertypen. Tre år är satt som ett uppföljningsförslag pga att de flesta recidiven har visat sig inträffa inom de tre första åren efter potentiellt botande behandling av primär-tumören.

CEA står för carcinoembryonic antigen, ett protein, som är inblandat i cell-adhesion och produceras ffa i tarmen under fosterutvecklingen. I vuxen ålder är värdet numerärt lågt. Vid olika typer av cancrar kan det bli förhöjt, och ffa vid tarmcancer. Det är dock ett relativt ospecifikt mätvärde då det bla påverkas av ex rökning, sköldkörtelförändringar eller olika inflammatoriska tillstånd både i och utanför tarmen. Vissa patienter producerar aldrig förhöjda CEA-värden trots att de diagnostiserats med tarm-cancer. Det finns en stor mängd forskning där man söker efter, och även har funnit, nya markörer. Men det behövs fortsatt utveckling av metoderna samt hur värdena ska tolkas, för att kunna använda dessa markörer.

Vanligaste metastaslokalen för kolorektal cancer är levern följt av lungorna. Detta pga kärlens vägar från tarmen, som kan föra med sig cancerceller. Möjligheten att behandla dessa recidiv har utvecklats med goda resultat avseende överlevnad. Förbättrade operationstekniker har tagits fram tillsammans med flertalet nya onkologiska behandlingsmöjligheter, och där sker utvecklingen fortsatt i högt tempo. Ytterligare en orsak till den förbättrade möjligheten till bot är införandet av multidisciplinära konferenser, MDK, där de olika specialiteterna som är inblandade i patientens omhändertagande, så som kirurger, onkologer, patologer, röntgenläkare med flera samlas och gemensamt kommer fram till ett förslag till individuellt behandlingsupplägg.

Kunskap om riskfaktorer för utveckling av cancern och dess recidiv, genetiska förhållanden i primärtumören, när och var man kan förvänta sig recidiv, vilken teknik som ska användas för upptäckt samt hur man bäst ska följa upp patienterna, är således av högsta vikt för att kunna uppnå ännu bättre överlevnadssiffror. För att bättre förstå dessa parametrar och med förhoppning om att kunna utveckla bästa uppföljnings- och behandlings-metoder av dessa patienter, genomfördes detta arbete.

En stor studie, COLOFOL-studien, som genomfördes 2006 till 2011, i Danmark, Sverige och Uruguay, jämförde två uppföljningsscheman av sammanlagt 2509 patienter som genomgått potentiellt botande behandling för kolorektal cancer. Data från denna studie angående patienter från Danmark och Sverige har använts. Tillsammans med journalgranskning av de 471 patienter, i dessa två länder, som detekterats med recidiv inom 5 år efter den i botande syfte, primära behandlingen av kolorektal-cancern.

Delarbete I

En sammanställning av COLOFOL-studien, genomgång av hur studien var upplagd och genomfördes, vilka patienter som ingick i studien samt om studiepopulationen var jämförbar med den tänkta patientgruppen, dvs med generaliserbara resultat. Fyra av de 23 centra i Danmark och Sverige, som ingick i studien granskades. Centra i Århus och Bispebjerg (Danmark), samt Malmö och Stockholm. Resultatet visade god överensstämmelse mellan inkluderade och valbara men icke inkluderade patienter avseende tumörstadier samt patient-fördelning. Resultaten från studien var därför användbara och trovärdiga, dvs generaliserbara.

Delarbete II

Uppföljning av resultaten av de 471 patienter som utvecklat recidiv inom fem år efter primär-operationen av de patienter som behandlats för kolorektalcancer inom COLOFOL-studien. Journalgenomgång av de ingående 23 centra i Sverige och Danmark med bedömning av diagnostik, tumörutbredning, recidiv-mönster och incidens, riskfaktorer, given onkologisk- och/eller kirurgisk behandling, intentionen

med behandlingen av recidiven Ett av resultaten från arbetet visade att fler recidiv än vad som tidigare visats, är behandlingsbara, med förbättrad överlevnad.

Delarbete III

Utvärdering av behandling och överlevnad av patienter med recidiv till levern inom fem år efter potentiellt botande behandling av kolorektal cancer. Antal, fördelning, tidsperspektiv samt behandlingsstrategier och överlevnad. Studien visade att patienter med levermetaser i hög grad bedöms vara tillgängliga för kirurgi med botande intention. Antalet metastaser har mindre betydelse för överlevnaden, om kirurgisk behandling ges, emedan storleken på metastaserna har betydelse för överlevnaden samt möjligheten till behandling. Resultaten pekade mot att patienter med högre risk för levermetastaser bör följas upp tätare än ordinarie uppföljningsprogram då resultaten visade en viss överlevnadsvinst efter tätare uppföljning. Ytterligare studier krävs dock.

Delarbete IV

Utvärdering av behandling och överlevnad för patienterna inom COLOFOL-studien, med recidiv till lungorna inom fem år efter botande behandling av kolorektal cancer. Patienter med lungmetastaser kan i högre utsträckning än vad som tidigare visats behandlas med kirurgi generellt. Till skillnad från tidigare studier sågs även att patienter med flera lungmetastaser och metastaser i båda lungorna kan behandlas med goda överlevnadsresultat. Kombinationen av kirurgi och onkologi visade på ökade överlevnadsvinster, men det krävs ytterligare studier för att kunna bekräfta resultaten.

Introduction

Colorectal cancer

Every year, more than 1.9 million new cases of ColoRectal Cancer (CRC) are detected globally, making it the third most common cancer in the world.[1] Only in Sweden, more than 7000 patients were diagnosed 2021. [4] Approximately two thirds of the CRC cases are found in the colon, and one third in the rectum. If treated, the 5-year relative overall survival (OS), is more than 65% in Sweden and is strongly dependent on the stage of the tumour when it is detected. Around 20-25% of CRC patients have any kind of synchronous metastases at the time of detection of the primary CRC. Many of these metastases are resectable with curative intent, together with treatment for the primary CRC. In Sweden in total almost 70% of patients detected with CRC with or without metastases, are treatable with curative intent. [5] Even if survival after detection has improved, CRC is still the second leading cause of cancer related death in the world, with almost 1 million deaths per year.[6] Death is mostly due to the presence of untreatable metastases at the time of detection of the primary tumour. This together with a considerable risk of recurrence of malignancy, even if the primary cancer was treated with curative intent, there are still 20-25% of the patients that develop any kind of metachronous metastases.

The liver is the most common site for metastases,[7] followed by the lungs.[8] Many studies show good survival after treatment of recurrences.[9, 10] Despite this, follow-up schedules after the first treatment of the CRC, with the purpose of finding any recurrence in time for treatment with curative intent, have not been established with consensus worldwide. [11] Nor how to treat the recurrences when detected.

Etiology

The colorectal canal begins, where the small bowel ends. The colon is approximately 1,5 meters long. It is made up of four parts: the right, the transverse, the descending, and the sigmoid colon. It continues into the rectum, which is approximately 15 cm long. The rectum ends at the anal verge. *(Figure 1)*

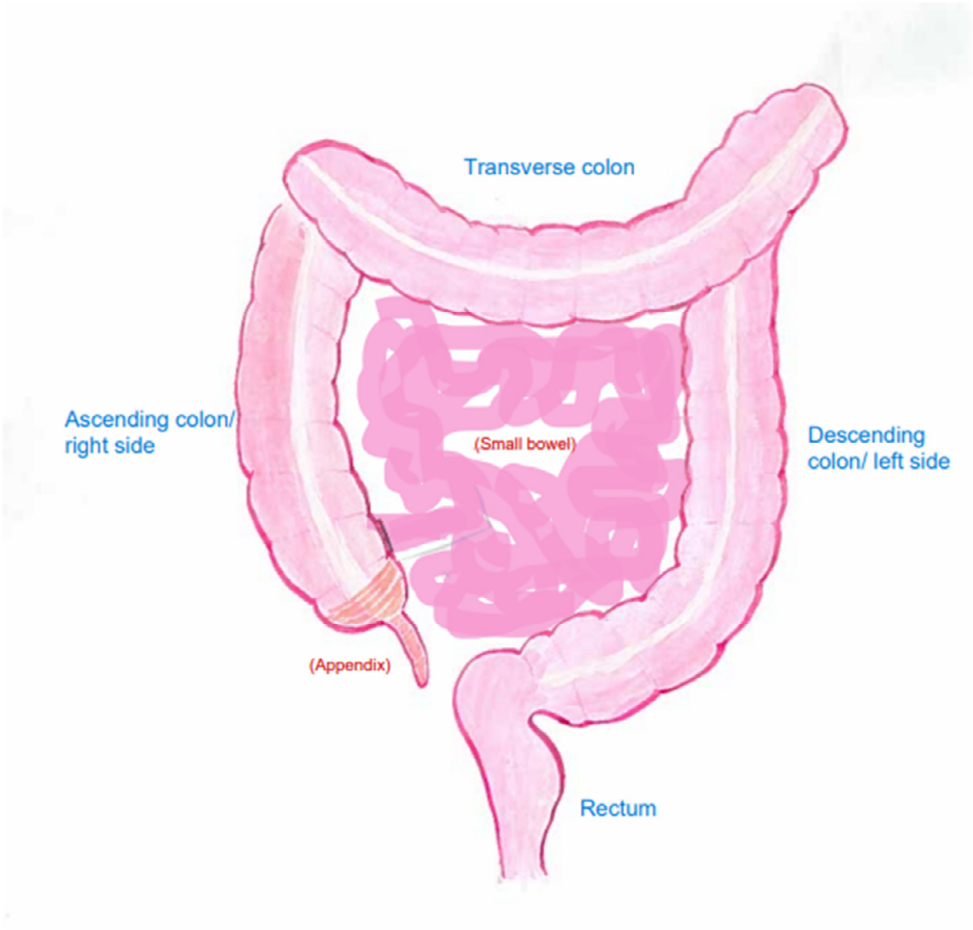

Figure 1 The colorectum

CRC develops from polyps, also called adenomas, in the gut mucosa.[12] In the western population, some reports show up to 50% of the population to have adenomas in the colon or rectum during their life, with an increasing number with increasing age. [13, 14] Slowly, usually in a time setting of 10-15 years, or even longer, the adenoma grows and at some stage the cells in the polyp become malignant and start to grow uncontrolled. [15, 16] This process is known as the adenoma cancer sequence, ACS, and causes the cells not to respond to the ordinary cell apoptosis program, i.e., programmed cell death.[17-20] *(Figure 2)*

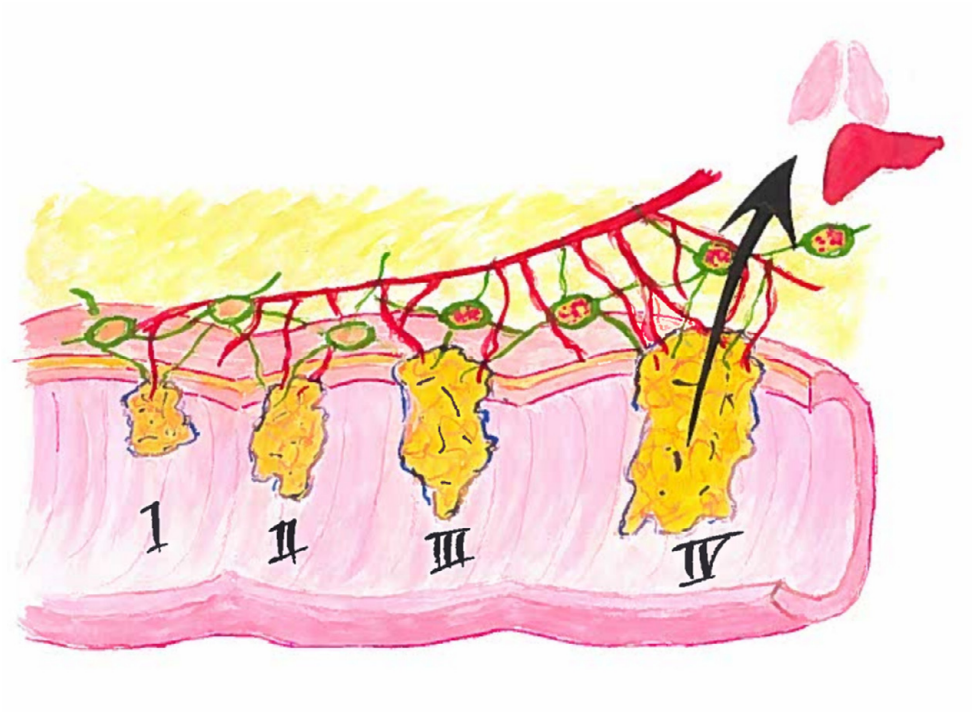

Figure 2 Colorectal stages

A mutation that inactivates the adenomatous polyposis coli gene, APC, is responsible for 80% of all tumours. It is inherited in an autosomal dominant way and generates both familial and sporadic colon cancer. [21, 22] The mutation causes a dysregulation of signaling pathways that leads to drug resistance, inhibition of apoptosis, induction of proliferation with invasion and migration, and can trigger cancer formation and metastases. [23]

In the late 70's, a protein called p53 was detected by Sir David Lane. When this protein is dysfunctional, p53 is found to be the basis for all cancer formations in humans. Normally it is present in all cells and guards the cell as a tumour suppressor from genetic disorders, "the guardian of the genome". [24] The protein is involved in a complex signaling network of other proteins. When this network is distorted, cancer is predisposed. Deeper understanding of the function of p53 might be one gateway of both detecting and treating cancer. [25]

Professor Sir David Lane

There is good knowledge about different pathways for the transformation from benign cells to malignant.[26] Etiologically, CRC is a heterogenous disease, meaning that it consists of not just one, but a setting of different factors causing the disease, with mutations in several genes. Mutations can be caused by genetic or epigenetic factors, or both. Epigenetic factors can cause changes affecting the on/off regulation of the genes, triggered by lifestyle behavior or environmental impact. Epigenetic factors are reversible, and unlike genetic factors, they do not change the DNA sequence. CRC classifies as familial, sporadic or inherited, depending of the origin of mutations.[27] Genes commonly affected are tumour- suppressor genes, DNA mismatch repair genes, and oncogenes. Inactivation of tumour-suppressor genes by mutations activates signaling pathways by different proteins that can initiate tumour growth. The mismatch repair system, a group of enzymes, repairs errors during the DNA replication. When this system is malfunctioned, tumours get hypermutated with chromosomal instability. Activating oncogenes, like BRAF and RAS, creates other signaling pathways promoting CRC, a complex interaction involving environmental influences, germ-line factors and somatic changes in the colorectal mucosa. DNA sequencing technology has found more than 800 genes involved in cancer-associated somatic mutations. [28-30] Mutations must occur in several different genes to cause most cancer formations.

Tumours with microsatellite instability, MSI, from impaired DNA mismatch-repair, account for around 15 % of colorectal cancer in Sweden. MSI tumours are more common in right-sided colon cancer, more often found in female patients and often found in hereditary tumours. Half of these tumours have a mutation in another gene, the BRAF gene, an oncogene that affects the formation of a cell protein, B-Raf, in part responsible for cell growth. It normally only turns on when cell growth is needed. When mutated, BRAF function is impaired and cell growth gets uncontrolled. BRAF mutations are found in nearly 10% of CRC. This gene does not appear in the hereditary form. [31-33]

Chromosomal instable neoplasia, CIN, accounts for 85% of CRC. It is more common in left-sided colon tumours and rectum, more frequent in men since rectal cancer is more common in males and associated with poor prognosis due to enhancing metastases and therapeutic resistance. CIN results from errors in cell mitosis, i.e., cell division. It is a central promoter of tumour evolution. [34-36]

So far, our methods and possibilities of detecting CRC are not optimal concerning early detection. Research aims to find noninvasive tests like molecular markers such as DNA, RNA, and different proteins. The goal is to find a cancer marker that is both safe and cheap, with a high positive and negative predictive value. It also must be easy to measure without harming the patient while enabling us to be one step ahead of cancer. [37, 38]

Risk factors

CRC used to be the elderly patients' cancer and age is still the most important risk factor. In Sweden, 29% of patients with colon cancer and 21% of patients with rectal cancer, are 80 years or older. The mean age is 72 years. It is still considered to be a rare cancer form in patients younger than 40 years, and only 5% are younger than 50 years. [39] Male and females are almost equally affected by colon cancer, whereas rectal cancer is twice as common in males. [40]

In the last decades, a higher number of younger patients are affected with CRC. Since the 1990s, there has been an increase of 50% among patients aged 20-49 years, and the increase is expected to continue. [2, 41] The cause of this is still elusive, but changes in environmental factors are probably responsible.[42] At the same time, a decrease in the incidence among elderly have been noted. This is probably due to screening programs, i.e., the pre-stages of cancer are found before cancer formation.[3, 43, 44]

So far, the most important risk factors for CRC are increasing age and lifestyle habits. And even if the distribution of cancer in the colon is evenly shared between male and female, all together there is a higher incidence of rectal cancer in men. Studies suggest that oestrogen might have a protective role in the development of CRC. [45] As with all cancer forms, no single factor is responsible for inducing CRC. And many risk factors are still to be revealed. [46]

Large studies have shown that high intake of red meat and processed food, lack of vegetables and low intake of fibers, sugar, obesity and low physical activity, smoking, and alcohol, are associated with an elevated risk of CRC. [47-50] This might be the explanation of the higher incidence of CRC in developed, middle- to high-income countries, most common in Australia, New Zealand, North America and western Europe, with a much lower incidence in Africa.[51] The theory is supported by reports about immigrants from low-income countries moving to middle- or high income countries. That the immigrants adopt to the new life habits

and over time have the same rate of cancer incidence as in their new country. [52, 53] More than 30% of all cancer forms are thought to be preventable with healthier habits. Efforts about primary prevention and its performance are debated, but healthier lifestyle choices are considered most effective. [54]

Comorbidities, as diabetes, are also considerable risk factors for CRC. [55, 56] As well as inflammatory bowel disorders (IBD), such as Crohn's disease or ulcerous colitis (UC), and those patients undergo special follow-up programs.[57, 58]

The mechanisms behind the carcinogenic influence of all those risk factors are unknown, but it is speculated that they affect the mucosa and the microbiota in the gut in a negative way, initiating cancer evolvement.[59, 60] Lately, an increasing interest has been paid to bacteria in the gut. Especially the balance of bacteria, as well as the variety, specifically the role they may play in cancer genesis.[61, 62] There are studies that have shown certain bacteria to be protective against, and other bacteria to be associated with, CRC. Much research is conducted to find ways to alter the microbiota in the gut to reduce the cancer risk, and maybe even enhance the human body itself to reduce the effect of carcinogenetic factors. [63, 64]

Preventing CRC is most important, as well as how to detect it. Finding tumour markers with high accuracy, must be a priority, as well as screening programs.[42, 65, 66] A high interest should be paid to risk factors. Especially with the new trend of early onset, resulting in an enormous rise in healthcare costs concerning treatment and follow-up. Besides the patients' suffering, the loss of labour due to treatment and rehabilitation renders considerable social consequences. Due to this change in age-patterns for CRC, more attention must be given to alarm symptoms even in younger patients**.** [67-69] As well as better information about known risk factors and prevention in the population.

Genetics

Families with hereditary factors, with not yet specified genes, account for 10-20% of the CRC cases.[70] Those patients are mostly found through the family history, and early screening programs for the members in those families are recommended in some countries.[71] Data shows that there is a higher risk for CRC for siblings and children of patients with colorectal polyps, with no specific genes associated, especially for early onset cancer. No particular screening is at hand (in place) for this cohort but is recommended. [72] A number of well-defined inherited syndromes account for 3-6% of all CRC, examples include non-polyposis (HNPCC/Lynch syndrome) or polyposis syndromes (FAP), and some others. [73] Patients with detected cancer promoting genes are followed even more rigorously and sometimes are recommended go through prophylactic colectomy due to the very high risk of cancer. [74, 75]

There are patients, without any specific cancer genes, who are found to have a high production of polyps in the gut, and therefore are followed with colonoscopy according to specific schedules, to detect and resect the polyps early on. [76]

Diagnostics

Most CRC cases are found when patients seek health care due to some specific gut symptoms. But some CRCs are found during the investigation for some other disease or in a follow-up program after some other cancer treatment.

Screening for CRC to prevent and find the cancer early is of high value. [77, 78] Screening has proven to be of such high value that most high industrial countries have had screening programs for many years. [79-81] Most of the programs consist of Fecal Immunochemical Test, FIT, for the ages of 50-74 years.[82] If a positive test result is found, complementary colonoscopy is performed. With the rising incidence of younger patients with CRC, guidelines are formed for the performance of screening at an earlier age. [83]

Symptoms of CRC are usually sparse.[84] Typical for the CRC is that it is common as a non-symptomatic malignancy, or at least has symptoms that are easy to be mistaken as less harmful. For example constipation, variations of fecal consistency or abdominal pain now and then. [85] This could be due to flexibility and the possibility for adaptation of the gut. It is not rarely discovered in another context, as found at an x-ray examination in the investigation for some other disease. Fatigue and/or anemia is most common for right-sided colon tumours. Changed stool patterns and visible blood in the feces, is more common the more distal the tumour. Weight loss or suspended stool is more common when the cancer is vast and already spread. Due to the few and hard to discover symptoms, many patients come to the attention of the health care systems late, and sometimes too late for cure.[86] Hence, a high number of patients are detected when seeking acute care for ileus, i.e., total intestinal obstruction. As many as 10-28% of colon cancer patients are reported to have acute obstruction as a first symptom. Unfortunately, that is in many cases, when the malignancy is already spread, with synchronous metastases. The outcome of this situation is bad, with a decreased short-term as well as long-term survival, compared with patients without ileus and CRC. The 5-year OS of patients presenting with ileus is almost half compared to those without. [87]

At the specialized surgical clinics, when CRC is diagnosed, a standardized health care program is performed. The CT scan of the thorax and abdomen is conducted to search for metastases, to estimate the size of the tumour, to detect visual lymph nodes, and to investigate if it affects any other organ. [88-90] Blood samples with carcino embryogenetic antigen, CEA, a protein marker for CRC, are measured.[91, 92] A rectoscopy followed by MRI of rectum if rectal tumour. [93, 94] Colonoscopies are performed to rule out any other malignancy in the bowel and to

take samples from the tumour for genetic and tumour specific analysis and to verify the site of the tumour.[95] A thorough examination of the patient, at the outpatient clinic, to assess the patient's capacity to undergo any treatment. The investigation is to determine the stage of the cancer, including search for any synchronous metastases. [96] When the result from this investigation is at hand, a multidisciplinary tumour board (MTB) is held, where the stage of the tumour is established, and a further treatment plan is proposed**.** [97]

The classification of the tumour is made following the TNM (Tumour, Node, Metastasis) system, (*Table 1)*

Table 1 The TNM-system

T	**Tumour**
Tx	The tumour is not accessible
T0	No evidence of tumour
Tis	Carcinoma in situ; intraepithelial or invasion of lamina propria
T1	Invasion of submucosa
T2	Invasion of muscularis propria
T3	Invasion of subserosa and perirectal tissue
T4	Penetration to the visceral peritoneum or invasion or adherent to adjacent organs or tissue
N	**Nodes**
N0	No regional lymph nodes
N1	Metastases in 1-3 lymph nodes
N2	Metastases in 4 or more lymph nodes
M	**Metastasis**
M0	None
M1	a: Metastasis to one distant organ, b: to more than one organ, c: to peritoneum

This system is designed by the American Joint Committee on Cancer (AJCC).[98] T gives a picture of the growth of the tumour, how many layers of the bowel that are involved or if it grows through all the layers, with tumour growth on the outside of the bowel, and if so, if it involves adjacent organs. N classifies any involvement of visible and suspicious lymph nodes, locally or regionally. Finally, M describes any metastases. This staging is the most valuable tool for suggesting a treatment plan at the MTB conference. Even though it is debated whether TNM by the radiology staging is reliable enough, it is still the most important tool for treatment planning. [99]

Another staging system, the UICC classification (Union for International Cancer Control) is used together with the TNM system, to form the treatment strategies. It gives a more combined picture of the tumour growth and spread. *(Table 2, Figure 2)*

Table 2 Staging system according to the UICC classification

Stage	T	N	M
I	T1-T2	NO	MO
II	T3-T4	NO	MO
III	T1-T4	N1-N2	MO
IV	Any T	Any N	M1 a-c

Liquid biopsies, i.e., blood tests, for circulating tumour DNA, ctDNA, and circulating tumour cells, CTCs, are some of the most upcoming and promising tumour markers.[100] Hopefully they will prove to be reliable indicators for evaluating the genomic profile for CRC. Though it depends on the volume of the cancer, studies have shown possibilities to detect CRC earlier than standard imaging procedures and to be more reliable than ordinary invasive biopsies. [101] It might also be a possibility to follow the patient after any treatment, to find any recurrence early enough to tailor new treatment plans. [102, 103]

In Sweden, a screening program for CRC is designed and accepted, but not yet totally set up in all our health care regions. FIT every second year, followed by a colonoscopy if positive test, is proposed as a screening method. [104][105] The recommendation is for the population aged 60-74 years. Studies are ongoing to find other methods, like blood tests, new CRC markers and biochemical traces from the cancer, as described earlier.[106] Still, the health centers must pay attention to alarm symptoms, especially in elderly patients. [107] They are obliged to start an investigation if alarm symptoms, with examination of the rectum and a colonoscopy to rule out the presence of CRC. [108, 109] Alarm symptoms are considered to be, according to the Swedish standardized investigation program for CRC, blood in feces, changed stool patterns for more than 4 weeks and/or anemia. [110] If there are any tumour findings, the patient is referred to specialized surgical clinics for further investigations.

Treatment

The patient's case is evaluated at a MTB, involving all the specialties managing the procedure of the patient, such as radiologist, oncologist, pathologist, surgeons with different sub-specialties, and nurses, to establish a strategy for treatment.[111-113] Once again, the decisions are highly dependent on the stage of the cancer.

The result from the MTB can be either with a curative or palliative intention. If curative intention, surgery is the standard treatment, with or without the

involvement of oncological treatment before (neoadjuvant; preoperative) or after (adjuvant; postoperative) the surgery. This also includes surgery for synchronous metastases, for example in the liver or in the lungs. Patients detected with liver metastases most often receive neoadjuvant treatment, especially in rectal cancer. Neoadjuvant treatment is given to downstage the metastases when considered curable, making them even more susceptible for surgery. With a widespread disease and the tumour and/or metastases are not surgically resectable, neoadjuvant treatment can be administered in an attempt to convert the situation to surgically resectable. Finding liver metastases, and to treat them, is most clinically relevant since they are most life limiting. [114]

If neoadjuvant treatment is given, a re-staging is done with CT scans, and MRI if rectal cancer, at the end of the treatment. Hopefully with the findings of downstaging of the TNM status. This re-evaluation gives a picture of the responsiveness to the oncological treatment, and also forms the planning for the next step, surgery.

Neoadjuvant therapy

Neoadjuvant oncological treatment consists of chemotherapy and/or radiotherapy. Advanced rectal cancer is commonly given neoadjuvant therapy before surgical treatment. [115] Colon cancer more rarely receives any oncological pre-treatment, if not an advanced situation, and then almost always only chemotherapy. The purpose of neoadjuvant therapy is to reduce the tumour burden, to shrink the tumour, and to reduce the risk of local and distant recurrence by elimination of circulating tumour cells in the blood stream and lymph system, as much as possible.[116, 117] As soon as a tumour is established anywhere in the body, circulating tumour cells in the blood stream are a fact.[118, 119] Many ongoing studies tries to find and use DNA and their genome of tumour cells, for screening, and for the development of therapies and treatment, to reduce the influence of both the primary cancer and the risk of metastases.[120] Promising results are already on the way but still not clinical standard.[121]

Radiotherapy is most of the time only used in the pre-treatment for rectal cancer. But it can be used as a palliation tool, in colon cancer, with the risk of harming organs in the vicinity.

Chemotherapy can be used on its own or combined with radiation, and vice versa.

Adjuvant therapy

After surgery, either for metastases, or for the primary tumour, and when the pathology result from the resection is at hand, a new MTB is held with an updated version of the TNM. After re-evaluation, a new treatment strategy is proposed. If surgery for metastases is performed first, it must be an R0 resection, i.e., a radical resection of the metastases, to proceed to surgery for the primary tumour.

The pathology result focuses on the growth of the tumour, if any lymph node is involved in the resected specimen, and if it is a radical resection with no cancer cells at the resected margins. Lymph node involvement or not is a key stone if further treatment is needed, as well as if radical resection is performed. This, together with a deep genetic investigation of the cells forming the tumour, forms the base for the need for adjuvant treatment, or not. Altogether, once again decided at MTB conference.

The purpose of chemotherapy is to reduce or eradicate the impact of resisting circulating cells and if there is any non-detected metastasis, thus lowering the recurrence risk. Data shows a decrease in relative risk for recurrence of up to 30%, if adjuvant treatment is given. [122] [123]

Palliative treatment

If palliative intention is decided at the MTB, it can involve oncological treatment with the purpose of reducing the tumour burden, to reduce symptoms and to slow down the tumour growth as long as possible.[124] In some cases, palliative treatment alters the intention and makes the tumour susceptible to curative treatment, a converted situation. If the tumour is not susceptible for oncological treatment, or if the status of the patient is poor due to comorbidity and therefore any treatment can do more harm than benefit, the patient will receive best supportive care (BSC).

Upcoming treatments

Several trials have been and are performed to evaluate the benefit of oncological neo- and adjuvant treatment, with the purpose of enhancing long term survival. And it is an ongoing process to adjust the oncological schedules, alongside the results from these trials.[116, 125-127] Nevertheless, huge improvements have been made in the last decades concerning chemotherapy treatment, due to enhanced classifications of the tumour cells genome, making it possible to target the treatment even more precisely. New substances have evolved including immunomodulating treatment.[128, 129] Hence, many new alternatives concerning oncological treatment, like for example immunotherapy, are sighted on the horizon and have so far shown very good results. The satisfactory results from these new treatments have led into a new era, where treatment towards organ preservation is studied. This is when the tumour has gone into total remission during the treatment, and instead of surgery, the former site of the tumour is frequently examined clinically and with imaging.[130] As a result of this, when patients are found to have no residual, according to MRI, or detectable, due to clinical examination, tumour left after neoadjuvant radiotherapy of rectal cancer treatment, so called complete response, a clinical trial, watch-and-wait, is under investigation.[131] The patient can choose not to be surgically resected, and instead to be followed-up through a special high

frequency program, with x-ray examinations and clinical evaluations. But there is still no consensus about this treatment form, with the ongoing trial.

Afterall, all those decisions are made due to the cancer stage, together with the consideration of the status of the patient, since any treatment for CRC is a challenge for the patient, both physically and psychologically. Therefore, the opinion and decision of the patient itself is also important. [132]

Metastatic disease

The development of metastases is complex and the understanding of the factors influencing the metastatic route of tumour cells is poor. [133] When a tumour is present, tumour cells migrate through adjacent venous blood- and lymphatic vessels to the portal or hemorrhoidal veins, vena cava and to the thoracic circulation. Therefore, the main pathways for metastases from CRC are to the liver and/or to the lungs. [8] The migrating cells must avoid all the defense mechanisms of the body and must survive long enough to establish growth in a distant organ. Suggesting that it requires a large number of migrating cells. [134] New evidence shows that cells probably might have migrated long before the primary tumour is detected. [135] This makes a request for better biomarkers and liquid biopsies even higher, to make it possible for tailoring and targeting neo- and adjuvant therapy. [136]

Liver metastases are the most common type of metastases in CRC. Liver metastases have been considered to be most accessible for treatment, oncological and surgically, and resection has been regarded as the only way of long-term survival. [137] Between 25-30% of all CRC patients develop liver metastases, resulting in a short survival time if untreated. If treated with curative intent, 5-year OS of 30-50% is reported, and in some recent studies even more than 50%. [7] Size, number and location of liver metastases have been considered to be limiting factors for treatment.[138] Indication for treatment has expanded due to improved surgical techniques. In most cases, liver metastases are treated with chemotherapy prior to surgery. Still the role of surgery and chemotherapy is elusive.[139, 140] Surgical treatment can be performed through a variety of techniques, with open or laparoscopic resection and/or ablation, vessel ligation or embolization as portal vein occlusion. In a few, very selected cases, liver transplants have been performed.[141, 142]

Lung metastases, the second most common site for metachronous metastases in CRC, have been more reluctantly treated as compared to liver metastases. One reason for this might be that compared to other distant metastases, lung recurrences grow relatively slowly, with a better overall survival. [143] The incidence is less well documented compared to liver metastases, but data of 5 to 10% is reported. Lung metastases have almost only been treated if spread to only one side of the lungs, with only a limited number of metastases present. Earlier reports shows that

if concomitant spread, the patient has in many cases been assessed as palliative, which has resulted in a most limited and selected patient cohort that was treated with curative intent, making the evidence-based data less reliable. The highest incidence of lung metastases is seen after low rectal cancer. Lung metastases are easier to detect even with less advanced imaging techniques and seldom require more than a CT-scan for both detection and classification. Since many decades, the efficacy of surgery has been debated.[144, 145] At the same time, the common opinion has been that without surgery there is no 5-year survival. One reason for the resistance to surgery might be that lung metastases respond well to chemotherapy and surgery has been considered to be too invasive and with a high postoperative morbidity. During the last 20 years, an increasing number of metastases have been prone to surgery, especially with new enhanced thoracoscopic techniques, less invasive. Oncological treatment has also evolved with stereotactic radiation and targeted therapies. [146] Combinations of all these therapies are nowadays common. Although, very few data are available concerning survival. [145] Nevertheless, rates of 40 to almost 70% 5-year OS are reported following surgery. However, these studies have highly selected cases and are not RCT.[147] Still no treatment algorithm is established.

Treatment of recurrences after curative surgery for CRC has changed considerably during the last decades. In the end of the last century, almost only one active chemotherapy was available. And only small and easy to access liver and lung metastases were treated surgically. From previously being assessed palliative if more than one organ with metastases we today have highly aggressive treatment forms like surgery for widespread recurrences to peritoneal and multiorgan resection with for example HIPEC-treatment (hyperthermic intraperitoneal chemotherapy). [148, 149]

Results

For colon cancer, the mean age is 73 at detection, and for rectal cancer 70 years. Results concerning survival after treatment of CRC are most promising. Relative survival has increased significantly over the last decades.[150] Even if an increasing number of patients younger than 50 years that are diagnosed with CRC, it is still less than 5% that are affected. In Sweden, the 5-year relative OS is more than 65% of all detected with CRC, 68% for colon and 69% for rectal cancer. A rate of 70% possible to treat with curative intent, is high. The survival for patients not possible to treat with curative intent, have also improved remarkably in the era of new and enhanced oncological treatments. [151][152]

With better possibility to treat recurrences, the question about how to follow-up all these patients are, and should be, an ongoing discussion and a matter of further trials.

Follow-up

One might think that frequent examinations would make the patient feel more secure. But many patients get distressed with numerous checkups and then wait for the results. [153]On the other hand, some patients want to feel the security of a tight contact with the health care system after the cancer treatment.[154] Taking this into consideration, there is also the cost for all the examinations, and not to forget, a considerable risk for the patient with for example exposure of radiation. Even if techniques of imaging have improved, standard procedures still need more accuracy. [155]

The main purpose of a follow-up program is to find any recurrence in time, so that the recurrence can be treated with a curative intent, hopefully leading to enhanced survival. Other benefits are patients support and monitoring, as well as the possibility to build a database for, for example, retrospective trials and investigations. Not until the beginning of this century, there was none or limited possibility of treating any recurrence of CRC. Follow-up was questioned. With the introduction of chemotherapy and better surgical and imaging techniques, both for the primary tumour, and for metastases, the attitude has changed in favor of any follow-up. The impact of finding recurrence early and how to treat them is still discussed, and the design and benefit of follow-up programs have been debated during the last three decades Therefore, the irresolution about the follow-up frequency. [156, 157]

Hence, there is still no established consensus about how to follow-up patients treated for CRC.[158] Numerous trials have been performed. Many trials have not been large enough, and without substantial biases, to produce a suggestion or result to form a follow-up schedule good enough to be widely accepted. Too many variations in follow-up programs have made several meta-analyses difficult to suggest follow-up regimens. [159, 160] This shows the difficulties of setting up a trial large enough to get enough power, to be able to recruit patients within a reasonable time, and to get a cohort without substantial bias, with the possibility of generalization.

The main issue with follow-up programs is the frequency of examinations. Intuitively, high frequency examinations would lead to earlier detection of recurrences, with a higher rate of curative treated cases and subsequent improved survival. However, no trial so far has been able to confirm this hypothesis. [160, 161]

A Cochrane analysis in 2019 with 19 studies including 13,216 patients came to the conclusion that intensive follow-up did not improve overall survival, even though a higher rate of recurrences were treated with curative intent. [153] Suggesting that how to follow-up CRC patients need further research.

Some of the largest trials presented, trying to produce facts about follow-up strategies, are described below.

The FACS study, a randomized clinical trial, was performed in the United Kingdom between 2003 to 2009.[162] It recruited 1202 patients, who had undergone curatively intended surgical treatment for CRC, with or without adjuvant treatment. The patients were randomized into four different follow-up groups. The first group had a blood test with CEA every 3 months for 2 years and then every half year for another 3 years. The second group underwent CT imaging of thorax and abdomen every half year for 2 years, then every year for another 3 years. The third group had the same CT scan system together with CEA. The fourth group was only followed-up if symptoms occurred but could have a CT-scan after 12 to 18 months if requested by the clinician. The primary outcome was the rate of surgical treatment with curative intent if any recurrence. Secondary outcome was overall and cancer specific mortality, time to recurrence, and survival if treatment for the recurrence. Of the 1202 participating patients, 199 were detected with recurrence within a mean follow-up time of 4.4 years. Of these, only 71 patients underwent treatment with curative intent, irrespective of staging. Although a higher rate of treated patients with recurrence, there was not any significant difference in survival comparing the three groups with scheduled follow-up with the minimal follow-up group. Their conclusion was that all patients that were followed up had more surgical treatment for their recurrence, with no advantage of combining CEA and CT. The conclusion was that if there is any survival benefit to any follow-up strategy, it is only small. They also discussed that early recurrences probably in reality are residual disease that was missed in the primary investigation of the CRC, due to poor imaging, and that they therefore were not true recurrences. Suggesting more thorough investigation of the patients for better staging before primary treatment.

The short coming of the study was low power due to few patients in each of the four arms, and limited possibility to estimate survival. Another explanation of the absence of difference in survival between the four follow-up regimens could be the small number of detected asymptomatic recurrences that were possible to treat with curative intent.

The GILDA trial, a European multicenter study, aiming to recruit 1500 patients.[163] The intention is to evaluate the impact on survival by more or less intensive follow-up of CRC after surgery with curative intent. The trial has recruited patients since 1998 but has not yet published any results indicating problems with having too slow inclusion rate.

The CEA second look trial in the UK had after 11 years still not recruited the aimed number of patients, i.e., 2000. [164] The trial was closed in advance following the advice from the monitoring board, who was assessed it unlikely to being able to show any survival advantages with the intended follow-up strategy, i.e., CEA prompted second-look surgery.

Some studies, including FACS and COLOFOL (described below), have shown a higher rate of treated recurrences by high follow-up but not rendering any survival benefit.[165] One possible explanation for this might be the difference of genome in different cancer cells. Therefore, early recurrence might be due to a more aggressive primary tumour genome, less susceptible for treatment, and even if found early, the possibility to treat with curative intent, might be impossible with existing regimens.[166]

A question is if some metastases are missed synchronous tumour tissue, due to their small size at the primary tumour investigation. Obviously, all cancer cells responsible for recurrences must have been spread already at the primary tumour formation. This is according to the knowledge of circulating tumour cells, even in an early stage of the primary tumour. If these cells, sooner or later, manage to develop to metastases, is due to the conditions at their new host organ, and its resistance against invasion. [167] Cells forming metastases cannot evolve by themselves if the primary tumour has been removed radically. Hence, the tumour cells should have been there all the time. Being just one of the problems with existing imaging techniques and tumour markers. Another problem is the role of subjectivity in every assessment, due to the skills of all the participating units in the treatment process. Artificial intelligence, AI, might in the near future enhance all considerations! [168, 169]

The COLOFOL trial

So far, the largest trial of follow-up in CRC, is the COLOFOL trial. [170] A trial that was set up due to the lack of consistent follow-up systems, and the absence of large enough studies to show how to follow-up patients after surgery for CRC. With the intention of evaluating the impact of high and low follow-up frequency schedules on survival benefits, a randomized prospective multicenter study, randomized controlled trial, RCT, was set up. The objectives were to investigate overall mortality, CRC-specific mortality, and CRC-specific recurrence among patients radically resected for stage II or III CRC. Follow-up was done with computed tomography of abdomen and thorax, and CEA. Initially, the trial was to be performed in Denmark, Sweden, Poland, Uruguay, UK, and Holland. Requirements for centers that participated were to recruit more than 30% of eligible patients and to recruit 25 patients annually. Small centers failed to follow this requirement, so inclusion was altered to 20 patients per year to still ensure quality. Four centers didn't manage to fulfill these new requirements, leaving three countries with 24 centers that managed to fulfil the recruitment obligations, in Sweden, Denmark, and Uruguay.[156] (*Figure 3)*

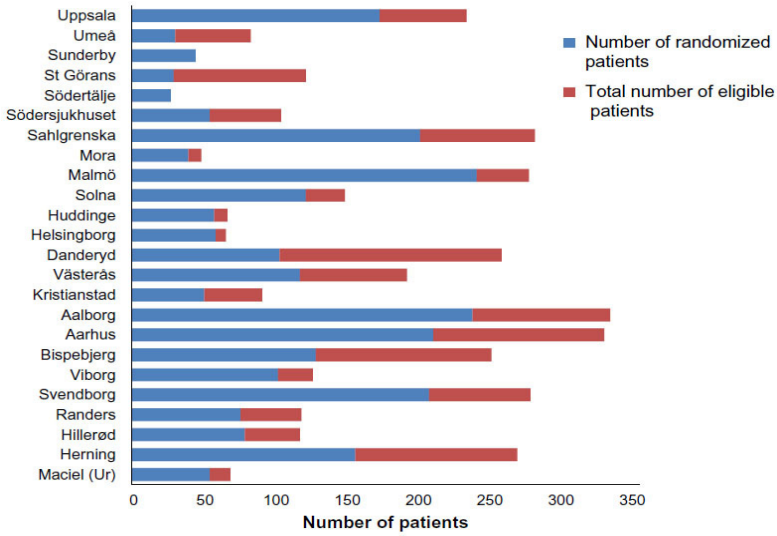

Figure 3 Participating centers the COLOFOL trial

The trial ran from 2006 to the end of 2010, with a 5-year follow-up time, ending in December 2015. The trial included 2509 patients between 18-75 years of age, radically resected for CRC stage II-III. The patients had to have a life-expectancy of more than two years due to any concomitant disease, for the reason to be able to be evaluated for any treatment, if detected with recurrence at the follow-up within three years, and for the possibility to be followed even if not in schedule, for five years. The patients had to be free of any synchronous metastases at the primary treatment for the CRC, and had to have a clean colon (i.e., a colonoscopy performed before or just after the first treatment for CRC to rule out any synchronous tumour in colon or rectum), and a blood test for carcino embryonic antigen, CEA. The CEA was then examined at every follow-up time. The design was as a pragmatic trial with wide inclusion criteria, and few exclusion criteria, to get a picture as close as possible to reality, reflecting the general patient cohort. (*Table 3)*

Table 3 Inclusion and exclusion criteria in the COLOFOL trial

Inclusion criteria	Exclusion criteria
RO	Lynch syndrome or FAP
Age ≤75 years	Local excision (TEM)
Written informed consent	Life expectancy <2 years
Clean colon	Inability or refusal to perform informed consent
Tumor stage II-III	Inability to comply with the control or intense follow-up program

The focus was detection of potentially curable asymptomatic recurrences, and primary outcomes were overall survival and disease-free survival. Symptomatic recurrence was also documented, with a description of the symptoms and how it was investigated. In the power calculation a 60% 5-year survival was estimated, with a 6% survival benefit in the high frequency follow-up group. The number of planned randomized patients was 2500. A total of 13,718 patients underwent treatment for colorectal cancer in the participating centers. Of these, 5,643 patients met the inclusion criteria, 4,445 patients were eligible, and 2509 were enrolled. Corresponding to an inclusion rate of 56,4% with a high variety among the centers. The most common reason for not including the patient was that they were not asked to take part, 17,1%. (*Figure 4)*

The randomization was to two arms. The total number of planned randomized patients was 2,500 with an expected dropout rate of 20%.

One arm was high frequency follow-up after radical treatment for CRC, with examinations with CT-scan after 6, 12, 18, 24 and 36 months. The other arm was low frequency follow-up with examinations after 12 and 36 months. After 36 months, as optional, a new colonoscopy was performed in both arms if no recurrence was found during the follow-up.

Of the 2509 patients included, 53 patients were from Uruguay, 11 patients were lost due to missing data and 3 patients were excluded. Resulting in 2442 patients for the analysis in this thesis.

In Denmark and Sweden, 23 centers participated, 8 sites in Denmark, and 15 sites in Sweden. *(Figure 3)*

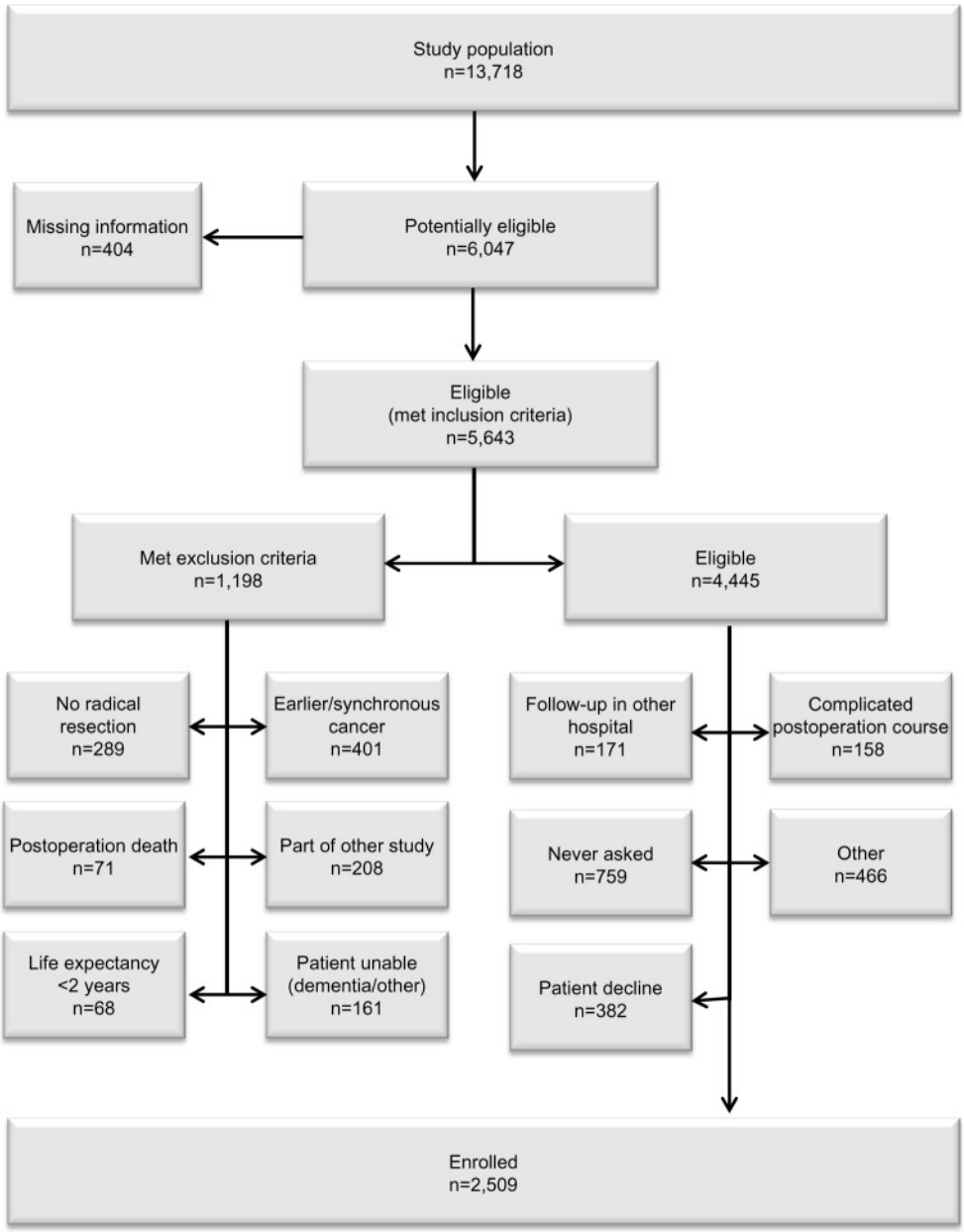

Figure 4 The consort diagram the COLOFOL trial

Of the 2442 patients that were randomized, 471 were detected with recurrence within 5 years after the primary colorectal treatment.

The overall purpose of the trial was to see if it was possible to enhance active treatment of detected recurrences, and to evaluate possible survival benefits with a more frequent follow-up.

Follow-up routines Sweden

The follow-up system in Sweden used to have a great variation from each county or health care area. From no follow-up at all, to a high frequency follow-up schedule for up to five years or more. Due to the reports and findings from the COLOFOL trial, the national guidelines and recommendations for the last years have been according to the low frequency follow-up arm. Hence, the most common follow-up system for CRC after surgery without synchronous metastases, with or without oncological treatment, is a CT-scan of the thorax and the abdomen, after one and three years after the primary tumour treatment, together with the lab-result for CEA. After three years if no recurrence is found, a colonoscopy is performed and thereafter every fifth year until the age of 75 years. If the patient is treated with synchronous metastases, an individual follow-up plan, more often, is established.

Hopefully in a new and most promising era with better cancer markers and liquid biopsies, patients do not have to be followed-up with more than a scheduled blood test, and imaging will be just to find the recurrence if positive test results of the markers. [171]

Present study

Aims

In this thesis we wanted to give an overall picture of CRC and its recurrences, prediction of risk factors, and when and where to expect recurrence. How the recurrences were found and treated and evaluate survival depending on given treatment. I.e., how to follow-up patients treated for colorectal cancer with curative intent to find recurrence susceptible for treatment, and enhanced survival. This was made with the opportunity of using the data from the COLOFOL trial and scrutinizing medical files from the patients in that study.

The main objectives of this thesis were to map recurrence incidence and pattern after radically resected colorectal cancer in a modern multimodal treated setting, and to evaluate treatment, and survival depending on treatment, after recurrences. The efficacy of treatment modalities was assessed by mortality risk in multivariable analyses. This was based on the data from the 2442 patients in the COLOFOL trial, together with data from scrutinized medical files from the 471 patients detected with any recurrence within five years after the primary treatment for CRC. Four articles are published. A fifth article is planned, i.e., a ten-year follow-up, with data on survival.

Papers

Paper I

A description of the design and recruitment procedure in the COLOFOL trial, comparing demographic characteristics between randomized patients and eligible patients, which were not included in the study. Based on the 1221 eligible patients in four centers out of 23, in Denmark and Sweden. The four centers were Bispebjerg, Århus, Stockholm, and Malmö, with 684 randomized patients. The results showed a very good resemblance between randomized and non-randomized eligible patients. Hence, the conclusion was that the results reflected the intended study population and results were possible to generalize.

Paper II

To describe patterns of recurrence and risk factors, and to show the possibility of curative treatment of any recurrence within five years after surgery with curative intent for CRC, comparing high- versus low-frequency follow-up. The cumulative incidence of recurrence was similar, as well as recurrence possible to treat with curative intent, comparing the two groups. No statistically significant difference in 5-years OS was noted. Almost half of the patients with recurrence was assessed possible for treatment with curative intent, a much higher number than reported since before. Patients with metastases confined to the liver, 75% were possible to treat with curative intent, with a high absolute survival benefit. Assessments in MDB may have enhanced the high figures of treatment with curative intent for both liver and lung recurrence. Risk factors such as smoking and LNR more than 0,25 had a higher impact on recurrence than earlier reports. Further investigation is required.

Paper III

Describes recurrence patterns of colorectal liver metastases after surgery for CRC with curative intent, and survival depending on treatment and follow-up strategy of these patients. A high number of recurrences to the liver were possible to treat with curative intent and high survival rates. Of the 2442 patients in the trial, 9,6% were detected with liver recurrence, whereof 52,3% were treated with curative intent with a 58% 5-year OS. A higher number of patients in the high frequency follow-up arm were treated with increased survival rates. More intense follow-up might be in favor for high-risk patients but need further investigations.

Paper IV

This study aimed to describe pulmonary recurrences in a modern multimodal setting, within five years after surgery with curative intent for CRC, and to evaluate the influence on survival due to management and treatment of the recurrence. Of the 2442 patients in the trial, 6,8% were detected with lung metastases as first recurrence, of which 37% were treated with curative intent. The 5-year OS was 7,5% if treated with chemotherapy only, compared to 55% if surgery only, and 72% when surgery was combined with chemotherapy. More lung recurrences are susceptible to resection than shown before. Surgery was significantly better for survival rates compared to chemotherapy alone. The combination of surgery and chemotherapy might be advantageous.

Materials and Methods

Data sources

The material and data for this thesis was the patient cohort from the COLOFOL trial. Out of the 2509 patients recruited to the trial, 53 patients from Uruguay had to be excluded for practical reasons. Eleven patients had missing data, and three patients were excluded for other reasons. Leaving 2442 patients in Denmark and Sweden for this study. Out of these, 471 patients were detected with any recurrence within the follow-up period of 5 years after treatment with curative intent for CRC, stage II-III. The medical files were scrutinized and data concerning date of surgery, neoadjuvant therapy, CEA, time of recurrence and method of detection, decisions in MTB, treatment of recurrence, adjuvant therapy, any second or third recurrence, and survival among many other data was collected and put together.

Ethics and approvals

All patients had to personally sign a written consent before embarking in the COLOFOL trial, and the trial was approved by the ethical committee of Uppsala University, 2004: M-453 (Sweden) and Copenhagen and Frederiksberg Scientific committee, KF 01-194/04 (Denmark)

Results

This thesis shows that follow-up may enhance survival after colorectal cancer treatment stage II-III, due to the possibility to find asymptomatic recurrences in time for curative considerations. It confirms earlier data of recurrence rates of 20-25 %, with no difference between Denmark and Sweden. The results also show that a higher number of patients, than shown before, are possible to treat even if multiple metastases in one location and/or in concomitant organs. Combination treatment of surgery and chemotherapy seems to be favorable.

A higher risk of recurrence was noted in primary rectal cancer, 27,4%, with a significantly higher risk of pulmonary metastases, 12,5%. Corresponding numbers for colon cancer were 18,3% and 4,5%. *(Figure 5)*

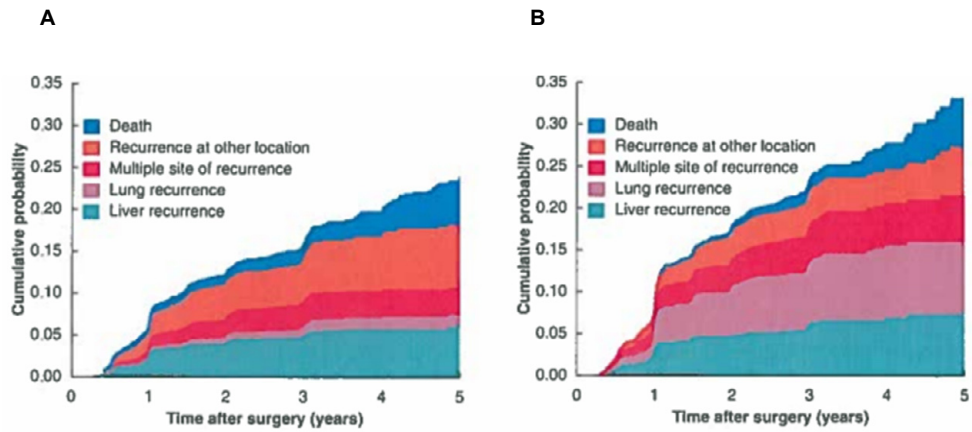

Figure 5 Cumulative incidence of recurrence after surgery for A; colonic cancer B; rectal cancer. Mortality as competing risk at both. (This figure is the corrected version from paper II)

The strongest risk factor for recurrence was found to be positive lymph node ratio more than 0,25, at the primary CRC resection. T4 cancer, cachexia at the time of surgery, diabetes mellitus and smoking were other independent risk factors for recurrence. Adjuvant chemotherapy proved to reduce the recurrence risk by 38%. An unexpected finding was that a daily intake of alcohol also reduced the risk, this however must be confirmed in further studies. A high proportion of patients with recurrence, 88,7%, were assessed in MTB, of which 53,7% were considered to be potentially curable and 47,8% were treated with curative intent. A much higher number of patients with only one location of recurrence were treated with potentially curative intent. Metastases confined to the liver had the highest treatment rate, 75,7% compared to those with metastases confined to the lungs, 59,6%. More than half of the patients that were treated for their recurrence, 54%, received pre- or postoperative chemotherapy. Of patients with recurrences detected by scheduled follow-up program, 54,5% were assessed to be possible for potentially curatively treatment, compared to 33,6% of those who were detected by non-scheduled examinations, due to symptoms or violation of the study protocol. The 5-year OS for all patients from the date of recurrence was 32%, corresponding to 58,6% if treated with curative intent, and 7,7% if palliative treatment or BSC. A significantly better survival rate for patients detected by scheduled examinations was noted, and a 7.6-fold higher survival rate if radical resection of the recurrence was performed.

The most common site of metastases was to the liver, 9,6% of all recurrences. In the cohort of patients with metastases confined to the liver, 56% of the recurrences were detected within the first year after treatment for the primary CRC. A high number of single metastases, 92,3%, were treated with curative intent. The size of the metastases mattered for the treatment consideration, where 93,8% of the patients with metastases sized 20 mm or smaller were treated with curative intent. Smaller metastases were independently associated with increased survival. The 5-year OS if recurrence to the liver was 34%. For the patients with recurrence confined to the liver, 76% were treated with curative intent, with a 5-year OS of 60%. No difference in OS was detected comparing early, within a year, or late, ≥ 13-60 months, detection of the recurrence to the liver. Patients with high frequency follow-up showed a better 5-year OS compared to the low frequency follow-up group. Probably due to early detection of small tumours in the liver with a high treatment rate. Despite this, comparing high and low frequency follow-up of the total study population, the long-term survival benefit was only 2% of patients with liver metastases. Intense follow-up might improve survival for high-risk patients, but cost-benefit must be taken into consideration and further investigations are needed.

The second most common site for metastases of CRC was to the lungs, with an incidence of 6,8%. Out of these, 54% were confined to the lungs, and 88% were detected within the scheduled follow-up time of three years. The lungs were the most frequent site for first recurrence after treatment for rectal cancer. Unlike other recurrences, T4 tumours were associated with a lower risk of lung recurrence. Generally, the 5-year OS if recurrence to the lungs was 28%. Treatment with curative intent with surgery, with or without oncologic treatment, was possible in 38% of all lung recurrences, with a 63% 5-year OS. If confined to the lungs, 66% received treatment with curative intent. Notable was that if treatment with curative intent, the combination of surgery and chemotherapy had a 5-year OS of 72% compared to 55% if only surgery was performed, and 7,5% if chemotherapy only was used. There was no increased risk of mortality following surgery if bilateral spread to the lungs. Hence, bilateral lung metastases should not be a contraindication for surgical treatment. No difference in mortality was found if early or late detection of the metastases at follow-up. Nevertheless, symptomatic detection outside the follow-up program increased the risk of mortality almost four times within 5 years after detection. This could probably be due to worse tumour biology. The combination of surgery and chemotherapy improved the 5-year OS, with a hazard ratio for mortality of 0,46 compared with surgery only. The results need further studies. *(Figure 6)*

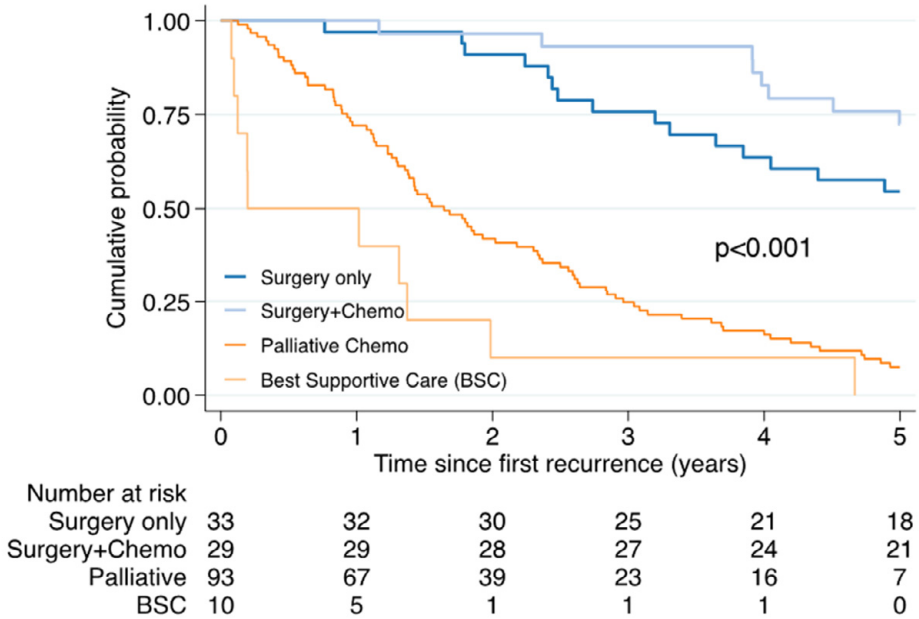

Figure 6; OS after lung metastases as first recurrence after curative resection for stage II and III, CRC, stratified on treatment. Kaplan-Meyer curves

Discussion

To treat metachronous recurrence after primary CRC is still in many aspects elusive. No follow-up or treatment algorithms are established for detection of metastases. Even if surgery and resection of the recurrence is known to have a good outcome for survival, the combination with chemotherapy is less common and studied. With a metachronous recurrence rate of 20-25% and with an increasingly younger population that are detected with CRC, prone to long time follow-ups, it is of significant importance to find better evidence how to prevent CRC, how to follow-up and how to treat recurrence after primary treatment for CRC to increase survival rates even more.

In this trial the risk of recurrence after curative treatment of primary CRC was overall a little lower compared with earlier estimations, but comparable with later studies. Probably a gratifying result of enhanced surgical techniques, improved imaging and better genetical understanding of the tumors with the ability to pinpoint oncological treatment with better neoadjuvant and adjuvant efficacy of the primary tumour. The larger number of assessments in MTB is also considered to provide a better plan and coordination of the treatment for the patients with metachronous metastases after primary treatment for CRC. [97, 172]

Notably, and not widely described, is the findings of the impact of high LNR (>0.25) for the recurrence rate. This knowledge together with the ability to have improved genetic data of the tumour can lead to better assessment in determining individually based adjuvant treatment at the MTB, in order to reduce the recurrence rate even further. The impact of smoking and other risk factors, influencing the recurrence rate, might also improve the figures in future study results.

The absolute survival benefit of all the patients who underwent treatment for recurrence confined to the liver only, 75%, is higher than reported before and should be considered at MTB. This is also true for patients surgically treated for metastases to the lungs, even if multiple and/or bilateral. The figures for therapy with a combination of surgery and chemotherapy showed higher survival rate and should be taken in considerations when treatment assessments are made. This also might be of interest in the selection criterions in the future. Somewhat of a game changer is also shown in the treatment of liver metastases with concomitant lung recurrence, for the better OS.

How to follow-up patients after potentially curative treatment for CRC, is still not totally investigated. Yet, results from the COLOFOL trial suggest that early metastases might be found and treated with curative intent if patients are frequently followed-up. The question is if these early detected metastases are truly metachronous, or synchronous but not found in the investigation of the primary CRC tumour. Another theory regarding early recurrence might be that these metastases have a more aggressive genome in their cells, and therefore early findings might not enhance survival.

Enhanced techniques for imaging could be helpful. Hopefully, artificial intelligence will help in the search for metastases, and override some of the subjective decisions in both pathology and imaging. [173, 174] New tumour markers in the blood, liquid biopsy, as ctDNA, is another interesting possibility in our search for detection of recurrences and high-risk patients. [101, 175-177] The new markers might rule out the "old" CEA, being debated and a not too accurate predictor.[178, 179]

Preventing CRC is most important, as well as how to detect it. Finding tumour markers with high accuracy, must be a priority, as well as screening programs.[42, 65, 66] A high interest should be paid to risk factors. Especially with the new tendency to affect younger patients to a higher degree, resulting in an enormous rise in healthcare costs concerning treatment and follow-up. Besides the patients suffering, the loss of labour due to treatment and rehabilitation is rendering in considerable social consequences. Due to this change in age-patterns for CRC, more attention must be taken for alarm symptoms even in younger patients**.** [67-69] As well as better information about known risk factors and prevention in the population.

Due to the enhanced survival after treatment for recurrence, and the prolonged survival even if palliative treatment, the time length of 5-years follow-up could be too short for making reasonable conclusions. I.e., some patients, even if only palliative care is given, live longer than 5 years after the primary diagnosis. Therefore, as an extended work to this thesis, a 10-year follow-up is planned, looking at overall survival.

However, long-term benefits of increased 5-year OS after early treatment of any recurrence, made possible by high frequent follow-up schedules, has not so far shown any differences in survival rate, confirming earlier summaries of the COLOFOL trial. More knowledge of tumour biology and further evolution of oncologic treatment, imaging possibilities, new tumour markers and surgical techniques might be the best aid to reduce the recurrence rate to even lower levels.

Conclusions

The results from the COLOFOL trial used in this thesis were reliable and generalizable. It is so far the largest trial concerning follow-up after treatment for colorectal cancer.

A majority of the liver recurrences were possible to treat with curative intent, with 76% of the patients treated when the metastases were confined to the liver. Resulting in a 5-year OS of 60%. More intense follow-up for selected patients might enhance survival in high-risk patients but needs further studies.

Lung recurrences, even if easier to treat when detected early, the 5-year OS was not affected by more frequent follow-up. A higher rate of lung metastases is amenable for surgical treatment, even if multiple and/or bilateral, than earlier reports. Adding chemotherapy showed a possible survival benefit but further trials are needed. Overall, symptomatic cases found outside scheduled follow-up had a worse prognosis.

The highest impact of risk factors for metachronous recurrence was LNR. Smoking had a more negative influence than earlier reports.

There was no difference in the 5-year OS between high or low follow-up frequencies after treatment of primary CRC. The best follow-up regimen is still to be found.

Strengths and limitations

The retrospective work might be a limitation although the cohort studied was from a randomized prospective trial.

The well-defined study population is a strength, as well as the size of the cohort and the follow-up time of 5 years together with the population-based registries from two nations, and the use of prospectively collected data.

Few involved study members in the work-up of every patient, and the meticulous scrutiny of medical files gives a good coherence with the data collected.

A limitation is that the cohort did not involve patients older than 75 years, and information about comorbidity was limited. Making it less generalizable in some aspects.

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Danish colleagues and co-workers, helping us with the collecting of data, making room for us when passing the strait

References

1. Sung, H., et al., *Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries.* CA Cancer J Clin, 2021. **71**(3): p. 209-249.
2. Dharwadkar, P., T.A. Zaki, and C.C. Murphy, *Colorectal Cancer in Younger Adults.* Hematol Oncol Clin North Am, 2022. **36**(3): p. 449-470.
3. Xi, Y. and P. Xu, *Global colorectal cancer burden in 2020 and projections to 2040.* Transl Oncol, 2021. **14**(10): p. 101174.
4. Petersson, J., et al., *Increasing incidence of colorectal cancer among the younger population in Sweden.* BJS Open, 2020. **4**(4): p. 645-658.
5. Regionala cancercentrum i samverkan. Nationellt kvalitetsregister för tjock - och ändtarmscancer. https://cancercentrum.se/samverkan/cancerdiagnoser/tjocktarm-och-andtarm-och-anal/tjock--och-andtarm/kvalitetsregister
6. Dekker, E., et al., *Colorectal cancer.* Lancet, 2019. **394**(10207): p. 1467-1480.
7. Engstrand, J., et al., *Colorectal cancer liver metastases - a population-based study on incidence, management and survival.* BMC Cancer, 2018. **18**(1): p. 78.
8. Riihimaki, M., et al., *Patterns of metastasis in colon and rectal cancer.* Sci Rep, 2016. **6**: p. 29765.
9. Schule, S., et al., *Long-term results and prognostic factors after resection of hepatic and pulmonary metastases of colorectal cancer.* Int J Colorectal Dis, 2013. **28**(4): p. 537-45.
10. Settmacher, U., et al., *Predictors of long-term survival in patients with colorectal liver metastases: a single center study and review of the literature.* Int J Colorectal Dis, 2011. **26**(8): p. 967-81.
11. Wille-Jorgensen, P., et al., *Effect of More vs Less Frequent Follow-up Testing on Overall and Colorectal Cancer-Specific Mortality in Patients With Stage II or III Colorectal Cancer: The COLOFOL Randomized Clinical Trial.* JAMA, 2018. **319**(20): p. 2095-2103.
12. Shussman, N. and S.D. Wexner, *Colorectal polyps and polyposis syndromes.* Gastroenterol Rep (Oxf), 2014. **2**(1): p. 1-15.
13. Witold, K., et al., *Adenomas - Genetic factors in colorectal cancer prevention.* Rep Pract Oncol Radiother, 2018. **23**(2): p. 75-83.
14. Corley, D.A., et al., *Variation of adenoma prevalence by age, sex, race, and colon location in a large population: implications for screening and quality programs.* Clin Gastroenterol Hepatol, 2013. **11**(2): p. 172-80.
15. Lepore Signorile, M., et al., *Colorectal Cancer Chemoprevention: A Dream Coming True?* Int J Mol Sci, 2023. **24**(8).

16. Asadzadeh Aghdaei, H., et al., *Polyp detection rate and pathological features in patients undergoing a comprehensive colonoscopy screening.* World J Gastrointest Pathophysiol, 2017. **8**(1): p. 3-10.
17. Kroemer, G. and J. Pouyssegur, *Tumor cell metabolism: cancer's Achilles' heel.* Cancer Cell, 2008. **13**(6): p. 472-82.
18. Zheng, X., et al., *Single-cell transcriptomic profiling unravels the adenoma-initiation role of protein tyrosine kinases during colorectal tumorigenesis.* Signal Transduct Target Ther, 2022. **7**(1): p. 60.
19. Smit, W.L., et al., *Driver mutations of the adenoma-carcinoma sequence govern the intestinal epithelial global translational capacity.* Proc Natl Acad Sci U S A, 2020. **117**(41): p. 25560-25570.
20. Bonnington, S.N. and M.D. Rutter, *Surveillance of colonic polyps: Are we getting it right?* World J Gastroenterol, 2016. **22**(6): p. 1925-34.
21. Kwong, L.N. and W.F. Dove, *APC and its modifiers in colon cancer.* Adv Exp Med Biol, 2009. **656**: p. 85-106.
22. Hankey, W., W.L. Frankel, and J. Groden, *Functions of the APC tumor suppressor protein dependent and independent of canonical WNT signaling: implications for therapeutic targeting.* Cancer Metastasis Rev, 2018. **37**(1): p. 159-172.
23. Ahmad, R., et al., *Emerging trends in colorectal cancer: Dysregulated signaling pathways (Review).* Int J Mol Med, 2021. **47**(3).
24. Sabapathy, K. and D.P. Lane, *Understanding p53 functions through p53 antibodies.* J Mol Cell Biol, 2019. **11**(4): p. 317-329.
25. Cheok, C.F. and D.P. Lane, *Exploiting the p53 Pathway for Therapy.* Cold Spring Harb Perspect Med, 2017. **7**(3).
26. Fayazfar, S., et al., *Identification of key candidate genes and pathways associated with colorectal aberrant crypt foci-to-adenoma-to-carcinoma progression.* Gastroenterol Hepatol Bed Bench, 2021. **14**(Suppl1): p. S41-S50.
27. Dariya, B., et al., *Colorectal Cancer Biology, Diagnosis, and Therapeutic Approaches.* Crit Rev Oncog, 2020. **25**(2): p. 71-94.
28. Markowitz, S.D. and M.M. Bertagnolli, *Molecular origins of cancer: Molecular basis of colorectal cancer.* N Engl J Med, 2009. **361**(25): p. 2449-60.
29. Sjoblom, T., et al., *The consensus coding sequences of human breast and colorectal cancers.* Science, 2006. **314**(5797): p. 268-74.
30. Wood, L.D., et al., *The genomic landscapes of human breast and colorectal cancers.* Science, 2007. **318**(5853): p. 1108-13.
31. Li, K., et al., *Microsatellite instability: a review of what the oncologist should know.* Cancer Cell Int, 2020. **20**: p. 16.
32. De' Angelis, G.L., et al., *Microsatellite instability in colorectal cancer.* Acta Biomed, 2018. **89**(9-S): p. 97-101.
33. Gelsomino, F., et al., *The evolving role of microsatellite instability in colorectal cancer: A review.* Cancer Treat Rev, 2016. **51**: p. 19-26.
34. Bakhoum, S.F. and L.C. Cantley, *The Multifaceted Role of Chromosomal Instability in Cancer and Its Microenvironment.* Cell, 2018. **174**(6): p. 1347-1360.

35. Drews, R.M., et al., *A pan-cancer compendium of chromosomal instability.* Nature, 2022. **606**(7916): p. 976-983.
36. Nguyen, B., et al., *Genomic characterization of metastatic patterns from prospective clinical sequencing of 25,000 patients.* Cell, 2022. **185**(3): p. 563-575 e11.
37. Zygulska, A.L. and P. Pierzchalski, *Novel Diagnostic Biomarkers in Colorectal Cancer.* Int J Mol Sci, 2022. **23**(2).
38. Kuipers, E.J., et al., *Colorectal cancer.* Nat Rev Dis Primers, 2015. **1**: p. 15065.
39. Regionala cancercentrum i samverkan. Kunskapsbanken. Bakgrund och orsaker. https://kunskapsbanken.cancercentrum.se/diagnoser/tjock-och-andtarmscancer/vardprogram/bakgrund-och-orsaker
40. Wong, M.C.S., et al., *Differences in Incidence and Mortality Trends of Colorectal Cancer Worldwide Based on Sex, Age, and Anatomic Location.* Clin Gastroenterol Hepatol, 2021. **19**(5): p. 955-966 e61.
41. Eng, C., et al., *A comprehensive framework for early-onset colorectal cancer research.* Lancet Oncol, 2022. **23**(3): p. e116-e128.
42. Burnett-Hartman, A.N., et al., *An Update on the Epidemiology, Molecular Characterization, Diagnosis, and Screening Strategies for Early-Onset Colorectal Cancer.* Gastroenterology, 2021. **160**(4): p. 1041-1049.
43. Araghi, M., et al., *Changes in colorectal cancer incidence in seven high-income countries: a population-based study.* Lancet Gastroenterol Hepatol, 2019. **4**(7): p. 511-518.
44. Simon, K., *Colorectal cancer development and advances in screening.* Clin Interv Aging, 2016. **11**: p. 967-76.
45. Abancens, M., et al., *Sexual Dimorphism in Colon Cancer.* Front Oncol, 2020. **10**: p. 607909.
46. Sninsky, J.A., et al., *Risk Factors for Colorectal Polyps and Cancer.* Gastrointest Endosc Clin N Am, 2022. **32**(2): p. 195-213.
47. Song, M., W.S. Garrett, and A.T. Chan, *Nutrients, foods, and colorectal cancer prevention.* Gastroenterology, 2015. **148**(6): p. 1244-60 e16.
48. Bardou, M., A.N. Barkun, and M. Martel, *Obesity and colorectal cancer.* Gut, 2013. **62**(6): p. 933-47.
49. Battaglia Richi, E., et al., *Health Risks Associated with Meat Consumption: A Review of Epidemiological Studies.* Int J Vitam Nutr Res, 2015. **85**(1-2): p. 70-8.
50. Liang, P.S., T.Y. Chen, and E. Giovannucci, *Cigarette smoking and colorectal cancer incidence and mortality: systematic review and meta-analysis.* Int J Cancer, 2009. **124**(10): p. 2406-15.
51. Baidoun, F., et al., *Colorectal Cancer Epidemiology: Recent Trends and Impact on Outcomes.* Curr Drug Targets, 2021. **22**(9): p. 998-1009.
52. McDonald, J.T., M. Farnworth, and Z. Liu, *Cancer and the healthy immigrant effect: a statistical analysis of cancer diagnosis using a linked Census-cancer registry administrative database.* BMC Public Health, 2017. **17**(1): p. 296.
53. McCoy, H.V., P.N. Ritchey, and C.B. McCoy, *Effects of migration on cancer incidence and resources for prevention and treatment in Florida.* Public Health Rep, 1992. **107**(4): p. 389-96.

54. Vineis, P. and C.P. Wild, *Global cancer patterns: causes and prevention.* Lancet, 2014. **383**(9916): p. 549-57.
55. Yu, G.H., et al., *Diabetes and Colorectal Cancer Risk: Clinical and Therapeutic Implications.* J Diabetes Res, 2022. **2022**: p. 1747326.
56. Lega, I.C. and L.L. Lipscombe, *Review: Diabetes, Obesity, and Cancer-Pathophysiology and Clinical Implications.* Endocr Rev, 2020. **41**(1).
57. Nebbia, M., N.A. Yassin, and A. Spinelli, *Colorectal Cancer in Inflammatory Bowel Disease.* Clin Colon Rectal Surg, 2020. **33**(5): p. 305-317.
58. Olen, O., et al., *Colorectal cancer in ulcerative colitis: a Scandinavian population-based cohort study.* Lancet, 2020. **395**(10218): p. 123-131.
59. Ocvirk, S., et al., *Fiber, Fat, and Colorectal Cancer: New Insight into Modifiable Dietary Risk Factors.* Curr Gastroenterol Rep, 2019. **21**(11): p. 62.
60. Hashemi Goradel, N., et al., *Fusobacterium nucleatum and colorectal cancer: A mechanistic overview.* J Cell Physiol, 2019. **234**(3): p. 2337-2344.
61. Gao, R., et al., *Gut microbiota and colorectal cancer.* Eur J Clin Microbiol Infect Dis, 2017. **36**(5): p. 757-769.
62. Marmol, I., et al., *Colorectal Carcinoma: A General Overview and Future Perspectives in Colorectal Cancer.* Int J Mol Sci, 2017. **18**(1).
63. Janney, A., F. Powrie, and E.H. Mann, *Host-microbiota maladaptation in colorectal cancer.* Nature, 2020. **585**(7826): p. 509-517.
64. O'Keefe, S.J., *Diet, microorganisms and their metabolites, and colon cancer.* Nat Rev Gastroenterol Hepatol, 2016. **13**(12): p. 691-706.
65. Moore, J.S. and T.H. Aulet, *Colorectal Cancer Screening.* Surg Clin North Am, 2017. **97**(3): p. 487-502.
66. Das, V., J. Kalita, and M. Pal, *Predictive and prognostic biomarkers in colorectal cancer: A systematic review of recent advances and challenges.* Biomed Pharmacother, 2017. **87**: p. 8-19.
67. Dairi, O., J.C. Anderson, and L.F. Butterly, *Why is colorectal cancer increasing in younger age groups in the United States?* Expert Rev Gastroenterol Hepatol, 2021. **15**(6): p. 623-632.
68. Patel, S.G., et al., *The rising tide of early-onset colorectal cancer: a comprehensive review of epidemiology, clinical features, biology, risk factors, prevention, and early detection.* Lancet Gastroenterol Hepatol, 2022. **7**(3): p. 262-274.
69. Mauri, G., et al., *Early-onset colorectal cancer in young individuals.* Mol Oncol, 2019. **13**(2): p. 109-131.
70. Hampel, H., et al., *Hereditary Colorectal Cancer.* Hematol Oncol Clin North Am, 2022. **36**(3): p. 429-447.
71. Hryhorowicz, S., et al., *Strong Hereditary Predispositions to Colorectal Cancer.* Genes (Basel), 2022. **13**(12).
72. Song, M., et al., *Risk of colorectal cancer in first degree relatives of patients with colorectal polyps: nationwide case-control study in Sweden.* BMJ, 2021. **373**: p. n877.

73. Kanth, P., et al., *Hereditary Colorectal Polyposis and Cancer Syndromes: A Primer on Diagnosis and Management.* Am J Gastroenterol, 2017. **112**(10): p. 1509-1525.
74. Heinimann, K., *[Hereditary Colorectal Cancer: Clinics, Diagnostics and Management].* Ther Umsch, 2018. **75**(10): p. 601-606.
75. Grover, S. and S. Syngal, *Genetic testing in gastroenterology: Lynch syndrome.* Best Pract Res Clin Gastroenterol, 2009. **23**(2): p. 185-96.
76. Ma, H., et al., *Pathology and genetics of hereditary colorectal cancer.* Pathology, 2018. **50**(1): p. 49-59.
77. Diaz-Tasende, J., *Colorectal cancer screening and survival.* Rev Esp Enferm Dig, 2018. **110**(11): p. 681-683.
78. Dekker, E. and D.K. Rex, *Advances in CRC Prevention: Screening and Surveillance.* Gastroenterology, 2018. **154**(7): p. 1970-1984.
79. Bretthauer, M., et al., *Effect of Colonoscopy Screening on Risks of Colorectal Cancer and Related Death.* N Engl J Med, 2022. **387**(17): p. 1547-1556.
80. Betesh, A.L. and F.H. Schnoll-Sussman, *Colorectal Cancer Screening in the Elderly.* Clin Geriatr Med, 2021. **37**(1): p. 173-183.
81. Kaminski, M.F., et al., *Optimizing the Quality of Colorectal Cancer Screening Worldwide.* Gastroenterology, 2020. **158**(2): p. 404-417.
82. Benard, F., et al., *Systematic review of colorectal cancer screening guidelines for average-risk adults: Summarizing the current global recommendations.* World J Gastroenterol, 2018. **24**(1): p. 124-138.
83. Gupta, S., *Screening for Colorectal Cancer.* Hematol Oncol Clin North Am, 2022. **36**(3): p. 393-414.
84. Holtedahl, K., et al., *Symptoms and signs of colorectal cancer, with differences between proximal and distal colon cancer: a prospective cohort study of diagnostic accuracy in primary care.* BMC Fam Pract, 2021. **22**(1): p. 148.
85. Adelstein, B.A., et al., *Most bowel cancer symptoms do not indicate colorectal cancer and polyps: a systematic review.* BMC Gastroenterol, 2011. **11**: p. 65.
86. Garborg, K., *Colorectal Cancer Screening.* Surg Clin North Am, 2015. **95**(5): p. 979-89.
87. Boeding, J.R.E., et al., *Ileus caused by obstructing colorectal cancer-impact on long-term survival.* Int J Colorectal Dis, 2018. **33**(10): p. 1393-1400.
88. Goiffon, R.J., A. O'Shea, and M.G. Harisinghani, *Advances in radiological staging of colorectal cancer.* Clin Radiol, 2021. **76**(12): p. 879-888.
89. Kijima, S., et al., *Preoperative evaluation of colorectal cancer using CT colonography, MRI, and PET/CT.* World J Gastroenterol, 2014. **20**(45): p. 16964-75.
90. Nasseri, Y. and S.J. Langenfeld, *Imaging for Colorectal Cancer.* Surg Clin North Am, 2017. **97**(3): p. 503-513.
91. Lewi, H., et al., *Pre-operative carcino-embryonic antigen and survival in patients with colorectal cancer.* Br J Surg, 1984. **71**(3): p. 206-8.
92. Wang, Y.R., J.X. Yan, and L.N. Wang, *The diagnostic value of serum carcino-embryonic antigen, alpha fetoprotein and carbohydrate antigen 19-9 for colorectal cancer.* J Cancer Res Ther, 2014. **10 Suppl**: p. 307-9.

93. Fernandes, M.C., M.J. Gollub, and G. Brown, *The importance of MRI for rectal cancer evaluation.* Surg Oncol, 2022. **43**: p. 101739.
94. Arya, S., et al., *Imaging and Management of Rectal Cancer.* Semin Ultrasound CT MR, 2020. **41**(2): p. 183-206.
95. Roncucci, L. and F. Mariani, *Prevention of colorectal cancer: How many tools do we have in our basket?* Eur J Intern Med, 2015. **26**(10): p. 752-6.
96. Mahmoud, N.N., *Colorectal Cancer: Preoperative Evaluation and Staging.* Surg Oncol Clin N Am, 2022. **31**(2): p. 127-141.
97. van de Velde, C.J., et al., *EURECCA colorectal: multidisciplinary mission statement on better care for patients with colon and rectal cancer in Europe.* Eur J Cancer, 2013. **49**(13): p. 2784-90.
98. Weiser, M.R., *AJCC 8th Edition: Colorectal Cancer.* Ann Surg Oncol, 2018. **25**(6): p. 1454-1455.
99. Chen, K., et al., *Pathological Features and Prognostication in Colorectal Cancer.* Curr Oncol, 2021. **28**(6): p. 5356-5383.
100. Vasseur, A., et al., *Clinical utility of circulating tumor cells: an update.* Mol Oncol, 2021. **15**(6): p. 1647-1666.
101. Dasari, A., et al., *ctDNA applications and integration in colorectal cancer: an NCI Colon and Rectal-Anal Task Forces whitepaper.* Nat Rev Clin Oncol, 2020. **17**(12): p. 757-770.
102. Zhou, H., et al., *Liquid biopsy at the frontier of detection, prognosis and progression monitoring in colorectal cancer.* Mol Cancer, 2022. **21**(1): p. 86.
103. Seeberg, L.T., et al., *Circulating tumor cells in patients with colorectal liver metastasis predict impaired survival.* Ann Surg, 2015. **261**(1): p. 164-71.
104. Införande av allmän tarmcancerscreening. Slutrapport och rekommendation. Version 1.0. Regionala cancercentrum i samverkan 2018. https://www.cancercentum.se/glabalassets/vara-uppdrag/prevention-tidig-upptackt/tarmcancerscreeenig/slutrapport_inofrnade_tarmcancerscrrening-18-02-28.pdf.
105. Screening för tjock- och ändtarmscancer. Rekommendation och bedömningsunderlag. https://www.socialstyrelsen.se/globalassets/sharepoint-dokument/artikelkatalog/nationnella-screeningprogram/2014-2-31.pdf
106. Lech, G., et al., *Colorectal cancer tumour markers and biomarkers: Recent therapeutic advances.* World J Gastroenterol, 2016. **22**(5): p. 1745-55.
107. Rasmussen, S., et al., *Predictive values of colorectal cancer alarm symptoms in the general population: a nationwide cohort study.* Br J Cancer, 2019. **120**(6): p. 595-600.
108. Provenzale, D., et al., *NCCN Guidelines Insights: Colorectal Cancer Screening, Version 2.2020.* J Natl Compr Canc Netw, 2020. **18**(10): p. 1312-1320.
109. Burt, R.W., et al., *Colorectal cancer screening.* J Natl Compr Canc Netw, 2013. **11**(12): p. 1538-75.
110. Nationellt vårdprogram tjock- och ändtarmscancer. https://kunskapsbanken.cancercentrum.se/diagnoser/tjock-och-andtarmscancer/vardprogram

111. Keller, D.S., et al., *The multidisciplinary management of rectal cancer.* Nat Rev Gastroenterol Hepatol, 2020. **17**(7): p. 414-429.
112. Palmer, G., et al., *Preoperative tumour staging with multidisciplinary team assessment improves the outcome in locally advanced primary rectal cancer.* Colorectal Dis, 2011. **13**(12): p. 1361-9.
113. Link, K.H., et al., *Patient-centered developments in colon- and rectal cancer with a multidisciplinary international team: From translational research to national guidelines.* World J Gastrointest Surg, 2021. **13**(12): p. 1597-1614.
114. Stewart, C.L., et al., *Cytoreduction for colorectal metastases: liver, lung, peritoneum, lymph nodes, bone, brain. When does it palliate, prolong survival, and potentially cure?* Curr Probl Surg, 2018. **55**(9): p. 330-379.
115. Quezada-Diaz, F.F. and J.J. Smith, *Neoadjuvant Therapy for Rectal Cancer.* Surg Oncol Clin N Am, 2022. **31**(2): p. 279-291.
116. Erlandsson, J., et al., *Tumour regression after radiotherapy for rectal cancer - Results from the randomised Stockholm III trial.* Radiother Oncol, 2019. **135**: p. 178-186.
117. Morton, D., et al., *Preoperative Chemotherapy for Operable Colon Cancer: Mature Results of an International Randomized Controlled Trial.* J Clin Oncol, 2023. **41**(8): p. 1541-1552.
118. Castro-Giner, F. and N. Aceto, *Tracking cancer progression: from circulating tumor cells to metastasis.* Genome Med, 2020. **12**(1): p. 31.
119. Paoletti, C. and D.F. Hayes, *Circulating Tumor Cells.* Adv Exp Med Biol, 2016. **882**: p. 235-58.
120. Lin, D., et al., *Circulating tumor cells: biology and clinical significance.* Signal Transduct Target Ther, 2021. **6**(1): p. 404.
121. Tan, Y. and H. Wu, *The significant prognostic value of circulating tumor cells in colorectal cancer: A systematic review and meta-analysis.* Curr Probl Cancer, 2018. **42**(1): p. 95-106.
122. Wu, C., *Systemic Therapy for Colon Cancer.* Surg Oncol Clin N Am, 2018. **27**(2): p. 235-242.
123. Auclin, E., et al., *Subgroups and prognostication in stage III colon cancer: future perspectives for adjuvant therapy.* Ann Oncol, 2017. **28**(5): p. 958-968.
124. Hegewisch-Becker, S., et al., *[Palliative treatment for colorectal cancer].* Onkologie, 2009. **32 Suppl 2**: p. 13-6.
125. Gosavi, R., et al., *Neoadjuvant chemotherapy in locally advanced colon cancer: a systematic review and meta-analysis.* Int J Colorectal Dis, 2021. **36**(10): p. 2063-2070.
126. Liu, F.Q. and S.J. Cai, *[Adjuvant and perioperative neoadjuvant therapy for colorectal cancer].* Zhonghua Wei Chang Wai Ke Za Zhi, 2019. **22**(4): p. 315-320.
127. Dos Santos, L.V., et al., *Timing of adjuvant chemotherapy in colorectal cancer.* Colorectal Dis, 2016. **18**(9): p. 871-6.
128. Kishore, C. and P. Bhadra, *Current advancements and future perspectives of immunotherapy in colorectal cancer research.* Eur J Pharmacol, 2021. **893**: p. 173819.

129. Li, Q.L., et al., *Genome-wide profiling in colorectal cancer identifies PHF19 and TBC1D16 as oncogenic super enhancers.* Nat Commun, 2021. **12**(1): p. 6407.
130. Zhang, X., et al., *Neoadjuvant Immunotherapy for MSI-H/dMMR Locally Advanced Colorectal Cancer: New Strategies and Unveiled Opportunities.* Front Immunol, 2022. **13**: p. 795972.
131. Vailati, B.B., et al., *Nonoperative Management of Rectal Cancer: The Watch and Wait Strategy.* Surg Oncol Clin N Am, 2022. **31**(2): p. 171-182.
132. Lopez-Trabada, D., et al., *[Medical oncological treatment of colorectal cancer in the elderly].* Soins Gerontol, 2022. **27**(154): p. 15-19.
133. Pretzsch, E., et al., *Mechanisms of Metastasis in Colorectal Cancer and Metastatic Organotropism: Hematogenous versus Peritoneal Spread.* J Oncol, 2019. **2019**: p. 7407190.
134. Langley, R.R. and I.J. Fidler, *The seed and soil hypothesis revisited--the role of tumor-stroma interactions in metastasis to different organs.* Int J Cancer, 2011. **128**(11): p. 2527-35.
135. Hu, Z., et al., *Quantitative evidence for early metastatic seeding in colorectal cancer.* Nat Genet, 2019. **51**(7): p. 1113-1122.
136. Sveen, A., S. Kopetz, and R.A. Lothe, *Biomarker-guided therapy for colorectal cancer: strength in complexity.* Nat Rev Clin Oncol, 2020. **17**(1): p. 11-32.
137. Akgul, O., et al., *Role of surgery in colorectal cancer liver metastases.* World J Gastroenterol, 2014. **20**(20): p. 6113-22.
138. Sasaki, K., et al., *The Tumor Burden Score: A New "Metro-ticket" Prognostic Tool For Colorectal Liver Metastases Based on Tumor Size and Number of Tumors.* Ann Surg, 2018. **267**(1): p. 132-141.
139. Zhang, W., B. Zhang, and X.P. Chen, *Adjuvant treatment strategy after curative resection for hepatocellular carcinoma.* Front Med, 2021. **15**(2): p. 155-169.
140. Lehmann, K., et al., *Chemotherapy before liver resection of colorectal metastases: friend or foe?* Ann Surg, 2012. **255**(2): p. 237-47.
141. Martin, J., et al., *Colorectal liver metastases: Current management and future perspectives.* World J Clin Oncol, 2020. **11**(10): p. 761-808.
142. Birrer, D.L., et al., *Multimodal treatment strategies for colorectal liver metastases.* Swiss Med Wkly, 2021. **151**: p. w20390.
143. Prasanna, T., et al., *The survival outcome of patients with metastatic colorectal cancer based on the site of metastases and the impact of molecular markers and site of primary cancer on metastatic pattern.* Acta Oncol, 2018. **57**(11): p. 1438-1444.
144. Treasure, T., et al., *Pulmonary metastasectomy: what is the practice and where is the evidence for effectiveness?* Thorax, 2014. **69**(10): p. 946-9.
145. Fiorentino, F. and T. Treasure, *Pulmonary metastasectomy: a call for better data collection, presentation and analysis.* Future Oncol, 2015. **11**(2 Suppl): p. 19-23.
146. Li, J., et al., *Expert consensus on multidisciplinary therapy of colorectal cancer with lung metastases (2019 edition).* J Hematol Oncol, 2019. **12**(1): p. 16.
147. Pfannschmidt, J., H. Dienemann, and H. Hoffmann, *Surgical resection of pulmonary metastases from colorectal cancer: a systematic review of published series.* Ann Thorac Surg, 2007. **84**(1): p. 324-38.

148. Klempner, S.J. and D.P. Ryan, *HIPEC for colorectal peritoneal metastases.* Lancet Oncol, 2021. **22**(2): p. 162-164.
149. Molla, M., et al., *Limited Liver or Lung Colorectal Cancer Metastases. Systemic Treatment, Surgery, Ablation or SBRT.* J Clin Med, 2021. **10**(10).
150. Li, N., et al., *Incidence, mortality, survival, risk factor and screening of colorectal cancer: A comparison among China, Europe, and northern America.* Cancer Lett, 2021. **522**: p. 255-268.
151. Regionalt cancercentrum. htpps://cancercentrum.se/syd/cancerdiagnoser/tjocktarm-andtarm-och-anal/tjock--och-andtarm/statistik
152. Vatandoust, S., T.J. Price, and C.S. Karapetis, *Colorectal cancer: Metastases to a single organ.* World J Gastroenterol, 2015. **21**(41): p. 11767-76.
153. Jeffery, M., B.E. Hickey, and P.N. Hider, *Follow-up strategies for patients treated for non-metastatic colorectal cancer.* Cochrane Database Syst Rev, 2019. **9**(9): p. CD002200.
154. Qaderi, S.M., et al., *Follow-up practice and healthcare utilisation of colorectal cancer survivors.* Eur J Cancer Care (Engl), 2021. **30**(5): p. e13472.
155. Chen, L.B., et al., *(18)F-DG PET/CT in detection of recurrence and metastasis of colorectal cancer.* World J Gastroenterol, 2007. **13**(37): p. 5025-9.
156. Wille-Jorgensen, P., et al., *An interim analysis of recruitment to the COLOFOL trial.* Colorectal Dis, 2009. **11**(7): p. 756-8.
157. Egenvall, M., et al., *No benefit of more intense follow-up after surgery for colorectal cancer in the risk group with elevated CEA levels - An analysis within the COLOFOL randomized clinical trial.* Eur J Surg Oncol, 2021. **47**(8): p. 2053-2059.
158. Bastiaenen, V.P., et al., *Consensus and controversies regarding follow-up after treatment with curative intent of nonmetastatic colorectal cancer: a synopsis of guidelines used in countries represented in the European Society of Coloproctology.* Colorectal Dis, 2019. **21**(4): p. 392-416.
159. Jeffery, M., B.E. Hickey, and P.N. Hider, *Follow-up strategies for patients treated for non-metastatic colorectal cancer.* Cochrane Database Syst Rev, 2007(1): p. CD002200.
160. Renehan, A.G., et al., *Impact on survival of intensive follow up after curative resection for colorectal cancer: systematic review and meta-analysis of randomised trials.* BMJ, 2002. **324**(7341): p. 813.
161. Jeffery, G.M., B.E. Hickey, and P. Hider, *Follow-up strategies for patients treated for non-metastatic colorectal cancer.* Cochrane Database Syst Rev, 2002(1): p. CD002200.
162. Primrose, J.N., et al., *Effect of 3 to 5 years of scheduled CEA and CT follow-up to detect recurrence of colorectal cancer: the FACS randomized clinical trial.* JAMA, 2014. **311**(3): p. 263-70.
163. Grossmann, E.M., et al., *Follow-up of colorectal cancer patients after resection with curative intent-the GILDA trial.* Surg Oncol, 2004. **13**(2-3): p. 119-24.

164. Treasure, T., et al., *The CEA Second-Look Trial: a randomised controlled trial of carcinoembryonic antigen prompted reoperation for recurrent colorectal cancer.* BMJ Open, 2014. **4**(5): p. e004385.
165. Tjandra, J.J. and M.K. Chan, *Follow-up after curative resection of colorectal cancer: a meta-analysis.* Dis Colon Rectum, 2007. **50**(11): p. 1783-99.
166. Tampakis, A., et al., *MAP17 Expression in Colorectal Cancer Is a Prognostic Factor for Disease Recurrence and Dismal Prognosis Already in Early Stage Disease.* Oncology, 2021. **99**(7): p. 471-482.
167. Akhtar, M., et al., *Paget's "Seed and Soil" Theory of Cancer Metastasis: An Idea Whose Time has Come.* Adv Anat Pathol, 2019. **26**(1): p. 69-74.
168. Hosny, A., et al., *Artificial intelligence in radiology.* Nat Rev Cancer, 2018. **18**(8): p. 500-510.
169. Niazi, M.K.K., A.V. Parwani, and M.N. Gurcan, *Digital pathology and artificial intelligence.* Lancet Oncol, 2019. **20**(5): p. e253-e261.
170. Hansdotter Andersson, P., et al., *The COLOFOL trial: study design and comparison of the study population with the source cancer population.* Clin Epidemiol, 2016. **8**: p. 15-21.
171. Marcuello, M., et al., *Circulating biomarkers for early detection and clinical management of colorectal cancer.* Mol Aspects Med, 2019. **69**: p. 107-122.
172. Valentini, V., et al., *Multidisciplinary Rectal Cancer Management: 2nd European Rectal Cancer Consensus Conference (EURECA-CC2).* Radiother Oncol, 2009. **92**(2): p. 148-63.
173. Udo, R., et al., *Predicting the prognosis of lower rectal cancer using preoperative magnetic resonance imaging with artificial intelligence.* Tech Coloproctol, 2023.
174. Wong, C., et al., *MRI-Based Artificial Intelligence in Rectal Cancer.* J Magn Reson Imaging, 2023. **57**(1): p. 45-56.
175. Huang, K., et al., *Circulating tumor DNA sequencing for colorectal cancers: A comparative analysis of colon cancer and rectal cancer data.* Cancer Biomark, 2019. **26**(3): p. 313-322.
176. Benesova, L., et al., *Significance of postoperative follow-up of patients with metastatic colorectal cancer using circulating tumor DNA.* World J Gastroenterol, 2019. **25**(48): p. 6939-6948.
177. Benhaim, L., et al., *Circulating tumor DNA is a prognostic marker of tumor recurrence in stage II and III colorectal cancer: multicentric, prospective cohort study (ALGECOLS).* Eur J Cancer, 2021. **159**: p. 24-33.
178. Lakemeyer, L., et al., *Diagnostic and Prognostic Value of CEA and CA19-9 in Colorectal Cancer.* Diseases, 2021. **9**(1).
179. Siskova, A., et al., *Colorectal Adenomas-Genetics and Searching for New Molecular Screening Biomarkers.* Int J Mol Sci, 2020. **21**(9).

Paper I

Clinical Epidemiology

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ORIGINAL RESEARCH

The COLOFOL trial: study design and comparison of the study population with the source cancer population

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Introduction: The COLOFOL trial, a prospective randomized multicenter trial comparing two follow-up regimes after curative surgical treatment for colorectal cancer, focuses on detection of asymptomatic recurrences. This paper aims to describe the design and recruitment procedure in the COLOFOL trial, comparing demographic characteristics between randomized patients and eligible patients not included in the study.

Materials and methods: COLOFOL was designed as a pragmatic trial with wide inclusion criteria and few exclusion criteria, in order to obtain a sample reflecting the general patient population. To be eligible, patients had to be 75 years or younger and curatively resected for stage II or III colorectal cancer. Exclusion criteria were hereditary colorectal cancer, no signed consent, other malignancy, and life expectancy less than 2 years due to concomitant disease. In four of the 24 participating centers, we scrutinized hospital inpatient data to identify all colorectal cancer patients who underwent surgery, in order to ascertain all eligible patients who were not included in the study and to compare them with enrolled patients.

Results: Of a total of 4,445 eligible patients, 2,509 patients were randomized (56.4% inclusion rate). A total of 1,221 eligible patients were identified in the scrutinized hospitals, of which 684 (56%) were randomized. No difference in age or sex distribution was observed between randomized and nonrandomized eligible patients. However, a difference was noted in tumor location and stage distribution, with 5.6% more patients in the randomized group having colon cancer and 6.7% more patients having stage II disease.

Conclusion: Patients in the two study arms were not only demographically similar, but also similar to nonincluded eligible patients, apart from stage and localization. The analyses will be stratified by these variables. Taken together, we conclude that our trial results will be robust and possible to extrapolate to the target population.

Keywords: trial design, source population, colorectal cancer, follow-up

Introduction

Follow-up after colorectal cancer surgery has three purposes: patient support, monitoring, and detection of asymptomatic recurrences to allow treatment with curative intent. However, it is not clear whether scheduled examinations and visits to the outpatient clinic have any survival benefit.[1] Existing trials have been too small to be able to detect a difference between arms. The majority were also conducted in the era before modern imaging techniques and/or before availability of modern multimodal treatment of metastatic disease.[2–8]

Meta-analyses of six randomized trials have indicated that more intense follow-up programs have a survival benefit.[9,10] However, the heterogeneity of the trials calls their results into question. For example, the control group in one trial involved more

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examinations than the exposed group in another trial.[5,6] Two of these trials showed a positive effect on survival. However, in one of them, this was explained by allocation of more patients with stage III disease to the control group.[4] In the other trial, all re-resections were performed on local recurrences, which were very frequent (19% and 25%, respectively),[8] indicating suboptimal primary treatment.

Thus, there is a strong need for a large randomized trial to evaluate different follow-up regimens for patients treated for colorectal cancer. The COLOFOL trial, launched in 2005, is a pragmatic trial focusing on detection of potentially curable recurrences. It evaluates two follow-up schedules in patients who underwent surgery for colorectal cancer with curative intent (http://www.colofol.com). Primary outcomes are overall survival and disease-free survival. By December 2010, target enrollment was reached, and recruitment was stopped. The trial is registered in the Clinical Trials Register (NCT00225641).

A randomized controlled trial represents the most unbiased method to compare different treatments between groups, because it prevents unmeasured and unknown confounding. However, trial inclusion procedures create the risk that the study population does not reflect the target population, due to too narrow inclusion criteria and/or nonrandom exclusion of eligible nonparticipants.[11] This leads to subsequent difficulty in extrapolating the results to the general patient population and might explain why trial-based treatment effects cannot always be reproduced in clinical series or registry-based studies.[12–15] A key factor in minimizing this risk is to ensure that the study population resembles the true population at risk. In this context, we aim, in this paper, to describe the design and recruitment procedure in the COLOFOL trial, comparing demographic characteristics in randomized patients and in eligible nonparticipants.

Materials and methods

This study targeted patients who underwent radical surgery for stage II or III sporadic colorectal cancer. To benefit from detection of a recurrence, a patient has to be fit enough to undergo chemotherapy and surgery for metastatic disease. Hence, the trial was restricted to patients ≤75 years of age with a life expectancy exceeding 2 years based on concomitant disease. Complete inclusion and exclusion criteria are provided in Table 1. All patients had to personally sign a written consent before embarking in the study and the trial was approved by the ethical committee of Uppsala University, 2004: M-453 (Sweden) and Copenhagen and Frederikberg Scientific committee, KF 01-194/04 (Denmark).

Requirements for participating as a study center were to recruit at least 30% of eligible patients and to recruit a total of 25 patients annually. Strict adherence to both requirements proved too difficult for smaller centres and it was later decided to implement a minimum inclusion of 20 patients as cut off to ensure quality. Four centers did not meet these targets and were dropped, leaving 24 recruitment centers in Denmark, Sweden, and Uruguay.

Table 1 Inclusion and exclusion criteria in the COLOFOL trial

Inclusion criteria	Exclusion criteria
R0 resection	Lynch syndrome or FAP
Age ≤75 years	Local excision (eg, TEM)
Written informed consent	Life expectancy <2 years
Clean colon	Inability or refusal to perform informed consent
Tumor stage II–III	Inability to comply with the control or intense follow-up program
Ability to perform informed consent	Participation in other clinical trials interfering with the COLOFOL study

Abbreviations: FAP, familial adenomatous polyposis; TEM, transanal endoscopic microsurgery.

Patients were randomized to either high-frequency or low-frequency follow-up. Both schedules included the same examinations at every follow-up appointment, ie, clinical examination, carcinoembryonic antigen (CEA) test, and computed tomography scan of the liver and thorax. A colonoscopy was required in the perioperative period to verify a clean colon, while further endoscopies were optional. Follow-up occurred at 12 and 36 months postoperatively in the low-frequency arm and at 6, 12, 18, 24, and 36 months in the high-frequency arm. Individualized cut-off levels for CEA were used in both arms, based on serum measurements 4 weeks postoperatively. Randomization was computerized in blocks, stratified by center and cancer stage. The size of the blocks was variable and unknown to the participating centers. We considered a 6% difference in survival as a minimal relevant difference between study arms. We performed a power calculation based on this assumption and estimated 5-year survival at 60%. With a calculated risk of type 1 error estimated at 5% and type 2 errors at 15%, we determined that 1,100 patients needed to be randomized in each group. The planned number of randomized patients was set at 2,500, with an expected dropout rate of approximately 20%.

Centers were instructed to register all eligible patients in the web-based study database with a reason for noninclusion, if applicable. In addition, the hospital inpatient rosters of four of the largest participating centers (Aarhus, Bispebjerg, Malmö and Stockholm), accounting for approximately 25% of all enrolled patients, were examined, in order to identify all patients undergoing colorectal cancer surgery during the recruitment period. Each patient was screened for eligibility, yielding a complete cohort of eligible patients who were not randomized, to serve as controls to the randomized cohort.

The Mann–Whitney *U*-test was utilized for group comparisons of continuous variables, in which a *P*-value of <0.05 was considered statistically significant. Prevalence ratios with 95% confidence intervals were calculated to compare categorical variables.

Results

Recruitment

A total of 13,718 patients underwent surgery for colorectal cancer in the 24 participating centers during the study period. Of these, 5,643 patients met the inclusion criteria. Subsequently, 1,198 (21.0%) were found to be ineligible, most commonly (34%) due to a synchronous or previous malignancy. Of the 4,445 remaining eligible patients, 2,509 were randomized (Figure 1). This corresponds to an inclusion rate of 56.4% among eligible patients, ranging from 17% to 92% in the different centers (Figure 2). The median number of randomized patients per center was 77, and the mean number was 107. The most common reasons for not including eligible patients were as follows: 1) patient was not asked to participate, n=759 (17.1%); 2) patient did not want to participate, n=382 (8.6%); 3) patient was followed at another hospital, n=171 (3.8%); and 4) other reasons, n=466 (10.5%). The study flow chart is provided in Figure 1. The recruitment rate was stable, with a median inclusion rate of 43 patients per month (interquartile range: 31–53) (Figure 3).

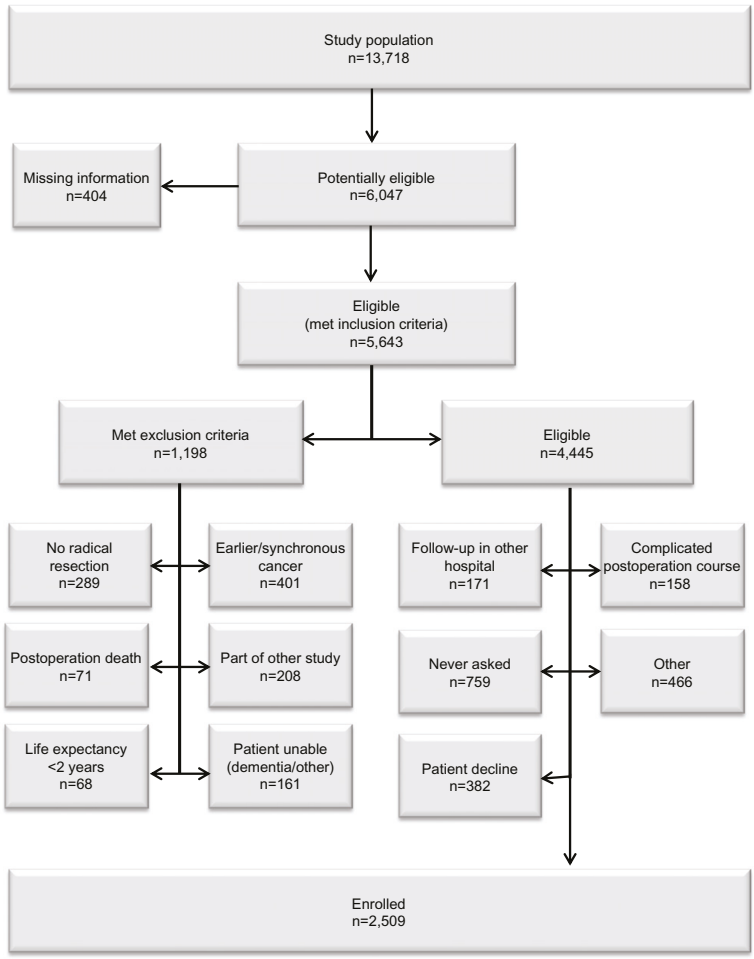

Figure 1 Consort diagram of the COLOFOL trial.

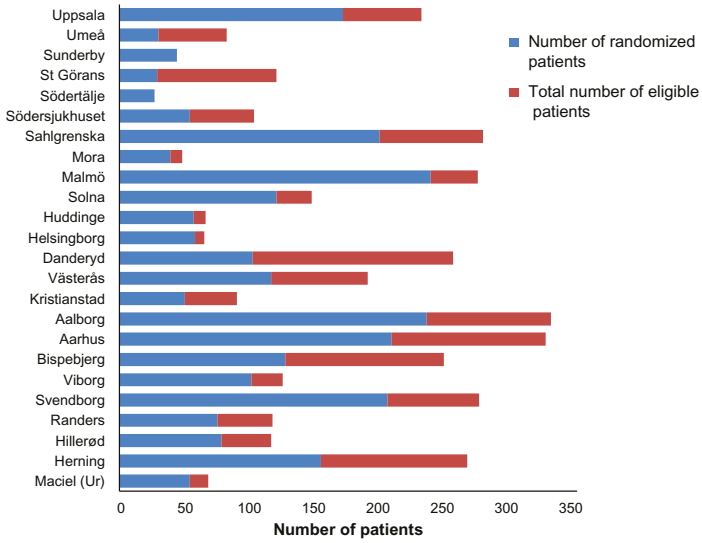

Figure 2 Randomized and eligible patients per center.

At the Aarhus, Bispebjerg, Malmö, and Stockholm centers, a total of 1,221 patients were identified as eligible based on examination of inpatient rosters. Of these, 684 were randomized, corresponding to an inclusion rate of 56% (range: 46%–82%). A total of 537 eligible patients were not randomized, among whom 387 (72%) were reported by study staff and 150 (28%) were missed originally.

Demographics

In the entire study group (n=2,509), the mean age was 64 years, and the distribution of tumor stage II and III was 54% and 46%, the male-to-female distribution was 55% to 45% and the colon-to-rectum distribution was 65% to 35%, without any differences between the two study arms.

In the sample of 1,221 patients from the Aarhus, Bispebjerg, Malmö, and Stockholm centers, as described in

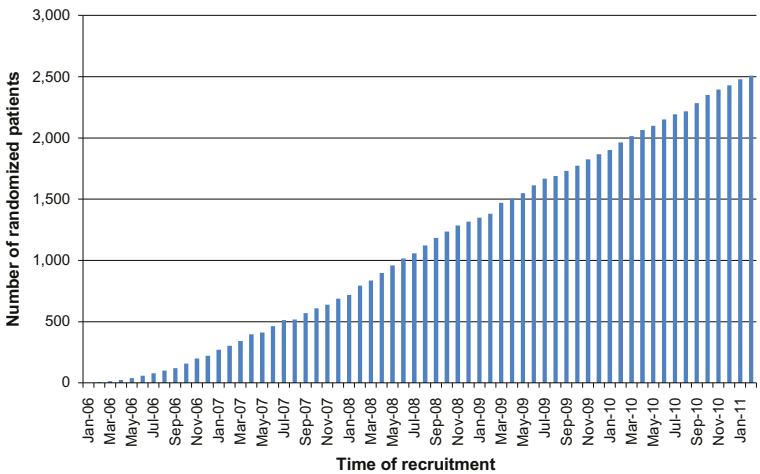

Figure 3 Inclusion rate.

the Material and methods section, no differences between randomized and nonrandomized patients were observed for age (median age of 65 years in both groups) or sex (60/40% male-to-female distribution in both groups). These figures were also comparable to the study cohort. However, there were differences in stage distribution and the proportions of colon and rectal cancers, with 6.7% more stage II disease (prevalence ratio 1.13 [1.02–1.26]) and 5.6% more colon cancers (prevalence ratio 1.11 [0.99–1.24]) in the randomized group (Table 2).

Patients with stage III disease were younger than patients with stage II disease; however, mean age in stage II and III did not differ significantly between the randomized and nonrandomized groups, 64.5 years and 62.6 years, respectively, in the nonrandomized group compared with 64.1 years and 62.8 years in the randomized group. A higher proportion of elderly (>70 years) was found in the nonrandomized group, both in stage II, 37.0% compared with 26.4% ($P<0.01$, χ^2) and stage III disease, 28.3% compared with 20.9% ($P<0.01$, χ^2).

Discussion

A total of 2,509 patients were randomized in the COLOFOL trial, making it by far the largest randomized trial of follow-up in the field of colorectal cancer. Although this large trial has sufficient power to unveil statistically significant differences, the question arises whether its results can be extrapolated to the target population of colorectal cancer patients. Our comparative analysis of randomized patients and eligible nonparticipants indicated that results of COLOFOL can be generalized.

When designing and performing a study, priorities are to include a well-defined study population based on strict criteria and to rule out the influence of confounders and external contributing factors. However, the risk remains that the results will be difficult to extrapolate to the target population of patients with a given condition. There are several examples of trials whose results could not be reproduced in the general population,[12,14,15] probably due to selection bias regarding comorbidity. Study designs thus represent a delicate balance.[11,14] In the COLOFOL trial, we chose a pragmatic design with wide inclusion criteria and few exclusion criteria.

Table 2 Demography of randomized patients and eligible but nonrandomized patients in four major hospitals, n=1,221

Demographic parameters	Randomized patients (N=684)	Nonrandomized eligible patients (N=537)
Median age, years (range)	65 (15–76)	65 (15–75)
Colon cancer, n (%)	385 (56)	272 (51)
Rectal cancer, n (%)	299 (44)	264 (49)
Stage II, n (%)	383 (56)	265 (49)
Stage III, n (%)	301 (44)	272 (51)
Male, n (%)	408 (60)	323 (60)
Female, n (%)	276 (40)	214 (40)

A potential trial weakness is that 43.6% of eligible patients were not randomized. Furthermore, the subanalysis based on hospital inpatient rosters revealed that true number of nonparticipating patients was higher, because only 72% of nonparticipating patients were originally reported. Our thorough analysis of nonparticipants showed good agreement between eligible nonparticipating patients and randomized patients in regard to age and sex distribution, but moderate, although statistically significant, differences in distribution by cancer stage and localization. The reasons for this are unclear. However, the protocol states that trial analyses will be stratified by stage and localization, which will compensate for these differences (though at the cost of power). No difference in mean age was noted between randomized and nonrandomized patients, whereas a higher proportion of elderly (>70 years) was found in the nonrandomized group. The reason for this is unclear but more comorbidity and inability to consent in this group might contribute. The true percentage of missed eligible patients seems to be higher than the estimated 43.6%. This is of minor importance, because the analysis of eligible nonparticipants indicated that the study cohort was comparable to the source population in respects other than stage and localization. Most likely, differences in localization will not affect the ability to generalize the trial results, because rates of metastasis are similar in colon and rectal cancers. In contrast, stage is the most important risk factor for developing metastases. However, stratification for this parameter should still yield large enough subgroups to permit generalization by stage.

Another shortcoming is a lack of information on comorbidity, except that patients with low life expectancy and patients with American Society of Anesthesiologists' classification of Physical Health score of 4, who were excluded. While randomization ensures that there is no risk for a systematic difference in comorbidity between the study groups, comorbidity can have an unrecognized impact on the generalizability of trial results.

The GILDA trial, another large trial in the field of colorectal cancer, has been recruiting patients since 1998, with the aim of randomizing 1,500 patients.[16] No results have been published so far indicating a slow inclusion rate. The CEA second look trial in the UK aimed to randomize 2,000 patients, but was stopped after 11 years of recruitment, and 1,474 patients enrolled, due to inability to show any survival benefit from CEA-guided second look

surgery.[17] The same negative results for CEA surveillance were reported by Jones et al.[18] Results from the "Follow-up After Colorectal Surgery" (FACS) trial, in which 1,202 patients were randomized to four different follow-up regimens, were published in 2014.[19] No advantage was found for any of the regimens. A higher percentage of recurrences were treated with curative intent in the follow-up regimens taken together, compared with minimal follow-up, but no survival benefit was found. Apart from a problem with power, this is probably due to the small possible positive effect, ie, the low rate of asymptomatic recurrences which can be cured by early intervention. One can speculate that this reflects tumor biology, as the correlation between early detection and prognosis is not as strong for metastases as for primary tumors. Compared with the FACS trial, the COLOFOL trial has four times as many patients in each study arm and thus a better chance to detect any difference. Analysis of the final 5-year COLOFOL data will provide strong evidence about the effectiveness of treatment of recurrences with curative intent. Its pragmatic design with wide inclusion criteria and uncomplicated inclusion procedures, reflected by a high and stable monthly recruitment rate, yielded a representative study population and faster recruitment than similar trials. The requirement that at least 30% of eligible patients be recruited at each center in the COLOFOL trial and its steady recruitment rate have decreased selection biases.

Randomized controlled trials are considered to provide the highest level of scientific evidence. Over 2,500 patients have been randomized in the COLOFOL trial, with a fairly high rate of inclusion. High technical requirements for imaging procedures, verification of a clean colon, standardized algorithms for work-up, and mandatory assessment by multidisciplinary boards enhance the possibility of fair comparison between the study groups. Taken together, all this will permit firm conclusions regarding any benefit on survival of high-frequency compared with low-frequency follow-up after curative surgery for colorectal cancer. Apart from differences in stage and localization (colon or rectum), which will be handled by stratification in the analyses, we found a strong similarity between participants and eligible nonparticipants. This indicates that it will be possible to extrapolate the results to the target population. Three-year data will be available in late 2015.

Acknowledgments

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Disclosure

The authors report no conflicts of interest in this work.

References

1. Baca B, Beart RW Jr, Etzioni DA. Surveillance after colorectal cancer resection: a systematic review. *Dis Colon Rectum*. 2011;54(8):1036–1048.
2. Komborozos VA, Skrekas GJ, Pissiotis CA. The contribution of follow-up programs in the reduction of mortality of rectal cancer recurrences. *Dig Surg*. 2001;18(5):403–408.

3. Rodriguez-Moranta F, Salo J, Arcusa A, et al. Postoperative surveillance in patients with colorectal cancer who have undergone curative resection: a prospective, multicenter, randomized, controlled trial. *J Clin Oncol*. 2006;24(3):386–393.
4. Secco GB, Fardelli R, Gianquinto D, et al. Efficacy and cost of risk-adapted follow-up in patients after colorectal cancer surgery: a prospective, randomized and controlled trial. *Eur J Surg Oncol*. 2002;28(4):418–423.
5. Makela JT, Laitinen SO, Kairaluoma MI. Five-year follow-up after radical surgery for colorectal cancer. Results of a prospective randomized trial. *Arch Surg*. 1995;130(10):1062–1067.
6. Ohlsson B, Breland U, Ekberg H, Graffner H, Tranberg KG. Follow-up after curative surgery for colorectal carcinoma. Randomized comparison with no follow-up. *Dis Colon Rectum*. 1995;38(6):619–626.
7. Kjeldsen BJ, Kronborg O, Fenger C, Jorgensen OD. A prospective randomized study of follow-up after radical surgery for colorectal cancer. *Br J Surg*. 1997;84(5):666–669.
8. Pietra N, Sarli L, Costi R, Ouchemi C, Grattarola M, Peracchia A. Role of follow-up in management of local recurrences of colorectal cancer: a prospective, randomized study. *Dis Colon Rectum*. 1998; 41(9):1127–1133.
9. Jeffery GM, Hickey BE, Hider P. Follow-up strategies for patients treated for non-metastatic colorectal cancer. *Cochrane Database Syst Rev*. 2002;1:CD002200.
10. Renehan AG, Egger M, Saunders MP, O'Dwyer ST. Impact on survival of intensive follow up after curative resection for colorectal cancer: systematic review and meta-analysis of randomised trials. *BMJ*. 2002; 324(7341):813.
11. Hulley SB, Cummings SR, Browner WS. *Designing Clinical Research: An Epidemiologic Approach*. Baltimore: Williams & Wilkins; 1988:xi, 247.
12. Sorbye H, Pfeiffer P, Cavalli-Bjorkman N, et al. Clinical trial enrollment, patient characteristics, and survival differences in prospectively registered metastatic colorectal cancer patients. *Cancer*. 2009; 115(20):4679–4687.
13. Peppercorn JM, Weeks JC, Cook EF, Joffe S. Comparison of outcomes in cancer patients treated within and outside clinical trials: conceptual framework and structured review. *Lancet*. 2004;363(9405):263–270.
14. Sorensen HT, Lash TL, Rothman KJ. Beyond randomized controlled trials: a critical comparison of trials with nonrandomized studies. *Hepatology*. 2006;44(5):1075–1082.
15. Hansen AB, Gerstoft J, Kirk O, et al. Unmeasured confounding caused slightly better response to HAART within than outside a randomized controlled trial. *J Clin Epidemiol*. 2008;61(1):87–94.
16. Grossmann EM, Johnson FE, Virgo KS, Longo WE, Fossati R. Follow-up of colorectal cancer patients after resection with curative intent-the GILDA trial. *Surg Oncol*. 2004;13(2–3):119–1124.
17. Treasure T, Monson K, Fiorentino F, Russell C. The CEA second-look trial: a randomised controlled trial of carcinoembryonic antigen prompted reoperation for recurrent colorectal cancer. *BMJ Open*. 2014; 4(5):e004385.
18. Jones RP, McWhirter D, Fretwell VL, McAvoy A, Hardman JG. Clinical follow-up does not improve survival after resection of stage I–III colorectal cancer: a cohort study. *Int J Surg*. 2015;17:67–71.
19. Primrose JN, Perera R, Gray A, Rose P, Fuller A, Corkhill A, et al. Effect of 3 to 5 years of scheduled CEA and CT follow-up to detect recurrence of colorectal cancer: the FACS randomized clinical trial. *JAMA*. 2014;311(3):263–270.

Paper II

Errata

In paper II, Figure 1

Time of detection of recurrences within 5 years following radical resection of stage II or III colorectal cancer, stratified by site of recurrence. The graphs B and C have changed places.

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Original Article

Patterns and resectability of colorectal cancer recurrences: outcome study within the COLOFOL trial

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Abstract

Background: Improvements in surgery, imaging, adjuvant treatment, and management of metastatic disease have led to modification of previous approaches regarding the risk of recurrence and prognosis in colorectal cancer. The aims of this study were to map patterns, risk factors, and the possibility of curative treatment of recurrent colorectal cancer in a multimodal setting.

Methods: This was a cohort study based on the COLOFOL trial population of patients who underwent radical resection of stage II or III colorectal cancer. The medical files of all patients with recurrence within 5 years after resection of the primary tumour were scrutinized. Follow-up time was 5 years after the first recurrence. Primary endpoints were cumulative incidence, site, timing, and risk factors for recurrence, and rate of potentially curative treatment. A secondary endpoint was survival.

Results: Of 2442 patients, 471 developed recurrences. The 5-year cumulative incidence was 21.4 (95 per cent c.i. 19.5 to 23.3) per cent. The median time to detection was 1.1 years after surgery and 87.3 per cent were detected within 3 years. Some 98.2 per cent of patients who had potentially curative treatment were assessed by a multidisciplinary tumour board. A total of 47.8 per cent of the recurrences were potentially curatively treated. The 5-year overall survival rate after detection was 32.0 (95 per cent c.i. 27.9 to 36.3) per cent for all patients with recurrence, 58.6 (51.9 to 64.7) per cent in the potentially curatively treated group and 7.7 (4.8 to 11.5) per cent in the palliatively treated group.

Conclusion: Time to recurrence was similar to previous results, whereas the 21.4 per cent risk of recurrence was somewhat lower. The high proportion of patients who received potentially curative treatment, linked to a 5-year overall survival rate of 58.6 per cent, indicates that it is possible to achieve good results in recurrent colorectal cancer following multidisciplinary assessment.

Introduction

Colorectal cancer is the second most common cause of cancer-related mortality worldwide[1]. Following surgery with curative intent, some 10–35 per cent of patients develop metachronous metastases[2–8]. This range of reported recurrences reflects changes in the accuracy of preoperative staging, as well as different postoperative imaging between centres and time periods. These imaging techniques have improved markedly over the past two decades enabling earlier detection of metastases, making preoperative staging and postoperative surveillance examinations more accurate. Adjuvant chemotherapy has been adopted widely to prevent some recurrences[8–10]. Considering all these factors, earlier estimates of the incidence of metachronous metastases and the likelihood of offering further treatment designed to achieve cure may now be inaccurate.

Follow-up programmes designed to detect recurrences that are possible to treat with curative intent are standard nowadays. Although large retrospective studies failed to prove any survival benefit from such programmes[11], small randomized trials that followed had some positive results, and subsequent systematic reviews and meta-analysis[12,13] indicated survival benefit after more frequent examinations. Later large, randomized trials, such as COLOFOL[14], GILDA[15] and FACS[16], could not establish a survival benefit from more frequent follow-up, although more recurrences in the high-frequency follow-up arm could be treated with curative intent. A Cochrane meta-analysis[17] came to the same conclusion. The optimal design of a follow-up programme after curative resection for colorectal cancer is still unclear and proof of benefit resulting from intensive follow-up is lacking .

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Whether a follow-up programme will lead to survival benefit depends on its ability to detect asymptomatic recurrences, and treat them with curative intent. The proportion of recurrences treated with curative intent varies markedly[6,18,19], reflecting differences in follow-up routines, multimodal treatment algorithms, and selection criteria for management of metastases. To optimize and individualize adjuvant therapies and design a surveillance programme with a positive effect on survival, it is important to know the risk factors and pattern of recurrences in a population of patients with colorectal cancer managed with modern multimodal treatment. This should include an understanding of patterns of recurrence amenable to treatment with curative intent. The aim of this study was to map the pattern of, and risk factors for, recurrences in a well defined population of patients with colorectal cancer who had undergone a multimodal treatment approach including curative surgery, and to evaluate the proportion of recurrences possible to treat with curative intent, based on the COLOFOL study cohort. Primary endpoints were the cumulative incidence, timing, and site of recurrence, risk factors for recurrence, and rate of potentially curatively treatment. Secondary endpoints were 5-year overall survival (OS) depending on recurrence site and mode of detection.

Methods

All patients in the study cohort were identified in the COLOFOL trial population. Detailed information on the COLOFOL trial study design and population has been reported previously[14,20]. This study was not included in the original study plan. In summary, the COLOFOL trial enrolled patients who underwent radical surgery for stage II or III sporadic colorectal cancer between 2006 and 2010 at 24 sites in Sweden (15), Denmark (8), and Uruguay (1). Patients had to be aged 18–75 years with a life expectancy exceeding 2 years based on co-morbidity. The objective of the study was to compare overall and cancer-specific mortality according to follow-up regimen. Patients were randomized to either high- or low-intensity follow-up, with contrast-enhanced multislice CT of the abdomen and thorax at certified centres, along with measurement of serum levels of carcinoembryonic antigen (CEA). Examinations were performed 6, 12, 18, 24, and 36 months after surgery (high-intensity group; 1253 patients) or at 12 and 36 months after surgery (low-intensity group; 1256 patients). A colonoscopy was required in the perioperative period to verify a clean colon, whereas further endoscopies were optional. All patients had to personally provide written consent before embarking in the study. The trial was approved by the ethical committee of Uppsala University (2004: M-453) in Sweden, and Copenhagen and Frederiksberg Scientific committee (KF 01–194/04) in Denmark.

All patients were followed prospectively for 5 years after resection of the primary tumour. For the present study, all patients registered with recurrences within 5 years after primary surgery in Sweden and Denmark were identified. The figures presented reflect recurrence rates within 5 years; late recurrences beyond that time were not covered. All medical files were scrutinized for detailed information on time point and type of recurrence, and means of detection and treatment, including both surgical and medical treatment for each recurrence. Patients from Uruguay were not included. Mortality was checked through the population registries in Denmark and Sweden. Follow-up time after first recurrence was 5 years in all but one patient.

Data collected included: age, sex, date of detection of the recurrence, location of recurrence, method of detection, surgical and medical treatment of the recurrence including adjuvant chemotherapy, and aim of treatment (curative or palliative). The same data were collected for any second- and third-line treatments, if given. Data collected from the time of primary surgery were: BMI, concurrent diseases (lung disease, diabetes, history of myocardial infarction), smoking and alcohol habits, CEA level, date of surgery, site of tumour, adjuvant radiotherapy and/or chemotherapy, urgency of operation (acute or elective), blood transfusion, postoperative complications, and detailed information in the pathology report.

Recurrence in mesenteric lymph nodes was defined as a local recurrence, whereas any recurrence in distant lymph nodes, including inguinal or para-aortic nodes, was defined as metastasis (M1). Anastomotic recurrences as well as retroperitoneal recurrences in the operative field of the bowel resection were considered local recurrences, whereas any other recurrence involving the peritoneum and/or omentum was defined as a peritoneal recurrence. Potentially curative treatment was defined as fulfilled resection or ablative treatment judged clinically as radical.

Time was measured from date of surgery to the first of the following events during 5-year follow-up: recurrence, death, or end of follow-up. The cumulative incidence of recurrence was computed using a competing-risk method, with death as a competing event and end of follow-up as a censoring event. Cumulative incidence reflects the probability of developing a recurrence during the time period, which also can be described as absolute risk during this interval. To facilitate readability, the term risk was used to describe the cumulative incidence during the study period.

Statistical analysis

All statistical analyses were carried out with Stata® version 16.1 (StataCorp, College Station, TX, USA). Figures for cumulative incidence in the presence of competing events were generated by means of the macro stcompet for Stata®[21]. Both the cumulative incidence of recurrence and cumulative incidence of competing event (death) were calculated with 95 per cent confidence interval. Hazard ratios (HRs) were calculated by cause-specific univariable and multivariable Cox proportional hazards regression to reflect the relative risk of recurrence between groups. In these analyses, death was a censoring event.

Secondary endpoints were: 5-year OS according to recurrence site and mode of detection. OS was computed using the Kaplan–Meier method and group comparisons were made by univariable and multivariable Cox proportional hazards regression.

The proportional hazards assumption was tested with Schoenfeld's residuals. When the assumption was violated ($P < 0.050$), the follow-up period was divided at 1 year into two intervals to achieve proportional hazards. All collected variables were included in the multivariable Cox regression analyses, and retained in the model if they were independently statistically significant or had $P < 0.200$ and a confounding effect (affected other HRs by more than 10 per cent). CEA was omitted from the analysis because there were too many missing values. $P < 0.050$ was considered statistically significant.

Results

A total of 2456 patients were randomized in the COLOFOL trial in Sweden and Denmark, of whom 14 were excluded as they did not fulfil the inclusion criteria or lacked information on recurrences. The present study involved 2442 patients, of whom 494 were registered with recurrences within 5 years after surgery. Following medical record review, 23 patients were reclassified without

recurrence as no recurrences could be confirmed. Of these, eight patients were diagnosed with a new primary colorectal cancer, seven with primary lung cancer, one with a suspected mesenteric metastasis that proved to be benign, and one with primary ovarian cancer; in six patients, no obvious explanation could be established. A total of 471 patients were therefore confirmed to have recurrent disease and constituted the cohort of patients with recurrences.

Risk, site, and timing of recurrences

The total cumulative risk of recurrence was 21.4 (95 per cent c.i. 19.5 to 23.3) per cent. It was 13.4 (11.4 to 15.6) per cent in stage II and 30.7 (27.6 to 33.9) per cent in stage III disease (*Table 1*). No difference in risk of recurrence was noted between the Swedish and Danish cohorts (data not shown).

In total, 328 patients (69.6 per cent) developed a first recurrence at a single site, whereas 143 (30.4 per cent) developed recurrences at multiple sites. The most common site of first recurrence was liver (9.6 per cent), followed by lung (6.8 per cent). Detailed information on site of recurrences is shown in *Table 2*. The median time to detection of recurrences was 1.1 years, and 87.3 per cent of the recurrences were detected within 3 years. The distribution, timing of detection, and cumulative incidence of all recurrences are presented in *Fig. 1a–c*.

Risk factors for recurrence

A higher risk of recurrence was noted in rectal compared with colonic cancer: 27.4 (95 per cent c.i. 23.9 to 31.2) and 18.3 (16.3 to 20.5) per cent respectively (*Table 3*); there was a significantly higher risk of pulmonary metastases in rectal cancer, at 12.5 (10.3 to15.0) per cent compared with 4.5 per cent (3.5 to 5.7) per cent in colonic cancer (*Fig. 1b,c*). No difference was noted between right- and left-sided colonic cancer. The independence and influence of different risk factors were tested in multivariable analyses. Among all risk factors, lymph node positivity was the strongest, with a HR of 4.71 (95 per cent c.i. 3.45 to 6.43) in the time period more than 1 to 5 years for a lymph node ratio (LNR) of greater than 0.25 (*Table 3*). Other independent risk factors were: T4 category, rectal cancer, cachexia, and diabetes mellitus. Regarding lifestyle factors, daily smoking was an independent risk factor, whereas a moderate daily intake of alcohol decreased the risk of recurrence. Postoperative adjuvant chemotherapy was given to 46.5 per cent of the patients (colon 52.6 per cent, rectum 35.2 per cent), with a reduction in recurrence risk of 38 per cent. Detailed information on risk factors is shown in *Table 3* and *Table S1*.

Assessment and treatment

Of the 471 patients with recurrences, 418 (88.7 per cent) were assessed by multidisciplinary tumour board (MDT) because of the first recurrence and a total of 253 (53.7 per cent) were assessed as potentially curable. Of these, 225 (47.8 per cent) were finally treated with intent to achieve cure. Among these, 98.2 per cent were assessed in a MDT meeting compared with 80.1 per cent of those not curatively treated ($P < 0.001$). In patients with recurrences confined to one location, 207 of 328 (63.1 per cent) were potentially curatively treated, compared with 17 of 89 (19.1 per cent) with recurrences in two locations, and only 3 of 54 patients (5.6 per cent) with recurrences at three or more sites. The highest rate of potentially curative treatment was noted for liver metastases (112 of 148 patients with liver metastases only). In comparison, 53 of 89 patients (59.6 per cent) with lung metastases only, 15 of 23 (65.2 per cent) with peritoneal metastases only, and 21 of 38 (55.3 per cent) with isolated local recurrences received potentially curative treatment (*Table 4*). Of the 225 potentially curatively treated patients, 122 (54 per cent) received preoperative or postoperative adjuvant chemotherapy, 99 (44 per cent) had surgery alone, and data were missing for four patients. In the group of patients in whom recurrences were detected by scheduled examinations, 54.5 per cent were considered potentially curatively treated compared with 33.6 per cent of patients whose recurrences were detected by non-scheduled examinations ($P < 0.001$).

Survival

The 5-year OS rate for all patients with recurrence (calculated from the date of detection) was 32.0 (95 per cent c.i. 27.9 to 36.3) per cent. Sex did not influence survival. Patients with recurrences confined to a single organ had a significantly higher 5-year OS rate (40.2 (95 per cent c.i. 34.9 to 45.5) per cent) than those with two sites (20.4 (12.8 to 29.4) per cent) or multiple sites (2 (0.2 to 8.5) per cent) of recurrence. Patients with recurrences detected by scheduled examinations had a significantly higher 5-year OS rate than those with recurrence detected by symptoms or other

Table 1 Recurrences within 5 years after radical resection for stage II or III colorectal cancer, stratified by tumour stage and primary tumour location

	No. of patients	Recurrences				
		All	Liver only	Lung only	Other location	Multiple locations
Overall	2442	471 (21.4)	148 (6.5)	89 (4.0)	91 (4.6)	143 (6.3)
Stage II	1315	161 (13.4)	64 (5.4)	29 (2.4)	30 (2.6)	37 (3.1)
T3 N0	1144	121 (11.5)	50 (4.7)	25 (2.3)	18 (1.7)	28 (2.8)
T4 N0	169	39 (25.7)	14 (9.7)	4 (2.4)	12 (8.3)	9 (5.3)
Missing	2	1	0	1	0	0
Stage III	1127	310 (30.7)	84 (7.8)	59 (5.8)	61 (7.1)	106 (10.1)
Total						
T1–3 N1	657	132 (23.4)	40 (6.4)	33 (5.2)	24 (5.5)	35 (6.3)
T1–3 N2	289	109 (41.8)	32 (11.2)	21 (9.2)	19 (8.5)	37 (12.9)
T4 N1	83	24 (31.5)	9 (12.8)	0	8 (10.3)	7 (8.4)
T4 N2	94	45 (48.2)	3 (3.2)	5 (5.3)	10 (10.7)	27 (29.0)
Missing	4	0	0	0	0	0
Location						
Colon	1585	264 (18.3)	90 (6.1)	21 (1.5)	59 (4.4)	94 (6.3)
Rectum	857	207 (27.4)	58 (7.4)	68 (8.6)	32 (5.1)	49 (6.3)

Values in parentheses are percentage cumulative risks at 5 years.

Table 2 First recurrence within 5 years in patients who underwent primary radical surgery for stage II or III colorectal cancer, stratified by location

Site of metastases	Liver	Lung	Peritoneum	Lymph nodes	Local	Other
Liver	148 (6.1)	23 (0.9)	5 (0.2)	11 (0.4)	6 (0.2)	1 (0.0)
Lung	23 (0.9)	89 (3.6)	0 (0)	8 (0.3)	7 (0.3)	1 (0.0)
Peritoneum	5 (0.2)	0 (0)	23 (0.9)	2 (0.1)	16 (0.7)	0 (0)
Lymph nodes	11 (0.4)	8 (0.3)	2 (0.1)	25 (1.0)	5 (0.2)	2 (0.1)
Local recurrence	6 (0.2)	7 (0.3)	16 (0.7)	5 (0.2)	38 (1.6)	1 (0.0)
Other	1 (0.0)	1 (0.0)	0 (0)	2 (0.1)	1 (0.0)	5 (0.2)
≥3 sites	41 (1.7)	39 (1.6)	26 (1.1)	33 (1.4)	21 (0.9)	21 (0.9)
Total	235 (9.6)	167 (6.8)	72 (3.0)	86 (3.5)	94 (3.8)	31 (1.3)

Values in parentheses are percentages.

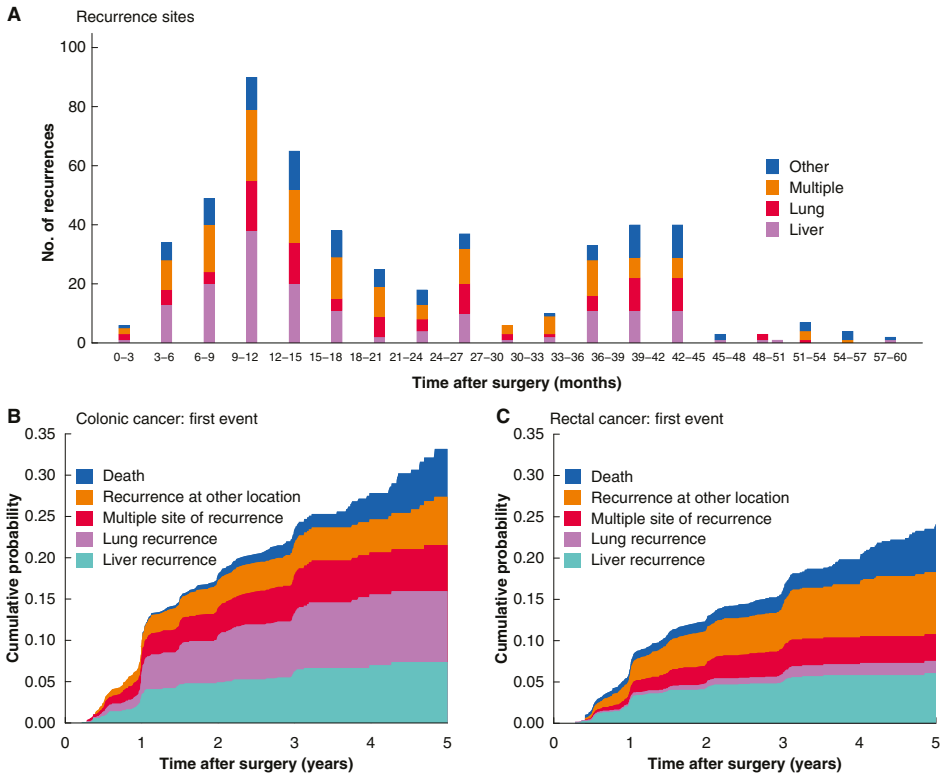

Fig. 1 Time of detection of recurrences within 5 years following radical resection of stage II or III colorectal cancer, stratified by site of recurrence.

A) Stratified by 3-month periods after randomization; B) cumulative incidence for colonic cancer (including mortality as competing risk), and C) cumulative incidence for rectal cancer (including mortality as competing risk).

reasons for examination (*Fig. 2a*). Survival is shown according to site of recurrence in *Fig 2b*. Patients with recurrences amenable to radical resection had a 7.6-fold higher 5-year OS rate than patients treated with palliative chemotherapy or best supportive care (58.6 *versus* 7.7 per cent) (*Fig. 2c*). HRs for 5-year mortality depending on mode of detection and site of recurrence (adjusted for age, sex, and follow-up regimen) are shown in *Table 5*.

Ad hoc analyses stratified by follow-up regimen

Of the 471 patients who developed recurrences, a total of 248 were detected in the group randomized to high-intensity follow-up compared with 223 in the group randomized to low-intensity follow-up. The cumulative incidence of recurrence was similar in the high- and low-intensity groups: 23.1 (95 per cent c.i. 20.3 to 26.0) and 19.7 (17.3 to 22.2) per cent respectively. Median time to

Table 3 Risk factors for recurrence within 5 years following curative resection of stage II or III colorectal cancer

	No. of patients	No. of recurrences* (%)	Cumulative incidence of recurrence at 5 years (%)†	Time period strata	Univariable Cox regression†		Multivariable Cox regression ($n = 2080$)†	
					Hazard ratio	*P*	Hazard ratio	*P*
Smoker								
No	1909	352 (18.4)	20.4 (18.4, 22.5)		1.00 (reference)		1.00 (reference)	
Yes, occasionally	24	8 (33.3)	33.9 (18.6, 56.6)		1.92 (0.95.3.86)	0.069	1.92 (0.90,4.08)	0.091
Yes, daily	371	87 (23.4)	26.9 (21.7, 33.1)		1.34 (1.06, 1.69)	0.015	1.46 (1.13, 1.89)	0.004
Missing	138	24 (17.4)						
Alcohol, daily intake								
None	1541	324 (21.0)	22.4 (20.2, 24.7)		1.00 (reference)		1.00 (reference)	
<3 drinks	505	82 (16.2)	19.9 (15.7, 25.0)		0. 0.76 (0.59, 0.96)	0.024	0.67 (0.52, 0.86)	0.002
≥3 drinks	110	21 (19.1)	25.9 (16.7, 38.7)		91 (0.58, 1.41)	0.658	0.89 (0.56, 1.41)	0.612
Missing	286	44 (15.4)						
BMI (kg/m^2)								
<18.5	56	18 (32.1)	33.3 (22.3, 47.7)		1.83 (1.13, 2.95)	0.014	1.59 (0.96, 2.63)	0.071
18.5–24.9	1088	208 (19.1)	21.4 (18.8, 24.4)		1.00 (reference)		1.00 (reference)	
25.0–29.9	932	179 (19.2)	21.6 (18.6, 24.9)		1.00 (0.82, 1.22)	0.965	1.00 (0.81, 1.24)	0.984
30.0–34.9	286	54 (18.9)	20.3 (15.8, 26.0)		0.97 (0.72, 1.31)	0.848	0.89 (0.63, 1.24)	0.484
≥35.0	77	12 (15.6)	15.9 (0.4, 26.4)		0.77 (0.44, 1.41)	0.417	0.86 (0.48, 1.56)	0.628
Missing	3	0 (0)						
Diabetes								
No	2224	416 (18.7)	20.7 (18.8, 22.7)		1.00 (reference)		1.00 (reference)	
Yes	218	55 (25.2)	28.2 (22.0, 35.8)		1.36 (1.02, 1.80)	0.033	1.51 (1.11, 2.06)	0.009
T category								
T1–3	2090	362 (17.3)	19.4 (17.5, 21.5)		1.00 (reference)		1.00 (reference)	
T4	347	109 (31.4)	33.5 (28.3, 39.4)		2.01 (1.62, 2.49)	<0.001	2.01 (1.58, 2.56)	<0.001
Missing	5	0 (0)						
Lymph node ratio‡								
Negative	1287	153 (11.9)	12.9 (11.0, 15.1)	0–1 year	1.00 (reference)		1.00 (reference)	
<0.1	426	72 (16.9)	20.4 (16.0, 25.9)	0–1 year	0.77 (0.46, 1.29)	0.322	1.17 (0.67, 2.03)	0.588
0.1–0.25	351	98 (27.9)	32.4 (26.8, 38.9)	0–1 year	1.21 (0.75, 1.93)	0.434	1.60 (0.95, 2.69)	0.075
>0.25	337	140 (41.5)	43.8 (38.1, 49.9)	0–1 year	3.81 (2.71, 5.35	<0.001	4.69 (3.16, 6.94)	< 0.001
Missing	41	8 (19.5)						
Negative				>1 to 5 years	1.00 (reference)		1.00 (reference)	
<0.1				>1 to 5 years	2.02 (1.43, 2.85)	<0.001	3.14 (2.12, 4.67)	<0.001
0.1–0.25				>1 to 5 years	3.60 (2.64, 4.92)	<0.001	5.32 (3.67, 7.73)	<0.001
>0.25				>1 to 5 years	4.71 (3.45, 6.43)	<0.001	6.39 (4.39, 9.29)	<0.001
Location								
Rectum	857	207 (24.2)	27.4 (23.9, 31.2)		1.00 (reference)		1.00 (reference	
Colon	1585	264 (16.7)	18.3 (16.3, 20.5)		0.65 (0.55, 0.78)	<0.001	0.60 (0.49, 0.74)	<0.001
Adjuvant treatment (postoperative)								
No	1306	216 (16.5)	18.2 (15.9, 20.7)		1.00 (reference)		1.00 (reference)	
Yes	1136	255 (22.4)	25.0 (22.2, 28.1)		1.40 (1.17, 1.68)	<0.001	0.62 (0.48, 0.80)	0.001

Values in parentheses are *percentages and †95 per cent confidence intervals. The following statistically non-significant or non-confounding risk factors were omitted from the multivariable analysis: age, sex, history of myocardial infarction, pulmonary disease, elective or emergency resection of primary tumour, severe postoperative complication after resection of primary lesion, postoperative blood transfusion. ‡Proportional hazards assumption not fulfilled (tested with Schoenfeld's residuals), so variable fractioned in two time periods.

Table 4 Proportion of curatively treated first recurrences within 5 years in patients primarily radically operated for colorectal cancer stage II and III, stratified by location

Site of metastases	Liver	Lung	Peritoneum	Lymph nodes	Local recurrence	Other
Liver	112 of 148	6 of 23	1 of 5	2 of 11	1 of 6	0 of 1
Lung	6 of 23	53 of 89	0 of 0	0 of 8	2 of 7	0 of 1
Peritoneum	1 of 5	0 of 0	15 of 23	0 of 2	3 of 16	0 of 0
Lymph nodes	2 of 11	0 of 8	0 of 2	6 of 25	2 of 5	0 of 2
Local recurrence	1 of 6	2 of 7	3 of 16	2 of 5	21 of 38	0 of 1
Other	0 of 1	0 of 1	0 of 0	0 of 2	0 of 1	0 of 5
>= 3 sites	1 of 40	1 of 39	0 of 26	0 of 33	0 of 21	1 of 21
Total	123 of 235	62 of 167	19 of 72	10 of 86	29 of 94	1 of 31

detection of recurrences was 1.39 years in the high-intensity and 1.03 years in the low-intensity groups (*Fig. 3*). A higher proportion of recurrences were detected by scheduled examinations in the high-intensity group (77.0 *versus* 59.4 per cent; $P < 0.001$).

The proportion of detected recurrences that it was possible to treat potentially curatively was also similar in the two groups (49.2 per cent with high- and 46.2 per cent with low-intensity follow-up). The 5-year OS rate, calculated from the date of detection

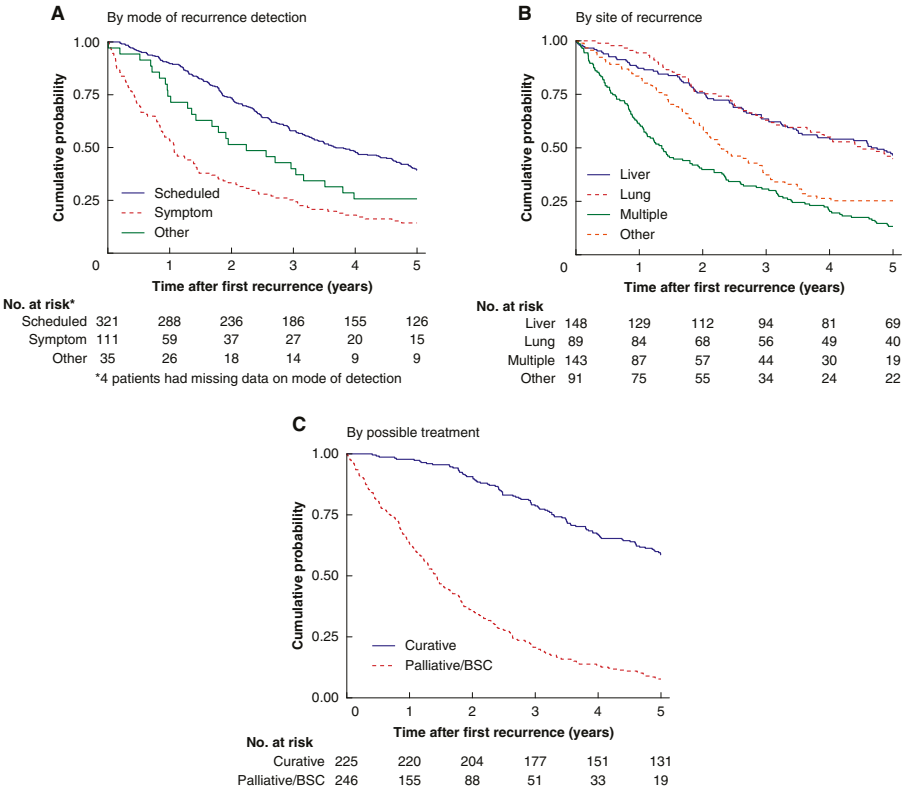

Fig. 2 Overall survival from date of first recurrence to death or 5-year follow-up, following radical resection of stage II or III colorectal cancer.
Stratified by A) mode of recurrence detection, B) site of recurrence, and C) possible treatment. *Data on mode of detection missing for four patients. BSC, best supportive care.

of recurrences, was better in the high-intensity group: 37.8 (95 per cent c.i. 31.8 to 43.9) *versus* 25.6 (20.0 to 31.4) per cent; however, this difference did not reach statistical significance in the multivariable analysis (*Table 5*).

Discussion

The recurrence risks of 13.4 per cent in stage II and 30.7 per cent in stage III colorectal cancer are lower than most earlier estimations[3,4], but in line with other recent studies[2,7,22], probably reflecting improvements in surgical technique, neoadjuvant treatment, imaging techniques, and structured work-up. Another important factor is the effect of adjuvant chemotherapy as standard care in high-risk stage II and stage III disease. The efficacy of adjuvant treatment in the present study was underlined in the adjusted multivariable analyses, which showed a 38 per cent decreased risk of recurrence. This was slightly higher than previous estimations[7,23], which might be due in part to the relatively high proportion of patients receiving this treatment in the present study.

Risk factors associated with recurrence were largely in agreement with previous reports, although the pronounced impact of high LNR (ratio of positive lymph nodes exceeding 0.25) is not widely recognized and merits consideration in the choice of adjuvant therapy. Smoking is a well known risk factor for developing cancer, including colorectal cancer; although described previously as a risk factor for increased risk of recurrence[24], this has not been reported widely. A finding of interest was that a moderate daily intake of alcohol was associated with a decreased risk of recurrent disease. This requires confirmation in a separate cohort.

It was possible to deliver potentially curative treatment in almost half of the patients with recurrences. Three-quarters of the patients with metastases confined to the liver only were potentially curatively treated, a higher proportion than reported previously[4,22,25–27]. Although a greater proportion of patients underwent resection, survival in the operated group was as high, or higher, than in previous reports[4,19,22,25,28–30], indicating an absolute survival benefit in this group. Compared with earlier reports[18,30–32], potentially curative treatments were also undertaken in higher proportions of patients also for isolated lung metastases (59.6 per cent), isolated peritoneal metastases (65.2 per cent), and isolated local recurrences (55.3 per cent). Among those with recurrences involving lymph nodes, treatment with curative

Table 5 Five-year overall survival after date of first recurrence in 471 patients following stage II or III curative resection of colorectal cancer

	Proportion of patients who died	5-year OS (%)	Time period strata	Univariable Cox regression		Multivariable Cox regression	
				Hazard ratio	P	Hazard ratio	P
Recurrence site							
Liver	79 of 148	46.6 (38.4, 54.4)		1.00 (reference)		1.00 (reference)	
Lung	49 of 89	44.9 (34.4, 54.9)		1.01 (0.71, 1.44)	0.97	1.24 (0.85, 1.81)	
Multiple sites	124 of 143	13.3 (8.3, 19.4)		2.85 (2.14, 3.78)	<0.001	2.60 (1.94, 3.49)	<0.001
Other sites	68 of 91	25.3 (16.9, 34.5)		1.88 (1.36, 2.60)	<0.001	1.76 (1.25, 2.49)	0.001
Time from surgery to recurrence (per year)				0.91 (0.81, 1.02)	0.098	0.84 (0.74, 0.94)	0.020
Time from surgery to recurrence by group (years)						Not included	
<1	127 of 180	29.4 (23.0, 36.2)		1.00 (reference)			
1 to <2	105 of 145	27.6 (20.6, 35.0)		1.01 (0.78, 1.31)	0.94		
2 to <3	54 of 86	37.2 (27.1, 47.3)		0.80 (0.58, 1.10)	0.17		
≥3	34 of 60	43.2 (30.5, 55.2)		0.69 (0.47, 1.00)	0.052		
Mode of recurrence detection*							
Scheduled	195 of 321	39.2 (33.9, 44.6)	0–1 year	1.00 (reference)		1.00 (reference)	
Symptom	95 of 111	14.3 (8.6, 21.5)	0–1 year	6.06 (3.91, 9.38)	<0.001	4.60 (2.95, 7.18)	<0.001
Other	26 of 35	25.7 (12.8, 40.8)	0–1 year	2.65 (1.27, 5.54)	0.010	2.40 (1.14, 5.03)	0.013
Scheduled			>1 to 5 years	1.00 (reference)		1.00 (reference)	
Symptom			>1 to 5 years	1.77 (1.26, 2.48)	0.001	1.55 (1.09, 2.19)	0.010
Other			>1 to 5 years	1.37 (0.83, 2.26)	0.214	1.48 (0.89, 2.47)	0.13
Follow-up regimen							
Low intensity	166 of 223	25.6 (20.0, 31.4)		1.00 (reference)		1.00 (reference)	
High intensity	154 of 248	37.8 (31.8, 43.9)		0.72 (0.56, 0.89)	0.003	0.80 (0.64, 1.01)	0.058
Sex							
M	185 of 271	31.7 (26.2, 37.3)		1.00 (reference)			
F	135 of 200	32.5 (26.1, 39.0)		1.02 (0.82, 1.27)	0.87		
Age at recurrence (per 10 years)				1.22 (1.06, 1.40)	0.006	1.29 (1.11, 1.50)	0.001
Age at recurrence by group (years)						Not included	
0–59	69 of 118	41.5 (32.6, 50.2)		1.00 (reference)			
60–69	135 of 198	31.8 (25.4, 38.3)		1.32 (0.99, 1.77)	0.058		
≥70	116 of 155	25.2 (18.6, 32.2)		1.65 (1.22, 2.22)	0.001		
Primary site							
Rectum	125 of 207	39.6 (32.9, 46.1)		1.00 (reference)		1.00 (reference)	
Colon	195 of 264	26.1 (21.0, 31.6)		1.52 (1.22, 1.92)	<0.001	1.34 (1.05, 1.70)	0.016

Values in parentheses are 95 per cent confidence intervals. OS, overall survival. Statistically non-significant or non-confounding risk factors were omitted from the multivariable analysis. *Proportional hazards assumption not fulfilled (tested with Schoenfeld's residuals), so variable fractioned in two time periods.

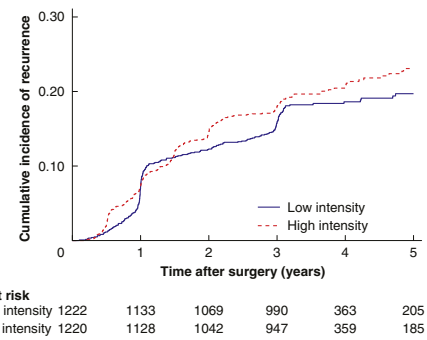

Fig. 3 Cumulative incidence of recurrences following radical resection of stage II or III colorectal cancer stratified by follow-up regimen

intent was considerably less frequent and possible in only 11 per cent if combined with other sites of recurrence. The high rate of assessment in MDT meetings may have been crucial in achieving these figures. An increased rate of metastases being allocated to resection with curative intent by assessment of organ specialists has been shown for liver metastases[33] and recurrences of colorectal cancer in general[34]. Improved diagnostics and chemotherapy strategies have also been proven for different diagnoses by MDT assessment[35].

Patients with recurrences detected by scheduled examinations had a better prognosis than those with recurrences detected by symptoms. This is probably affected by lead time bias as these recurrences are detected earlier but might also be associated with the higher proportion of potentially curatively treated recurrences in this group. If so, it indicates a benefit of the follow-up programme, although examinations were quite limited in both study arms. The high HR (4.60) for mortality associated with recurrences detected by symptoms during the first year indicates that this group consisted of fast-growing aggressive tumours, possibly with a poor chance of long-term survival. Although interval cancer was an independent risk factor for mortality also in the later time period, the impact was much less (HR 1.55). Recurrence of colonic cancer was an independent risk factor for mortality compared with rectal cancer (HR 1.34), possibly related to the proportion of tumours with microsatellite instability (MSI) in the colon, but no data were available on MSI status.

Patients who received potentially curative treatment had a 5-year OS rate of 58.6 per cent, similar to or slightly higher than earlier results[25,29,34,36], indicating that the increased rate of treatment translated into cure. This is further supported by the 5-year OS rate of 32.0 per cent in the whole group of patients with recurrences. The fact that patients aged over 75 years were not included in the study is likely to have influenced these survival

figures. Although outcome was worse for patients whose recurrences were detected within 1 year, the 5-year OS rate in this group was still 29.4 per cent, so early recurrences should not be regarded as a contraindication to treatment with curative intent. These data indicate that structured follow-up, although quite limited, combined with MDT assessment can provide good results in recurrent colorectal cancer.

A limited number of recurrences were detected after the scheduled follow-up time of 3 years, suggesting that this duration of follow-up is sufficient. As expected, recurrences were detected earlier in the high-intensity group during the period of scheduled examinations. This is also reflected by a higher rate of recurrences detected by scheduled examinations in this group. A larger number of recurrences were detected in the high-intensity group after the 3 years of scheduled follow-up, which explains the longer median time to detection of all recurrences in this group. The reason why more recurrences were detected in this group after the period of scheduled examinations is elusive.

The 5-year OS rate after first recurrence was higher in the high-intensity group (calculated from date of detection), probably reflecting lead time bias considering that recurrences were detected earlier on as a result of more frequent examinations. In the multivariable analysis, the HR did not reach statistical significance. Earlier detection might be associated with smaller, treatable recurrences. As more recurrences were detected after 3 years in the group with high-intensity follow-up, this might also have been a factor, as these late recurrences probably have a more favourable prognosis, supported by the multivariable analysis showing a HR of 0.84 per year . In the main study, including the total COLOFOL trial population, no difference in overall or colorectal cancer-specific mortality was noted between the randomization groups, calculated from date of operation of the primary tumour ($P = 0.43$ and $P = 0.52$)[14].

The major strength of this study is that it was based on a prospectively created data set of recurrences in the framework of a randomized trial with scheduled follow-up, all medical files were scrutinized for detailed data on every recurrence, work-up at diagnosis involved colonoscopy and high-resolution multislice CT of liver and lungs, and a high proportion of recurrences were assessed in MDT meetings. The generalizability is therefore likely to be good, based on an inclusion rate of 56.4 per cent in the main study, and good resemblance between the study population and eligible non-randomized patients according to a drop-out analysis[20]. The cut-off age of 76 years or older for inclusion in the study may also have influenced the proportion of patients treated with curative intent for recurrences.

The main limitation is that scheduled follow-up was limited to 3 years. Thus, recurrences detected between 3 and 5 years after primary surgery were not detected by scheduled examinations but by symptoms or a local follow-up protocol. There is a risk of underestimation of recurrences as a result. As follow-up in the study was 5 years, recurrences that occurred later than 5 years after operation were not registered and the total risk of recurrences might be higher than the 5-year risk presented.

Despite radical primary operation and a high proportion of patients treated with adjuvant chemotherapy, 21.4 per cent of patients with stage II or III colorectal cancer had recurrences. Structured follow-up, although limited, and meticulous MDT review, resulted in a high proportion of recurrences being amenable to potentially curative treatment with subsequent long-term survival.

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Supplementary material

Supplementary material is available at *BJS Open* online.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018;**68**:394–424
2. Malakorn S, Ouchi A, Hu CY, Sandhu L, Dasari A, You YN *et al.* Tumor sidedness, recurrence, and survival after curative resection of localized colon cancer. *Clin Colorectal Cancer* 2021;**20**: e53–e60
3. Galandiuk S, Wieand HS, Moertel CG, Cha SS, Fitzgibbons RJ Jr, Pemberton JH *et al.* Patterns of recurrence after curative resection of carcinoma of the colon and rectum. *Surg Gynecol Obstet* 1992;**174**:27–32
4. Manfredi S, Bouvier AM, Lepage C, Hatem C, Dancourt V, Faivre J. Incidence and patterns of recurrence after resection for cure of colonic cancer in a well defined population. *Br J Surg* 2006;**93**: 1115–1122
5. Gunawardene A, Desmond B, Shekouh A, Larsen P, Dennett E. Disease recurrence following surgery for colorectal cancer: five-year follow-up. *N Z Med J* 2018;**131**:51–58
6. van Gestel YR, de Hingh IH, van Herk-Sukel MP, van Erning FN, Beerepoot LV, Wijsman JH *et al.* Patterns of metachronous

metastases after curative treatment of colorectal cancer. *Cancer Epidemiol* 2014;**38**:448–454
7. Osterman E, Glimelius B. Recurrence risk after up-to-date colon cancer staging, surgery, and pathology: analysis of the entire Swedish population. *Dis Colon Rectum* 2018;**61**:1016–1025
8. Bockelman C, Engelmann BE, Kaprio T, Hansen TF, Glimelius B. Risk of recurrence in patients with colon cancer stage II and III: a systematic review and meta-analysis of recent literature. *Acta Oncol* 2015;**54**:5–16
9. Jonker DJ, Spithoff K, Maroun J; Gastrointestinal Cancer Disease Site Group of Cancer Care Ontario's Program in Evidence-based Care. Adjuvant systemic chemotherapy for stage II and III colon cancer after complete resection: an updated practice guideline. *Clin Oncol (R Coll Radiol)* 2011;**23**:314–322
10. Meyers BM, Cosby R, Quereshy F, Jonker D. Adjuvant chemotherapy for stage II and III colon cancer following complete resection: a Cancer Care Ontario systematic review. *Clin Oncol (R Coll Radiol)* 2017;**29**:459–465
11. Kievit J, Bruinvels DJ. Detection of recurrence after surgery for colorectal cancer. *Eur J Cancer* 1995;**31A**:1222–1225
12. Jeffery GM, Hickey BE, Hider P. Follow-up strategies for patients treated for non-metastatic colorectal cancer. *Cochrane Database Syst Rev* 2002; CD002200
13. Renehan AG, Egger M, Saunders MP, O'Dwyer ST. Impact on survival of intensive follow up after curative resection for colorectal cancer: systematic review and meta-analysis of randomised trials. *BMJ* 2002;**324**:813
14. Wille-Jørgensen P, Syk I, Smedh K, Laurberg S, Nielsen DT, Petersen SH *et al.*; COLOFOL Study Group. Effect of more *versus* less frequent follow-up testing on overall and colorectal cancer-specific mortality in patients with stage II or III colorectal cancer: the COLOFOL randomized clinical trial. *JAMA* 2018;**319**:2095–2103
15. Rosati G, Ambrosini G, Barni S, Andreoni B, Corradini G, Luchena G *et al.*; GILDA working group. A randomized trial of intensive *versus* minimal surveillance of patients with resected Dukes B2–C colorectal carcinoma. *Ann Oncol* 2016;**27**:274–280
16. Primrose JN, Perera R, Gray A, Rose P, Fuller A, Corkhill A *et al.*; FACS Trial Investigators. Effect of 3 to 5 years of scheduled CEA and CT follow-up to detect recurrence of colorectal cancer: the FACS randomized clinical trial. *JAMA* 2014;**311**:263–270
17. Jeffery M, Hickey BE, Hider PN, See AM. Follow-up strategies for patients treated for non-metastatic colorectal cancer. *Cochrane Database Syst Rev* 2016; (**11**)CD002200
18. Kodeda K, Derwinger K, Gustavsson B, Nordgren S. Local recurrence of rectal cancer: a population-based cohort study of diagnosis, treatment and outcome. *Colorectal Dis* 2012;**14**:e230–e237
19. Simmonds PC, Primrose JN, Colquitt JL, Garden OJ, Poston GJ, Rees M. Surgical resection of hepatic metastases from colorectal cancer: a systematic review of published studies. *Br J Cancer* 2006;**94**:982–999
20. Hansdotter Andersson P, Wille-Jorgensen P, Horvath-Puho E, Petersen SH, Martling A, Sorensen HT *et al.* The COLOFOL trial: study design and comparison of the study population with the source cancer population. *Clin Epidemiol* 2016;**8**:15–21
21. Gooley TA, Leisenring W, Crowley J, Storer BE. Estimation of failure probabilities in the presence of competing risks: new representations of old estimators. *Stat Med* 1999;**18**:695–706
22. Ikoma N, You YN, Bednarski BK, Rodriguez-Bigas MA, Eng C, Das P *et al.* Impact of recurrence and salvage surgery on survival after multidisciplinary treatment of rectal cancer. *J Clin Oncol* 2017;**35**:2631–2638
23. Shah MA, Renfro LA, Allegra CJ, Andre T, de Gramont A, Schmoll HJ *et al.* Impact of patient factors on recurrence risk and time dependency of oxaliplatin benefit in patients with colon cancer: analysis from modern-era adjuvant studies in the Adjuvant Colon Cancer End Points (ACCENT) database. *J Clin Oncol* 2016;**34**:843–853
24. Walter V, Jansen L, Hoffmeister M, Ulrich A, Chang-Claude J, Brenner H. Smoking and survival of colorectal cancer patients: population-based study from Germany. *Int J Cancer* 2015;**137**:1433–1445
25. Adam R, Hoti E, Bredt LC. Evolution of neoadjuvant therapy for extended hepatic metastases—have we reached our (non-resectable) limit? *J Surg Oncol* 2010;**102**:922–931
26. Dexiang Z, Li R, Ye W, Haifu W, Yunshi Z, Qinghai Y *et al.* Outcome of patients with colorectal liver metastasis: analysis of 1613 consecutive cases. *Ann Surg Oncol* 2012;**19**:2860–2868
27. Stangl R, Altendorf-Hofmann A, Charnley RM, Scheele J. Factors influencing the natural history of colorectal liver metastases. *Lancet* 1994;**343**:1405–1410
28. Elferink MA, de Jong KP, Klaase JM, Siemerink EJ, de Wilt JH. Metachronous metastases from colorectal cancer: a population-based study in North-East Netherlands. *Int J Colorectal Dis* 2015;**30**:205–212
29. Kopetz S, Chang GJ, Overman MJ, Eng C, Sargent DJ, Larson DW *et al.* Improved survival in metastatic colorectal cancer is associated with adoption of hepatic resection and improved chemotherapy. *J Clin Oncol* 2009;**27**:3677–3683
30. Zellweger M, Abdelnour-Berchtold E, Krueger T, Ris HB, Perentes JY, Gonzalez M. Surgical treatment of pulmonary metastasis in colorectal cancer patients: current practice and results. *Crit Rev Oncol Hematol* 2018;**127**:105–116
31. Kodeda K, Nathanaelsson L, Jung B, Olsson H, Jestin P, Sjovall A *et al.* Population-based data from the Swedish Colon Cancer Registry. *Br J Surg* 2013;**100**:1100–1107
32. Amelung FJ, Consten ECJ, Siersema PD, Tanis PJ. A population-based analysis of three treatment modalities for malignant obstruction of the proximal colon: acute resection *versus* stent or stoma as a bridge to surgery. *Ann Surg Oncol* 2016;**23**:3660–3668
33. Folprecht G, Gruenberger T, Bechstein WO, Raab HR, Lordick F, Hartmann JT *et al.* Tumour response and secondary resectability of colorectal liver metastases following neoadjuvant chemotherapy with cetuximab: the CELIM randomised phase 2 trial. *Lancet Oncol* 2010;**11**:38–47
34. Segelman J, Singnomklao T, Hellborg H, Martling A. Differences in multidisciplinary team assessment and treatment between patients with stage IV colon and rectal cancer. *Colorectal Dis* 2009;**11**:768–774
35. Specchia ML, Frisicale EM, Carini E, Di Pilla A, Cappa D, Barbara A *et al.* The impact of tumor board on cancer care: evidence from an umbrella review. *BMC Health Serv Res* 2020;**20**:73
36. de Waal Malefyt R, Haanen J, Spits H, Roncarolo MG, Te Velde A, Figdor C *et al.* Interleukin 10 (IL-10) and viral IL-10 strongly reduce antigen-specific human T cell proliferation by diminishing the antigen-presenting capacity of monocytes via downregulation of class II major histocompatibility complex expression. *J Exp Med* 1991;**174**:915–924

Paper III

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ORIGINAL ARTICLE

High resection rates of colorectal liver metastases after standardized follow-up and multimodal management: an outcome study within the COLOFOL trial

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Abstract

Background: Outcome after colorectal liver metastases (CRLM) resection has improved over time, despite increased resection rates. Hence, it's crucial to identify all patients possible to treat with curative intent. The objectives of this study were to map recurrence pattern, treatment strategy and survival depending on treatment and follow-up strategy.

Methods: In the COLOFOL-trial, patients with radically resected stage II-III colorectal cancer were randomized to high-frequency (6, 12, 18, 24 and 36 months; HF) or low-frequency (12 and 36 months; LF) follow-up. In this study, all CRLM within 5 years were identified and medical files scrutinized. Overall survival (OS) was analysed in uni- and multivariable analyses. Primary endpoint was 5-year OS.

Results: Of 2442 patients, 235 (9.6%) developed metachronous CRLM of which 123 (52.3%) underwent treatment with curative intent, resulting in 5-year OS of 58%. Five-year OS for patients with CRLM was 43% after HF versus 24% after LF. The survival benefit was confirmed for HF 8 years from resection of the primary tumour, HR 0.63 (CI 0.46–0.85).

Conclusion: A high proportion of metachronous CRLM was possible to treat with curative intent, yielding high survival rates. More intense follow-up after colorectal cancer resection might be of value in high-risk patients.

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Introduction

The liver is the most common site of metastases in colorectal cancer (CRC) and approximately 25% of all patients develop colorectal liver metastases (CRLM) at some point in time. As higher incidences of CRLM have been reported historically, it is possible that earlier detection of the primary tumours and modern use of adjuvant chemotherapy could decrease recurrence rates further.[1,2] Improved preoperative staging also enables more metastases to be detected synchronously, subsequently lowering the proportion of metachronous metastases, which affect about 10% of all patients. Long term survival for patients after resection and/or ablation of CRLM is constantly improving, and 5-year OS survival rates over 50% have been reported in national cohorts, despite increasing resection rates.[3,4] Survival in palliative chemotherapy has also improved, but 5-year OS rates are still reported to be below 10%.[5,6] This indicates the importance of

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identifying all patients with CRLM possible to treat with curative intent.

The benefit of intense follow-up programs for early detection of recurrences is debated. The main goal of follow-up programs is early detection of recurrences, with subsequently improved possibilities of curative treatment due to less severe tumour stage. Several studies have been performed to evaluate the impact of intensity of postoperative imaging and measurement of serum carcinoembryonic antigen (CEA), without convincing proof of any survival benefit from more intense follow-up regimens.[7–9] Among them, the COLOFOL trial randomized 2509 patients radically treated for CRC (stage II-III) to either high- or low-frequency follow-up. This did not show any differences in 5-year overall mortality or cancer specific mortality between the randomization groups.

Prognostic factors for mortality in metastatic disease have been well described, with the conclusion that patient factors and primary tumour characteristics, such as lymph node status and vascular invasion together with metastatic pattern, are of great importance for prognosis.[10–14] Beyond patient selection, also choice of surgical technique and adding of preoperative and postoperative adjuvant chemotherapy is of relevance.[15–17] However, selection criteria for curatively intended treatment of CRLM are not fully established and have varied over time and between centers. At the same time, individual assessment in multidisciplinary boards including presence of liver surgeon expertise has been proven important.[18–20] The COLOFOL trial protocol stipulated that all recurrences detected at follow-up should be discussed in a multidisciplinary therapy board, in which the possibility for metastasectomy should be evaluated.

Based on a multimodal treated population diagnosed with CRC, the objectives of this study were to map liver recurrence pattern, treatment strategy and survival depending on treatment and follow-up strategy.

Methods

The COLOFOL trial was a prospective randomized multicenter trial, with 24 participating centers in Denmark, Sweden and Uruguay, comparing high- and low-frequency follow-up of patients radically treated for CRC (stage II-III) between 2006 and 2010. Eligible patients had to be 75 years or younger with a life expectancy based on co-morbidity of at least two years. The patients were further required to have at least one imaging procedure of liver and lungs before primary surgery to rule out synchronous metastases and a colonoscopy to rule out synchronous colorectal tumours. A total of 2509 patients were randomized to either high-frequency (at 6, 12, 18, 24 and 36 months) or low-frequency (at 12 and 36 months) examinations with multislice CT scan of the thorax and abdomen and measurement of CEA. Patients were followed prospectively for 5 years after primary tumour resection and primary outcomes were overall and cancer specific mortality.[7]

For the present study, patients registered in Denmark (8 study sites) and Sweden (15 study sites) with any kind of recurrences within 5 years after resection of the primary CRC were identified and medical files were scrutinized. For pragmatic reasons, the one participating center in Uruguay was not included. Data collected included patient- and primary tumour-characteristics, time to recurrence, metastatic distribution, detailed information on surgical and medical treatment, multidisciplinary assessment, intention- and outcome of treatment, surgical and/or ablative technique, and oncological treatment at any point in time, including palliation. Data on any 2nd and 3rd recurrences were also retrieved. Mortality was checked via the Danish and Swedish population registers where all deaths are continuously registered. Follow-up time after first recurrence was 5 years in all but one patient.[21]

To include all metastases detected in the scheduled 1-year control, the time frame was set to 0–13 months and defined as early metachronous metastases. Curatively intended treatment was defined as radically resected or ablated liver metastases, and when present, also radical treatment of extra-hepatic disease. The study was approved by Copenhagen and Frederiksberg Scientific committee (KF 01–194/04) in Denmark and the Regional Ethical committee in Uppsala (2004:M453 and amendment (2016-07-22)).

Statistics

Predictive factors for treatment with curative intent of all patients with liver metastases were analyzed by means of uni- and multivariable Poisson regression. Five-year overall survival (OS) was measured from date of detection of CRLM to death or end of follow-up within 5 years.

To compensate for the lead-time bias in comparison of survival between randomization arms (high- or low-frequency follow-up), analysis of conditional probability of survival was performed. Overall survival (OS) was measured from date of resection of the primary tumour to death or end of follow-up within 8 years, where patients entered the analysis at time of detection of liver recurrence. To reduce excessive effect of early deaths when few cases are at risk, not attributable to follow-up regimen, patients with liver metastases that died within one year of the primary tumour resection were excluded from the analysis.

OS was computed using the Kaplan–Meier method and group comparisons were analyzed by logrank test, uni- and multivariable Cox proportional hazards regression. The proportional hazards assumption was tested with Schoenfeld's residuals. To further explore any differences in survival, 5-year restricted mean survival (RMS) was calculated as complement to 5-year OS, to get a better impression on loss of life-time (in years) during the 5-year follow-up time. In the multivariable analyses, all collected variables from the univariable analyses were put in the analysis and kept in the model if they were independently statistically significant or had a p-value <0.20 and a confounding effect (*i.e.* effected other HRs with more than 10%).

To test difference of recurrence characteristics between high- and low-frequency follow-up groups Fisher's exact test or Wilcoxon rank sum test was used. P-values <0.05 were considered statistically significant. When appropriate, 95% confidence intervals (CI) are presented in parenthesis. All statistical analyses were carried out with Stata version 16.1 (Stata Corp, College Station, Texas, USA).

Results

Metastatic pattern

A total of 2442 patient were included in the study population and 471 (19.3%) patients were confirmed to have recurrent disease within 5 years after primary surgery. A total of 235 patients (9.6%) developed CRLM as 1st recurrence. Out of these, 148 (63.0%) patients had tumors confined to the liver whereof 78 (33.2%) patients had single metastases. Fifty-six percent of the metastases were detected within the first 13 months after operation of the primary tumour (Table 1).

Treatment with curative intent

Out of the total cohort of patients with liver metastases as 1st recurrence, 220 (93.6%) patients were assessed in a multidisciplinary tumour board. A total of 123 (52.3%) patients underwent surgical resection and/or ablation therapy with a curative intent, resembling 5.0% of all patients in the COLOFOL cohort. Out of the 78 patients with single metastasis, 72 (92.3%) were treated with curative intent compared to 5 out of 24 (20.8%) patients with more than 5 metastases. More than 5 metastases and concomitant metastases in other organs were the only risk factors for not being treated with curative intent in multivariable analysis (Supplementary Table 1). Although size was not an independent selection criterion in the multivariable analysis, 45/48 (93.8%) of the patients with largest sized liver metastasis 20 mm or smaller (without any other metastatic site) were treated with curative intent compared to 8/20 (40.0%) of all patients with largest sized liver metastasis ≥50 mm.

Out of all patients treated with curative intent, 93 (75.6%) patients were treated with resection only, 20 (16.3%) patients with ablation therapy only, and 9 (7.3%) patients with a combination of resection and ablation. One patient had complete remission after neoadjuvant chemotherapy and was not subject for surgical treatment. Out of these 123 patients, 106 (86.2%) were treated with chemotherapy at some point in time (after primary surgery and/or before or after liver surgery; Table 1). Out of the 112 patients not treated with curative intent, 96

Table 1 Liver recurrences and resection rates and chemotherapy for those with a curatively intended treatment of first liver recurrence

	CRLM as 1st recurrence n	Curatively intended treatment n ([a])	Adjuvant chemo after CRC n (%)	Chemo before or after liver surgery n (%)	Chemo at some time point n (%)
Total	235	123[b] (52)	68 (55)	73 (59)	106 (86)
Liver metastases only	148	112 (76)	60 (54)	64 (57)	96 (86)
No of tumours:					
≤ 1	78	72 (92)	39 (54)	39 (54)	61 (85)
2–4	44	34 (77)	18 (53)	20 (59)	29 (85)
≥ 5	24	5 (21)	2 (40)	5 (100)	5 (100)
Missing	2	1 (50)	1 (100)	0	1 (100)
Max size (mm):					
≤ 20	48	45 (94)	28 (62)	22 (49)	39 (87)
21–30	40	31 (78)	13 (42)	17 (55)	26 (84)
31–50	34	24 (71)	14 (58)	16 (67)	20 (83)
> 50	20	8 (40)	3 (38)	7 (88)	8 (100)
Missing	6	4 (67)	2 (50)	2 (50)	3 (75)
Liver + lung only	23	6 (26)	4 (67)	5 (83)	5 (83)
Liver + other/multiple	64	5 (8)	4 (80)	4 (80)	5 (100)
Time to recurrence					
<13 months	129	72 (56)	40 (56)	39 (54)	60 (83)
≥13–60 months	106	51 (48)	28 (55)	34 (67)	46 (90)
Low-frequency FU	113	56 (50)	37 (66)	32 (57)	49 (88)
High-frequency FU	122	67 (55)	31 (46)	41 (61)	57 (85)

Values in parenthesis are percentages of patients treated with curative intent unless indicated otherwise.
[a] Values in parenthesis are percentages of all 1st liver recurrences.
[b] 93 patients were treated with resection only, 20 patients with ablation therapy only and 9 patients with a combination of resection and ablation. One patient had complete remission after neoadjuvant chemotherapy and was not subject for surgical treatment. FU, Follow-up.

(85.7%) were treated with palliative chemotherapy. After curatively intended treatment, 77 (62.6%) patients developed a 2nd recurrence out of which 41 (53.2%) patients were subject for further treatment with curative intent. Out of these, 25 (61.0%) patients developed a third recurrence of which 7 (28.0%) patients were again treated with curative intent (Supplementary Table 2).

Survival

Survival data for all patients and the group treated with curative intent depending on metastatic pattern, time of detection, and follow-up regimen are presented in Table 2. The 5-year OS calculated from date of detection for all patients with liver metastases was 34% (CI 28%–40%) and median survival was 36.5 (CI 29.8–42.1) months. Patients treated with curative intent had a 5-year OS of 58% (CI 48%–66%) (median not reached) whereas patients treated with palliative intention or best supportive care had a 5-year OS of 7% (CI 3%–13%) (Table 2; Fig. 1) and median survival of 14.7 (CI 10.7–17.1) months. There was no difference in 5-year OS between early (<13 months) and late (≥13–60 months) detected metachronous metastases (33% and 34% respectively; $p = 0.60$).

In multivariable analysis, risk factors for death within 5 years after detection of liver metastases were: age ≥70 years (HR 1.89, CI 1.14–3.08); medium sized (21–30 mm compared to ≤20 mm) liver metastases (HR 1.79, CI 1.14–2.82); liver metastases ≥50 mm (HR 2.52, CI 1.55–4.11); ≥5 liver metastases (HR 3.18, CI 2.02–5.00); combined liver and lung metastases (HR 2.35, CI 1.35–4.08); and other synchronous or multiple locations of metastases (HR 2.67, CI 1.78–4.00). Rectal cancer was associated with a lower risk compared to colon cancer (HR 0.64 and HR 0.44 compared to left and right sided colon cancer respectively; Supplementary Table 3). The median follow-up time was 9.7 (IQR 8.5–10.3) years for patients alive at end of follow-up and 2.2 (IQR 0.9–4.4) years for those who died.

High/low frequency follow-up

The 5-year OS for patients after detection of liver metastases in the high-frequency follow-up randomization group was 43% (CI 34%–51%) and 5-year RMS was 3.2 years (CI 2.9–3.6) compared to 24% (CI 17%–32%) and 2.7 years (CI 2.4–3.0) in the low-frequency group (Table 2; Fig. 2A).

In the conditional probability of survival analysis with follow-up start at date of CRC resection, the patients randomized to

Table 2 Overall survival and 5-year restricted mean survival from date of first liver recurrence for all patients with liver metastases and for patients treated with curative intent

	All liver metastases			Curatively intended treated liver metastases		
	N	5-year OS % (range)	5-year RMS Years (range)	n	5-year OS % (range)	5-year RMS Years (range)
Total	235	34 (28–40)	3.0 (2.7–3.2)	123	58 (48–66)	4.2 (4.0–4.4)
Liver met only	148	47 (38–54)	3.6 (3.3–3.8)	112	60 (50–68)	4.2 (4.0–4.4)
No of tumours:						
≤ 1	78	55 (43–65)	3.9 (3.6–4.3)	72	60 (47–70)	4.2 (3.9–4.5)
2 – 4	44	48 (33–61)	3.7 (3.3–4.2)	34	62 (43–76)	4.3 (3.9–4.7)
≥ 5	24	21 (8–31)	2.2 (1.4–2.9)	5	60 (13–88)	4.7 (4.0–5.3)
Missing	2	–	–	1	–	–
Max size (mm):						
≤ 20	48	63 (47–74)	4.1 (3.7–4.5)	37	67 (51–78)	4.3 (3.9–4.6)
21–30	40	40 (25–55)	3.6 (3.1–4.1)	31	52 (33–67)	4.1 (3.7–4.6)
31–50	34	44 (27–60)	3.5 (3.0–4.0)	7	58 (36–75)	4.1 (3.7–4.6)
> 50	20	30 (12–50)	2.6 (1.7–3.5)	8	62 (23–86)	4.4 (3.4–5.4)
Missing	6	–		4		
Liver met + lung	23	13 (3–30)	2.6 (1.9–3.2)	6	17 (8–52)	3.7 (3.1–4.4)
Liver met + other	64	11 (5–20)	1.8 (1.4–2.2)	5	60 (13–88)	3.9 (2.5–5.2)
Detected within < 13 months	129	33 (25–41)	3.0 (2.7–3.4)	72	56 (43–66)	4.2 (3.9–4.4)
Detected ≥ 13–60 months	106	34 (25–43)	2.9 (2.5–3.2)	51	61 (46–73)	4.2 (3.8–4.5)
Low-frequency FU	113	24 (17–32)	2.7 (2.4–3.0)	56	46 (33–59)	3.9 (3.6–4.3)
High-frequency FU	122	43 (34–51)	3.2 (2.9–3.6)	67	67 (55–77)	4.4 (4.1–4.7)

Values in parenthesis are 95% confidence intervals. OS, overall survival; LM, liver metastases; RMS, restricted mean survival; FU, follow-up.

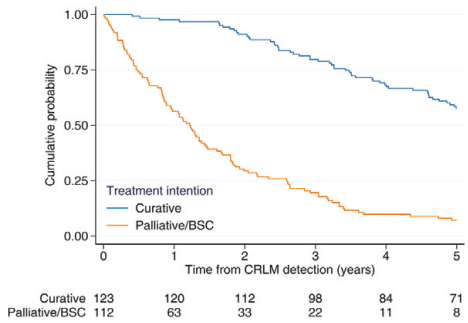

Figure 1 Overall survival after 1st liver recurrence following radical resection of colorectal cancer stage II and III, stratified on treatment intention. BSC, best supportive care.

high-frequency follow-up had significantly better 8-year OS ($p < 0.001$; Fig. 2B) and significantly lower HR for mortality within 8 years compared to low-frequency follow-up, i. e 0.61 (CI 0.44–0.86) in multivariable analysis (Table 3). When not excluding patients who died from CRLM during the first year after resection of the primary tumour (n = 9), the HR was 0.66 (CI 0.48–0.92) in favour to the high-frequency follow-up group in multivariable analysis.

The median follow-up time for patients alive at end of follow-up was 11.0 years (IQR 10.2–11.7) and 3.8 years (IQR 2.3–5.8) for those who died. There was no significant difference between the follow-up groups regarding extra-hepatic dissemination or number of liver tumours, but there was a significant difference in size of metastases with significantly larger tumours in the low-frequency follow-up group ($p = 0.039$; Supplementary Table 4).

Discussion

Fifty-two percent of all patients with liver recurrences and over 92% of patients with solitary liver metastases within 5 years after radical resection of CRC (stage II-III) were subject to liver resection or ablation with curative intent. Albeit the high proportion of operated cases, the long-term OS of about 60% is well in line with or better than previous reports. The combination of a higher proportion of operated patients and simultaneously a high 5-year OS in the whole group of patients with CRLM suggests that indications for treatment of CRLM with curative intent can be widened and underlines the importance of assessment in multimodal therapy boards that includes liver specialists.

Even though high rates of CRLM after radically treated colorectal cancer of about 25–35% are still frequently referred to,[22,23] the recurrence rate after radically treated CRC with modern use of adjuvant chemotherapy is clearly lower in modern retrospective reports.[6,24,25] Thorough preoperative work-up of CRC patients with high-resolution contrast-enhanced CT-scans enables more accurate screening for synchronous liver metastases enhancing the possibility of liver resection at time of primary disease. We perceive that the rate of about 10% metachronous CRLM in total, and 6% for recurrences confined to the liver – as found in this well-defined cohort of radically treated stage II-III CRC prospectively observed in standardized follow-up programs – reflect modern data on recurrent liver disease.

The fact that three quarters of all patients with metastases confined to the liver and 92% of solitary liver metastases were treated with resection and/or ablation therapy, is in accordance with the intention of the COLOFOL trial. Included patients were all 75 years or younger at time of inclusion, and had a life-expectancy of more than 2 years in respect of co-morbidity, aiming at being possible to treat with curative intent in case of recurrent disease. Notably, more than half of all patients with metachronous CRLM were treated with curative intent. Moreover, a large proportion of patients with a second or third recurrence after radically resected CRLM (53 and 61% respectively) underwent curatively intended treatment. These high resection numbers emphasize the benefit of standardized follow-up and individual evaluation. In this study, >90% of all patients were subject to assessment in a multidisciplinary tumour board after detection of first liver recurrence. Interestingly, only number of liver metastases ($\geq$5) and synchronous extra-hepatic spread were significantly associated with lower resection rates in multivariable analysis, whereas primary tumour stage and time of detection (within 13 months or later) did not affect the probability of curatively intended treatment or long-term survival. Thus, patients with previously regarded unfavorable prognostic factors are still likely to be subject for treatment of metastases when technically possible with good results. This further underlines the need for organ specialists in the MDT assessments.

The 5-year OS rates for patients with CRLM was high. One third of all patients with liver metastases and about 50% of patients with metastases confined to the liver were alive after 5 years, irrespective of treatment. In the group of patients treated with curative intent, the 5-year OS was about 60%, independent of extrahepatic spread. This figure is higher than for most national- and multicenter reports.[26] Although all patients in the COLOFOL trial were $\leq$75 years at inclusion and with limited co-morbidity, this points to a survival benefit of widened indications for treatment of CRLM with a curative intent. This is further emphasized by the poor OS of only 7% for palliatively treated patients. In contrast to these encouraging results, the 5-year OS was only 13% in patients with combined liver and lung metastases and still only 20% in the small group that went on to curatively intended treatment. The latter figure is lower compared to most published data and the reason for this is obscure. Earlier reports have stipulated better long-term survival for late metachronous metastases,[27] but in this study there was

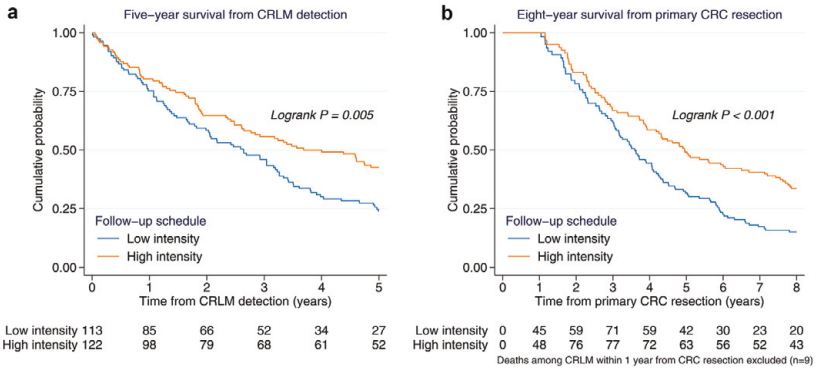

Figure 2 Overall survival for patients with liver recurrences following radical resection of colorectal cancer stage II and III, stratified on follow-up schedule. a) 5-year survival from date of detection and b) 8-year survival conditional on having survived the first year after resection of primary colorectal tumor. Time measured from date of resection of primary tumor and delayed entry of patients in the analyses at date of detection of liver metastases.

no survival difference between metastases detected during the 1st year of follow-up and later on.

In this study of patients that developed liver metastases as 1st recurrence, a survival benefit was noted in the subgroup randomized to high-frequency follow-up. This finding was not expected and is inevitably affected by a lead-time bias when analyzed from date of detection of CRLM, as metastases in the high-frequency follow-up group are potentially detected at an earlier stage. However, treatment delay has been identified as a risk factor for death for primary colorectal cancer,[28] and when long term survival (8 years) was analyzed from date of primary tumour resection, a significant survival benefit remained in the multivariable analysis. This result is supported by the finding that patients in the high-frequency follow-up group were more likely to undergo treatment with curative intent and had smaller tumours, which were independently associated with increased survival. Moreover, a higher proportion of patients detected in between scheduled examinations were noted in the low-frequency group, which was associated with a worse prognosis in the multivariable analysis. Theoretically, more patients with fast growing tumours with aggressive biology would be found and treated in the high-frequency follow-up group. However, second recurrences (at any site) after radical treatment of CRLM were more common in the low-frequency follow-up group.

Although a clear difference in survival between follow-up groups was noted in this study, the problem remains to identify the group of patients that will develop CRLM, already at the time of primary tumor resection. Moreover, one must consider that even if, as proposed in this material, an improved 5-year OS of about 20% for all patients with CRLM by high-frequency compared to low-frequency follow-up after the primary CRC surgery exists, it corresponds to a long-term survival benefit of less than 2% of the total study population and cost-benefit must be taken under consideration. Notably, we did not find any differences in survival in lung metastases depending on follow-up regimen[29] and the small difference in total numbers probably explains why no difference could be detected in the main study on the whole trial population. Taken together, although these findings have to be interpreted with caution, they evoke the hypothesis that high-frequency follow-up could be of benefit in patients with high risk of recurrence, such as LNR >0.25, T4 tumors, and/or extramural vascular invasion. This warrants a randomized trial, although with the challenging problem of selecting the right patients.

Biomarkers, including CEA and circulating tumor DNA (ctDNA) could be of additional value to identify a cohort with high risk of recurrences that theoretically would benefit from more intensive follow-up. However, a post-hoc analysis of the high-risk group with elevated CEA-levels, before or after primary surgery, has been performed within the COLOFOL trial population without any noted survival benefit from high-frequency follow-up.[30] Although detectable levels of ctDNA after CRC resection is associated with high rates of cancer recurrence, it may take several months before recurrent disease can be verified by imaging techniques and a potential survival benefit from early recurrence detection with ctDNA screening is yet to be proven. However, also preoperative ctDNA is associated with increased risk of recurrence and might be of value in defining a high-risk group.[31,32]

The most important strength of this study is the well-defined cohort of patients, all meticulously worked-up perioperatively and prospectively followed for five years postoperatively. This enables good possibilities to study incidence and treatment of metachronous liver metastases. Further, all medical records were

Table 3 Eight-year overall survival from primary tumor resection and uni- and multivariable Cox proportional hazards regression for patients with liver recurrences in the Colofol trial

	Number of patients (n = 226)[a]	8-year Overall survival (95% CI)	Univariable Cox regression		Multivariable Cox regression	
			HR (95% CI)	P	HR (95% CI)	P
Follow-up						
Low-frequency	111 (49%)	15% (9%–22%)	Ref.		Ref.	
High-frequency	115 (51%)	34% (25%–42%)	0.57 (0.42–0.78)	<0.001	0.61 (0.44–0.86)	0.004
Gender						
Males	136 (60%)	22% (16%–29%)	Ref.			
Females	90 (40%)	27% (18%–36%)	0.91 (0.66–1.24)	0.538		
Age						
0–59	55 (24%)	40% (27%–53%)	Ref.		Ref.	
60-69	98 (43%)	19% (12%–27%)	1.76 (1.16–2.66)	0.008	1.82 (1.16–2.84)	0.009
≥ 70	73 (32%)	19% (11%–28%)	1.87 (1.21–2.89)	0.005	2.04 (1.27–3.26)	0.003
BMI						
< 18.5	5 (2%)	0%	5.03 (1.96–12.9)	0.001	5.00 (1.72–14.6)	0.003
18.5–25	96 (42%)	27% (19%–36%)	Ref.		Ref.	
> 25	125 (55%)	23% (16%–30%)	1.14 (0.83–1.56)	0.420	0.93 (0.67–1.30)	0.680
Alcohol						
No alcohol	150 (66%)	26% (19%–33%)	Ref.			
Less than 3 drinks	42 (19%)	21% (10%–34%)	1.17 (0.79–1.74)	0.440		
3 or more drinks	10 (4%)	24% (5%–51%)	1.05 (0.49–2.27)	0.894		
Missing	24 (11%)					
Smoking						
No, occasionally	174 (77%)	25% (19%–31%)	Ref.			
Yes, daily	41 (18%	21% (11%–34%)	1.12 (0.76–1.66)	0.573		
Missing	11 (5%)					
Diabetes						
No	197 (87%)	25% (19%–31%)	Ref. [b]			
Yes	29 (13%)	22% (9%–38%)	0.97 (0.62–1.51)	0.877		
Primary tumour site						
Colon, other	92 (41%)	25% (17%–34%)	Ref.		Ref.	
Right side	49 (22%)	14% (6%–24%)	1.45 (0.98–2.15)	0.064	1.69 (1.10–2.60)	0.017
Rectum	85 (38%)	30% (20%–39%)	0.88 (0.62–1.25)	0.473	0.96 (0.67–1.39)	0.843
Stage						
Stage II	85 (38%)	35% (25%–45%)	Ref.		Not Included	
Stage III	141 (62%)	18% (12%–24%)	1.62 (1.16–2.25)	0.004		
T-stage						
T1-3	179 (79%)	27% (21%–33%)	Ref.		Ref.	
T4	47 (21%)	15% (7%–26%)	1.43 (0.99_2.06)	0.054	1.49 (1.00–2.21)	0.048
LNR						
Neg	80 (35%)	36% (25%–46%)	Ref.		Ref.	
> 0 – <0.1	33 (15%)	29% (15%–45%)	1.20 (0.73–1.99)	0.476	1.02 (0.61–1.72)	0.937
0.1 – < 0.25	41 (18%)	11% (4%–22%)	2.07 (1.34–3.21)	0.001	1.70 (1.07–2.69)	0.024
> 0.25	65 (29%)	17% (10%–27%)	1.68 (1.13–2.49)	0.010	1.58 (1.05–2.38)	0.030
Missing	7 (3%)					

Table 3 (*continued*)

	Number of patients (n = 226)[a]	8-year Overall survival (95% CI)	Univariable Cox regression		Multivariable Cox regression	
			HR (95% CI)	P	HR (95% CI)	P
Primary chemotherapy						
No	90 (40%)	33% (23%–43%)	Ref.			
Yes	136 (60%)	19% (13%–25%)	1.55 (1.12–2.14)	0.008		

Time measured from date of resection of the primary tumor and delayed entry of patients in the analyses at date of detection of liver metastases. Patient inclusion in the analysis was conditional on having survived the first year after the primary resection.
[a] Patients with liver metastases that died within one year of the primary tumour resection were excluded from the analysis (n = 9).
[b] The proportional hazard rates assumption was not fulfilled in the Cox proportional hazard regression and the hazard ratio should be interpreted as the mean over the 8-year period.

reviewed for all detected recurrences, although retrospectively. This study only comprises metachronous metastases and results are thus not generalizable to synchronous disease. Age and co-morbidity could influence the possibility of and outcome after curatively intended treatment. All patients in the COLOFOL trial were 75 years or younger at inclusion and had a life expectancy of more than 2 years, based on co-morbidity. Patients aged over 75 years are underrepresented in many liver resected cohorts, although relative survival for those selected do not seem to be inferior.[14,33]

A majority of all patients with liver recurrences after CRC were possible to treat with curative intent and with high survival rates. Specifically, 76% of all patients with recurrences confined to the liver were treated with curative intent with a 5-year OS of 60%. These impressive results were gained although follow-up was not extensive in neither randomization arm, which points out the importance of meticulous work-up and assessment in multidisciplinary boards. More intense follow-up might be of value in high-risk patients but needs further studies.

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This study was not preregistered in an independent, institutional registry. All methods and data are available to other researchers on request.

Conflict of interest

None to declare.

References

1. Manfredi S, Lepage C, Hatem C, Coatmeur O, Faivre J, Bouvier AM. (2006) Epidemiology and management of liver metastases from colorectal cancer. *Ann Surg* 244:254–259.
2. Engstrand J, Nilsson H, Stromberg C, Jonas E, Freedman J. (2018) Colorectal cancer liver metastases - a population-based study on incidence, management and survival. *BMC Cancer* 18:78.
3. Scherman P, Syk I, Holmberg E, Naredi P, Rizell M. (2021) Impact of patient, primary tumor and metastatic pattern including tumor location on survival in patients undergoing ablation or resection for colorectal liver metastases: a population-based national cohort study. *Eur J Surg Oncol* 47:375–383.
4. Booth CM, Nanji S, Wei X, Biagi JJ, Krzyzanowska MK, Mackillop WJ. (2016) Surgical resection and peri-operative chemotherapy for colorectal cancer liver metastases: a population-based study. *Eur J Surg Oncol* 42:281–287.
5. Stangl R, Altendorf-Hofmann A, Charnley RM, Scheele J. (1994) Factors influencing the natural history of colorectal liver metastases. *Lancet* 343:1405–1410.
6. Elferink MA, de Jong KP, Klaase JM, Siemerink EJ, de Wilt JH. (2015) Metachronous metastases from colorectal cancer: a population-based study in North-East Netherlands. *Int J Colorectal Dis* 30:205–212.
7. Wille-Jorgensen P, Syk I, Smedh K, Laurberg S, Nielsen DT, Petersen SH *et al*. (2018) Effect of more vs less frequent follow-up testing on overall and colorectal cancer-specific mortality in patients with stage II or III colorectal cancer: the COLOFOL randomized clinical trial. *JAMA* 319:2095–2103.
8. Primrose JN, Perera R, Gray A, Rose P, Fuller A, Corkhill A *et al*. (2014) Effect of 3 to 5 years of scheduled CEA and CT follow-up to detect recurrence of colorectal cancer: the FACS randomized clinical trial. *JAMA* 311:263–270.
9. Rosati G, Ambrosini G, Barni S, Andreoni B, Corradini G, Luchena G *et al*. (2016) A randomized trial of intensive versus minimal surveillance of patients with resected Dukes B2-C colorectal carcinoma. *Ann Oncol* 27:274–280.
10. Smith MD, McCall JL. (2009) Systematic review of tumour number and outcome after radical treatment of colorectal liver metastases. *Br J Surg* 96:1101–1113.
11. Mann CD, Metcalfe MS, Leopardi LN, Maddern GJ. (2004) The clinical risk score: emerging as a reliable preoperative prognostic index in hepatectomy for colorectal metastases. *Arch Surg* 139:1168–1172.
12. Fong Y, Fortner J, Sun RL, Brennan MF, Blumgart LH. (1999) Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. *Ann Surg* 230:309–318. discussion 318-321.
13. Sasaki K, Morioka D, Conci S, Margonis GA, Sawada Y, Ruzzenente A *et al*. (2018) The tumor burden score: a new "Metro-ticket" prognostic

tool for colorectal liver metastases based on tumor size and number of tumors. *Ann Surg* 267:132–141.
14. Scherman P, Syk I, Holmberg E, Naredi P, Rizell M. (2020) Influence of primary tumour and patient factors on survival in patients undergoing curative resection and treatment for liver metastases from colorectal cancer. *BJS Open* 4:118–132.
15. Kopetz S, Chang GJ, Overman MJ, Eng C, Sargent DJ, Larson DW *et al*. (2009) Improved survival in metastatic colorectal cancer is associated with adoption of hepatic resection and improved chemotherapy. *J Clin Oncol* 27:3677–3683.
16. Kawaguchi Y, Kopetz S, Panettieri E, Hwang H, Wang X, Cao HST *et al*. (2022) Improved survival over time after resection of colorectal liver metastases and clinical impact of multigene alteration testing in patients with metastatic colorectal cancer. *J Gastrointest Surg* 26:583–593.
17. Adam R, Hoti E, Bredt LC. (2010) Evolution of neoadjuvant therapy for extended hepatic metastases–have we reached our (non-resectable) limit? *J Surg Oncol* 102:922–931.
18. Homayounfar K, Bleckmann A, Helms HJ, Lordick F, Ruschoff J, Conradi LC *et al*. (2014) Discrepancies between medical oncologists and surgeons in assessment of resectability and indication for chemotherapy in patients with colorectal liver metastases. *Br J Surg* 101:550–557.
19. Folprecht G, Gruenberger T, Bechstein WO, Raab HR, Lordick F, Hartmann JT *et al*. (2010) Tumour response and secondary resectability of colorectal liver metastases following neoadjuvant chemotherapy with cetuximab: the CELIM randomised phase 2 trial. *Lancet Oncol* 11:38–47.
20. Basendowah M, Awlia AM, Alamoudi HA, Ali Kanawi HM, Saleem A, Malibary N *et al*. (2021) Impact of optional multidisciplinary tumor board meeting on the mortality of patients with gastrointestinal cancer: a retrospective observational study. *Cancer Rep (Hoboken)* 4:e1373.
21. Hansdotter P, Scherman P, Petersen SH, Mikalonis M, Holmberg E, Rizell M *et al*. (2021) Patterns and resectability of colorectal cancer recurrences: outcome study within the COLOFOL trial. *BJS Open* 5.
22. Manfredi S, Bouvier AM, Lepage C, Hatem C, Dancourt V, Faivre J. (2006) Incidence and patterns of recurrence after resection for cure of colonic cancer in a well defined population. *Br J Surg* 93:1115–1122.
23. Galandiuk S, Wieand HS, Moertel CG, Cha SS, Fitzgibbons RJ, Jr., Pemberton JH *et al*. (1992) Patterns of recurrence after curative resection of carcinoma of the colon and rectum. *Surg Gynecol Obstet* 174:27–32.
24. Malakorn S, Ouchi A, Hu CY, Sandhu L, Dasari A, You YN *et al*. (2021) Tumor sidedness, recurrence, and survival after curative resection of localized colon cancer. *Clin Colorectal Cancer* 20:e53–e60.
25. Osterman E, Glimelius B. (2018) Recurrence risk after up-to-date colon cancer staging, surgery, and pathology: analysis of the entire Swedish population. *Dis Colon Rectum* 61:1016–1025.
26. Dexiang Z, Li R, Ye W, Haifu W, Yunshi Z, Qinghai Y *et al*. (2012) Outcome of patients with colorectal liver metastasis: analysis of 1,613 consecutive cases. *Ann Surg Oncol* 19:2860–2868.
27. Landreau P, Drouillard A, Launoy G, Ortega-Deballon P, Jooste V, Lepage C *et al*. (2015) Incidence and survival in late liver metastases of colorectal cancer. *J Gastroenterol Hepatol* 30:82–85.
28. Hanna TP, King WD, Thibodeau S, Jalink M, Paulin GA, Harvey-Jones E *et al*. (2020) Mortality due to cancer treatment delay: systematic review and meta-analysis. *BMJ* 371:m4087.
29. Hansdotter P, Scherman P, Nikberg M, Petersen SH, Holmberg E, Rizell M *et al*. (2023) Treatment and survival of patients with metachronous colorectal lung metastases. *J Surg Oncol*.
30. Egenvall M, Martling A, Veres K, Horvath-Puho E, Wille-Jorgensen P, Hoirup Petersen S *et al*. (2021) No benefit of more intense follow-up after surgery for colorectal cancer in the risk group with elevated CEA levels - an analysis within the COLOFOL randomized clinical trial. *Eur J Surg Oncol* 47:2053–2059.
31. Reinert T, Petersen LMS, Henriksen TV, Larsen MO, Rasmussen MH, Johansen AFB *et al*. (2022) Circulating tumor DNA for prognosis assessment and postoperative management after curative-intent resection of colorectal liver metastases. *Int J Cancer* 150:1537–1548.
32. Nors J, Henriksen TV, Gotschalck KA, Juul T, Sogaard J, Iversen LH *et al*. (2020) IMPROVE-IT2: implementing noninvasive circulating tumor DNA analysis to optimize the operative and postoperative treatment for patients with colorectal cancer - intervention trial 2. Study protocol. *Acta Oncol* 59:336–341.
33. Booth CM, Nanji S, Wei X, Mackillop WJ. (2015) Management and outcome of colorectal cancer liver metastases in elderly patients: a population-based study. *JAMA Oncol* 1:1111–1119.

Appendix A. Supplementary data

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Paper IV

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RESEARCH ARTICLE

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Treatment and survival of patients with metachronous colorectal lung metastases

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Abstract

Introduction: The lungs are the second most common site for metachronous metastases in colorectal cancer. No treatment algorithm is established, and the role of adjuvant chemotherapy is unclear. This study aimed to map pulmonary recurrences in a modern multimodal treated population, and to evaluate survival depending on management.

Methods: Retrospective study based on the COLOFOL-trial population of 2442 patients, radically resected for colorectal cancer stage II–III. All recurrences within 5 years were identified and medical records were scrutinized.

Results: Of 165 (6.8%) patients developing lung metastases as first recurrence, 89 (54%) were confined to the lungs. Potentially curative treatment was possible in 62 (37%) cases, of which 33 with surgery only and 29 with surgery and chemotherapy combined. The 5-year overall survival (5-year OS) for all lung recurrences was 28%. In patients treated with chemotherapy only the 5-year OS was 7.5%, compared with 55% in patients treated with surgery, and 72% when surgery was combined with chemotherapy. Hazard ratio for mortality was 2.9 (95% confidence interval 1.40–6.10) for chemotherapy only compared to surgery.

Conclusion: A high proportion of metachronous lung metastases after colorectal surgery were possible to resect, yielding good survival. The combination of surgery and chemotherapy might be advantageous for survival.

KEYWORDS
follow-up, lung recurrence, prognosis, risk factors

1 | INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer globally.[1,2] Thanks to improvements over time in surgery, imaging, and chemo radio-therapy, the prognosis has significantly improved.[3,4] Between 40% and 50% of the cases develop metastases at some time point,[5] half of which are as metachronous metastases. Metastasizing disease is still associated with poor prognosis and CRC is the second most common cause of cancer-related death.[2,6] However, an increasing proportion of metastases is now treated with curative intent using multimodal treatment approaches.

Most patients are allocated to follow-up programs after primary tumor resection, aiming at detecting recurrences early to enable treatment with curative intent. The optimal design of follow-up programs is however elusive, though recent studies, among them the COLOFOL trial, suggested that there was no survival benefit of intense follow-up programs.[7–12]

The liver is the most common site for recurrences after treatment for primary CRC. Resection of liver metastases is well-established, although the role of combined chemotherapy is not fully understood.[13–15] The lungs are the second most common site for metachronous metastases. Although the incidence and pattern of lung metastases in the modern era of multimodal treatment are less known, recent studies point at an incidence between 5% and 10%.[16–18] During the last two decades, surgery has become more common in the treatment of lung metastases even if its relative value is questioned,[19–22] as lung metastases respond to chemotherapy.[15,23] Nevertheless, 5-year overall survival (OS) rates between 40% and 68% have been reported following metastasectomy of lung metastases,[24–27] suggesting that lung resection might have curative potential. Further, several studies have reported good long-term-survival rates following combined resection, or ablation, of lung and liver metastases of CRC.[28–30] The selection criteria for pulmonary metastasectomy, (i.e., number, size, uni-, or bilateral metastases) are not established, and the role of adjuvant chemotherapy is not well studied and still elusive.

The aims of this study were to map the incidence and pattern of metachronous lung recurrences following radical resection of colorectal cancer in a modern multimodal setting and to evaluate the long-term survival depending on management. Primary endpoints were pattern of lung metastases and 5-year survival after detection of lung metastases. Secondary objectives were risk factors for lung recurrence and mortality after diagnosis.

2 | METHODS

This study was based on the COLOFOL trial population. The COLOFOL trial was a prospective randomized multicenter trial including patients radically treated for CRC stage II–III in Denmark, Sweden, and Uruguay between 2006 and 2010. Patients were randomized to either low- or high frequency follow-up programs with the objectives to compare overall and cancer-specific mortality depending on follow-up regimen. At follow-up, both groups were examined with contrast-enhanced multi-slice CT-scans of thorax and abdomen and measurements of carcinoembryonic antigen (CEA). The low-frequency follow-up group was followed up at 12 and 36 months after surgery (1256 patients) and the high frequency follow-up group, at 6, 12, 18, 24, and 36 months (1253 patients). The study had few exclusion criteria and wide inclusion criteria aiming to high generalizability. A drop-out analysis verified good resemblance between the study population and the source cancer population.[31] Detailed information has been presented earlier.[32] In brief, patients had to be 18–75 years of age with a life expectancy of more than 2 years due to comorbidity. A thorough work-up to rule out synchronous tumors was mandatory, including a thoraco-abdominal CT or MRI and colonoscopy.[12]

From the COLOFOL trial population in Sweden and Denmark, all patients registered with recurrences to the lungs as first recurrence, within 5 years after primary resection were identified. The medical files were scrutinized, and time to recurrence, reason for detection, location, number of metastases, if assessed in multidisciplinary boards, aim of treatment (i.e., palliative or curative) and detailed information of all surgical and medical treatment of the recurrence were noted. This was also done for any second or third recurrence.

Data collected from the original study protocols included: age, gender, date of primary surgery, comorbidity, alcohol, and smoking habits, TNM- classification of the primary tumor and follow-up regimen according to randomization. Further, location of the primary tumor, and use of adjuvant treatment in connection to the primary operation was registered. Over-all mortality was checked by population registries in Sweden and Denmark. Time to lung recurrence was calculated from the date of surgery of the primary tumor. Follow-up time after lung recurrence was 5 years in every case.

2.1 | Statistics

Pattern of lung recurrences are presented as time to recurrence after primary surgery, and distribution of the metastases are presented as proportion of the total trial population and of lung recurrences. To test differences of distribution of lung metastases depending on patient and primary tumor characteristics, the Fisher's exact test was used.

Five-year OS was computed using the Kaplan–Meier method and also stratified on treatment strategies. Time was measured from date of detection of first lung metastases to date of death

or end of follow-up at 5 years. Restricted 5-year mean survival was also calculated to give a better impression of differences in life-span. To evaluate the impact of surgery, chemotherapy, timing, and distribution of lung metastases, as well as patient and primary tumor characteristics on survival after lung recurrence, uni-, and multivariable Cox proportional hazards regression models were used. All variables were tested with Schoenfeld's residuals and fulfilled the proportional hazards assumption. Uni- and multivariable Cox proportional regression models were also used for evaluation of risk factors for developing lung recurrences.

All variables presented above were placed in the univariable analyses. In the multivariable analyses, all collected variables from the univariable analyses were placed in the analysis and kept in the model if they were independently statistically significant or had a $p < 0.20$ and a confounding effect (i.e., effected other hazard ratios with more than 10%). When appropriate, 95% confidence intervals (CIs) are presented in parenthesis. All statistical analyses were carried out with Stata version 16.1 (Stata Corp). $p < 0.05$ were considered significant.

3 | RESULTS

Of the 2442 randomized patients included in Sweden and Denmark, a total of 471 (19%) patients developed a recurrence within 5 years after surgery of the primary CRC and 165 (6.8%) had lung metastases as first recurrence. In 89 (54%) of 165 patients the recurrences were confined to the lungs, and in 76 (46%) patients concomitant spread to other organs was present. Detailed information on the distribution of metastases is presented in Tables 1 and 2. Of the 165 patients with lung recurrences, 146 (88%) were detected within the follow-up period of 3 years (Table 1). The remaining 19 (12%) patients were detected within 5 years but later than the scheduled COLOFOL follow-up program.

The lungs were the most frequent site for first recurrence in rectal cancer (100/207, 48%) and it was significantly more common as first site of recurrence compared to colon cancer (65/264, 25%), ($p = 0.001$) (Supporting Information: Table 1). There were no significant differences in age, gender, or primary tumor characteristics between lung recurrence and other sites of recurrences, with the exception of T4 tumors, which were associated with a lower risk of lung metastases relative to other recurrences (Supporting Information: Table 1). Of 165 patients with lung recurrences, 152 (92%) were assessed in multidisciplinary boards (MDK). Sixty-two patients (38%) underwent resection with curative intent, whereas 88 (53%) received palliative chemotherapy and 15 (9%) best supportive care. Of the 89 patients with recurrences confined to the lungs, 53 (60%) underwent resection with curative intent. Only 6 of the 23 patients with concomitant recurrences to lung and liver and 3 out of 50 patients with concomitant recurrences in the lungs and any other site underwent treatment with curative intent (Table 2).

The 5-year OS for all first recurrences to the lungs was 28% (95% CI 21%–35%) (Table 1). If confined to the lungs the OS was 45% (CI 34%–55%), which was superior to recurrences in multiple organs including lungs (OS 8% (CI 3.1%–15%)) ($p < 0.001$) (Figure 1). In the 62 patients resected with curative intent, the 5-year OS was 63% (CI 50%–74%) (Table 2). In comparison, the 5-year OS in the group treated with chemotherapy only was 7% (3%–13%) ($p < 0.001$) (Figure 2 and Table 2). Numerical, but not statistically significant, differences in OS were noted in the surgically treated group depending on single, multiple, uni-lateral, or bilateral metastases confined to the lung - (Table 2). In the multivariate analysis, adjusted for distribution of metastases and reason for detection, a hazard ratio for mortality of 2.9 (CI 1.4–6.1) was noted for the nonoperated group compared to the resected group (Table 3). Of the 62 patients treated with curative intent, 33 had surgery only, with a 5-year OS of 55%, whereas 29 patients had surgery combined with chemotherapy, resulting in a 5-year OS of 72% ($p = 0.106$). In multivariable analysis (adjusted for distribution and multiples of metastases, mode of detection and location of primary tumor) the hazard ratio for mortality for the combined therapy was 0.46 (CI 0.19–1.12; $p = 0.087$) compared with surgery only (Table 3). Detection of recurrences outside scheduled examinations and recurrences in multiple organs were associated with significantly increased mortality (Table 3). Of the 62 patients treated with curative intent, 36 (58%) had a second recurrence (Table 1).

4 | DISCUSSION

The incidence of metachronous lung recurrences following radically resected stage II–III CRC was 7%, of which a high proportion (38%) was treated surgically, with or without adjuvant chemotherapy. The place for surgical resection in the treatment of lung metastases of colorectal origin is not established, but our results showed a significantly higher 5-year OS in the surgically treated group (63%) compared to the group treated with chemotherapy only (7%). Further, a possible survival benefit by the combination of metastasectomy and adjuvant chemotherapy was noted. The 5-year OS for patients treated with curative intent for lung metastases, irrespective of single or multiple metastases, treatment with surgery alone or combined with chemo, was generally higher than earlier reported.[33–36]

A large proportion (66%) of patients with metastases confined to the lungs were treated with curative intent, whereas only a sparse number of patients were treated with curative intent if concomitant spread to any other location. Even though several studies report good results by surgical treatment of combined lung and liver metastases,[30,37] in this study only 6 of 17 patients with synchronous recurrences to lungs and liver were treated with curative intent, with a 5-year OS of only 17%, which is less than reported by others.[38,39] The reason for this discrepancy was unclear, but suboptimal selection of patients and the small number of patients in the present study probably contributed. Interestingly, the 5-year OS rates in palliatively treated patients were similar irrespective of concomitant spread to the liver or not (14% vs. 12%) but higher than earlier reported.[40] The

TABLE 1 Incidence and pattern of lung metastases within 5 years following curative resection of colorectal cancer stage II and III and 5-year overall survival after detection of lung recurrences, stratified on distribution of metastases

	Number of lung recurrences (*N*)	Proportion of total population[a] (%)	Proportion of lung recurrences (%)	*p* Value[b]	5-year OS (95% CI)
All lung metastases	165	6.8	-		28 (21–35)
Lung only	89	3.6	53.9		45 (34–55)
Single met	41	1.7	24.8		66 (49–78)
≥2, unilateral	15	0.6	9.1		53 (26–74)
≥2, bilateral	31	1.3	18.8		13 (4–27)
Lung + liver	23	0.9	13.9		13 (3–30)
Lung + other location	53	2.2	32.1		6 (1–4)
Missing	2	0.1			
Time from surgery to recurrence					
<1 year	51	2.1	30.9		22 (12–34)
1 to <3 years	95	3.9	57.6		27 (19–37)
≥3 years	19	0.8	11.5		47 (24–67)
Gender					
Male	98	4.0	59.4	0.292	30 (21–39)
Female	67	2.7	40.6		25 (16–36)
Age[c]	39	1.8	27.3	0.674	33 (20–48)
0–59	68	3.1	45.4		27 (17–37)
60–69	58	1.8	27.3		24 (13–38)
≥70					
Location					
Right colon	27	1.1	16.4	<0.001	7 (1–21)
Left colon	34	1.4	20.6		18 (7–32)
Rectum	100	4.1	60.6		38 (29–47)
Other	4	0.2	2.4		0
T-stage, primary					
T1–T3	135	5.5	81.8	0.134	31 (24–39)
T4	30	1.2	18.2		13 (4–28)
Lymph node ratio (LNR), primary[d]					
0	47	2.0	28.7	<0.001	32 (19–45)
<0.1	24	1.0	14.6		38 (19–56)
0.1–0.25	39	1.6	23.8		26 (13-40)
>0.25	54	2.2	32.9		22 (12–34)

[a]*N* = 2442.
[b]Fisher's exact test.
[c]At recurrence.
[d]1 case missing data.

reason for the surprisingly small difference in survival between surgically treated and palliatively treated patients in the subgroup with concomitant liver metastases was elusive, but the relatively small numbers made the result less reliable. All patients with synchronous lymph node involvement and the vast majority of patients with synchronous spread to any other locations were treated palliatively, without any long-term survivors. The mortality hazard ratio was almost six times higher if concomitant spread to any other

TABLE 2 Treatment strategy, 5-year overall survival and 5-year restricted mean survival in metachronous lung metastases from stage II–III colorectal cancer ($n = 2442$), stratified on location and distribution of metastases

	First recurrence (*n*)	Treatment with curative intent (*n*)		Restricted 5-year mean survival months (CI)	5-year overall survival (CI)	Second recurrence[a]	Treatment with curative intent (*n*)		Third recurrence[a]
Lung metastases only	89	Yes	53	52 (48–56)	66% (52%–77%)	29	Yes	12	6
		No	36	31 (26–37)	14% (5%–27%)	-	No	17	-
Single metastasis	41	Yes	36	54 (49–58)	72% (55%–84%)	17	Yes	8	4
							No	7	-
		No	5	32 (17–47)	20% (1%–58%)	-	-		-
≥2, unilateral	15	Yes	12	48 (37–58)	58% (27%–80%)	8	Yes	1	0
							No	8	-
		No	3	29 (4–54)	33% (1%–77%)	-			-
≥2, bilateral	31	Yes	5	52 (42–60)	40% (5%-75%)	4	Yes	3	2
							No	1	-
		No	26	30 (24–37)	8% (1%–22%)	-			-
Missing	2	Yes	0	-	-	-		-	-
		No	2	45 (24–60)	-	-		-	-
Lung + liver	23	Yes	6	45 (37–53)	17% (1%–52%)	4	Yes	3	1
							No	1	-
		No	17	26 (17–35)	12% (2%–31%)	-	-		-
Lung + lymph node	7	Yes	0	-	-	-	Yes	-	-
							No	-	-
		No	7	37 (22–52)	0%	-	-		-
Lung + other	46	Yes	3	60 (60–60)	100%	3	Yes	3	2
							No	0	-
		No	43	15 (11–19)	0%	-	-		-
Total	165	Yes	62	52 (49–55)	63% (50%–74%)	36	Yes	18	9
							No		-
		No	103	24 (21–28)	7% (3%–13%)	-	-		-

[a]Any recurrence.

location in addition to the lungs, although somewhat lower after adjustment for treatment. The very poor prognosis in this group warrants studies on more refined multimodal treatment including more aggressive chemotherapy in this group of patients.

In the group of 89 patients with metastases confined to the lungs, the 5-year OS was clearly superior in the group of patients treated surgically compared to those treated with chemotherapy only (66% vs. 14%), confirmed in multivariate analyses. An increased risk of mortality was noted in the multivariable analysis for bilateral spread compared to unilateral spread but not when adjusted for treatment, indicating that bilateral spread should not be a contra-indication for surgical resection. No difference in mortality risk was noted depending on early or late detection of lung metastases. However, detection due to symptoms had a 3.5–3.9 times increased risk of mortality within 5 years after detection. This finding evoked the idea that more intense follow-up could be of value, but no difference in survival was noted due to follow-up regimen. The worse prognosis in symptomatic cases could possibly be due to worse tumor biology. The subgroup analysis of surgically treated patients compared to surgically treated combined with chemo-therapy pointed to a possible survival benefit by the addition of chemotherapy, which indicating a need for a randomized trial.

Several previous case series have shown good survival rates following surgical treatment of pulmonary metastases,[41–44] but due

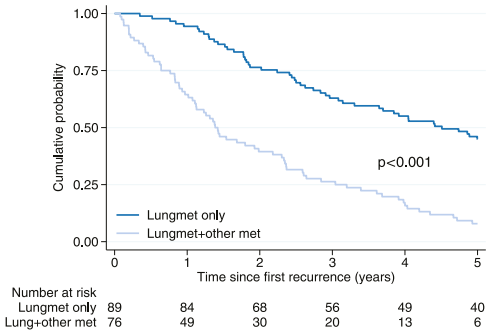

FIGURE 1 Overall survival in lung metastases as first recurrence after curative resection for stage II and III colorectal cancer stratified on lung metastases only and lung metastases + other sites of synchronous recurrences. Kaplan–Meyer curves, logistic regression.

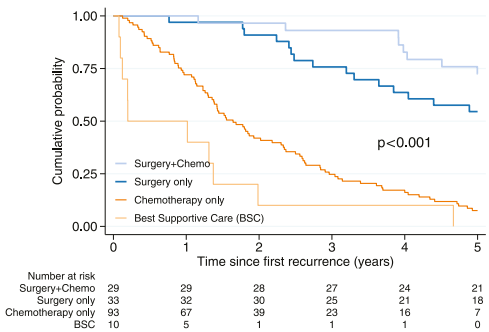

FIGURE 2 Overall survival in lung metastases as first recurrence after curative resection for stage II and III colorectal cancer stratified on treatment. Kaplan–Meyer curves, logistic regression.

the subsequent risk of selection bias and the lack of control groups the generalizability of these results is problematic. The survival figures following surgical treatment in the present cohort-based study was at least as good as previous reports and significantly better compared to the group with chemotherapy only, suggesting a survival benefit for metastasectomy. In contrast with the results of the current study, the only randomized trial, by Milosevic and co-workers,[35] reported an estimated 5-year OS after metastasectomy of 36.4%, which was not significantly better compared to the control group without treatment (29.6%). Probable explanations for these divergent results are that only a small proportion (93/419) of the eligible patients in Milosevic's trial was randomized at 2.7 years in median after primary surgery, suggesting selection bias. The high survival rate in the nontreated group supports the hypothesis that a subgroup of biologically less aggressive tumors was randomized. Moreover, some cross-over occurred, and subsequent chemotherapy was performed in the control group. The 5-year OS in the present study in a similar cohort of patients with pulmonary metastases confined to the lungs was 45%, compared to 29.6%–36.4% in Milosevic study. This superior survival in the whole group in the present study further indicated a survival benefit by the surgical treatment.

Taken together, our results show good long term survival following treatment with curative intent of metachronous lung metastases of colorectal origin confined to the lungs and a possible survival benefit by the addition of adjuvant chemotherapy. Considering the poor 5-year OS in patients with chemotherapy only or best supportive care, the findings raise the question whether indications for surgical treatment of lung metastases could be widened. These findings warrant a randomized trial evaluating the impact on survival of adjuvant chemotherapy.

The primary limitation of this study was the retrospective design, making group comparisons potentially ambiguous. This was in part compensated for by multivariable analyses adjusted for known confounding factors. Further, the influence of severe comorbidity

TABLE 3 Mortality hazard rate ratio (HR) within 5 years after date of diagnosis of lung metastases as first recurrence following curative resection of colorectal cancer stage II and III, calculated by Cox regression

	No. of patients	Univariable cox HR 95% CI		Multivariable cox HR 95% CI		Multivariable cox including treatment HR 95% CI	
Location							
Lung only, single met	14/41	1.0		1.0		1.0	
≥ 2, unilateral	7/15	1.6	0.66–4.8	2.0	0.78–4.9	1.93	0.76–4.89
≥2, bilateral	27/31	4.1	2.1–7.9	3.7	1.9–7.1	1.66	0.76–3.65
Lung + other location	70/76	6.5	3.6–12	5.7	3.1–10	2.74	1.32–5.67
Missing	1/2						
Time to recurrence[a]							
Per year	119/165	0.95	0.78–1.2				

(Continues)

TABLE 3 (Continued)

	No. of patients	Univariable cox HR 95% CI		Multivariable cox HR 95% CI		Multivariable cox including treatment HR 95% CI	
Per year group							
<1 year	40/51	1.00					
1 to <3 years	69/95	0.90	0.61–1.3				
≥3 years	10/19	0.57	0.28–1.1				
Recurrence detected by[b]							
Scheduled examination	83/125	1.0		1.0		1.0	
Symptom	23/24	4.3	2.7–7.0	3.9	2.3–6.4	3.48	2.09–5.80
Other	12/15	1.8	0.96–3.2	1.7	0.89–3.2	2.21	1.15–4.25
Follow-up							
Low intensity	59/78	1.0					
High intensity	60/87	0.87	0.61–1.2				
Gender							
Male	69/98	1.0					
Female	50/67	1.2	0.80–1.7				
Age[c]							
Per 10 years	119/165	1.2	0.94–1.5				
Per age group: 0–59	26/39	1.0					
60–69	48/68	1.2	0.94–1.5				
≥70	45/58	1.5	0.90–2.4				
Location							
Right colon	25/27	1.0		1.0		1.0	
Left colon	28/34	0.59	0.34–1.0	0.76	0.44–1.32	1.07	0.61–1.88
Rectum	62/100	0.31	0.20–0.50	0.55	0.33–0.90	0.76	0.46–1.26
Other	0/4						
T-stage (primary tumor)							
T1–T3	93/135	1.0					
T4	26/30	1.6	1.0–2.4				
Lymph node ratio (primary tumor)							
0	32/47	1.0					
<0.1	15/24	0.89	0.48–1.6				
0.1–0.25	29/39	1.1	0.66–1.8				
>0.25	42/54	1.2	0.78–2.0				
Treatment							
Surgery only	15/33	1.0				1.0	
Surgery + chemo	8/29	0.52	0.22–1.2			0.46	0.19–1.12
No surgery	96/103	4.7	2.7–8.2			2.92	1.40–6.10

Note: All variables fulfilled proportional hazards assumption (tested with Schoenfeld's residuals). Statistically nonsignificant or nonconfounding risk factors were left out from the multivariable analyses.

[a]From surgery for primary tumor.

[b]One case with missing data.

[c]At recurrence.

on survival and treatment options was limited, as this was an exclusion criterion in the COLOFOL study.

The strength of the study was the use of prospectively collected data on a very well-defined population with thorough work-up of every patient, the meticulous scrutiny of medical records in every case of reported recurrence, and that it was a cohort study including all lung metastases.

5 | CONCLUSION

This study gives a contemporary picture of the pattern of colorectal cancer lung metastases using current multimodal treatment, showing an incidence of 6.8% of metachronous lung metastases and a high proportion of resectability (38%). Five-year OS following surgical resection was encouraging (63%) and superior to chemotherapy only. Metastasectomy should be considered in metachronous lung metastases, regardless of uni- or bi-lateral spread. The addition of adjuvant chemotherapy to lung metastasectomy appears to improve clinical outcomes but needs to be verified in further randomized trials.

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DATA AVAILABILITY STATEMENT

The ethical approval for this study prohibits us from sharing any patient related data besides aggregated figures.

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REFERENCES

1. Dekker E, Tanis PJ, Vleugels JLA, Kasi PM, Wallace MB. Colorectal cancer. *Lancet*. 2019;394(10207):1467-1480.
2. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2021;71(3):209-249.
3. Birgisson H, Talbäck M, Gunnarsson U, Påhlman L, Glimelius B. Improved survival in cancer of the colon and rectum in Sweden. *Eur J Surg Oncol*. 2005;31(8):845-853.
4. Swedish colorectal cancer registry (SCRCR). Sveriges Kommuner och regioner. May 11, 2021. https://skr.se/en/kvalitetsregister/hittaregister/registerarkiv/tjockochandtarmscancer.44565.html
5. Filip S, Vymetalkova V, Petera J, et al. Distant metastasis in colorectal cancer patients-do we have new predicting clinico-pathological and molecular biomarkers? A comprehensive review. *Int J Mol Sci*. 2020;21(15):5255.
6. Guren MG. The global challenge of colorectal cancer. *Lancet Gastroenterol Hepatol*. 2019;4(12):894-895.
7. Primrose JN, Perera R, Gray A, et al. Effect of 3 to 5 years of scheduled CEA and CT follow-up to detect recurrence of colorectal cancer: the FACS randomized clinical trial. *JAMA*. 2014;311(3):263-270.
8. Grossmann EM, Johnson FE, Virgo KS, Longo WE, Fossati R. Follow-up of colorectal cancer patients after resection with curative intent-the GILDA trial. *Surg Oncol*. 2004;13(2-3):119-124.
9. Treasure T, Macbeth F. The GILDA trial finds no survival benefit from intensified screening after primary resection of colorectal cancer: the PulMiCC trial tests the survival benefit of pulmonary metastasectomy for detected asymptomatic lung metastases. *Ann Oncol*. 2016;27(4):745.
10. Egenvall M, Martling A, Veres K, et al. No benefit of more intense follow-up after surgery for colorectal cancer in the risk group with elevated CEA levels—an analysis within the COLOFOL randomized clinical trial. *Eur J Surg Oncol*. 2021;47(8):2053-2059.
11. Mant D, Gray A, Pugh S, et al. A randomised controlled trial to assess the cost-effectiveness of intensive versus no scheduled follow-up in patients who have undergone resection for colorectal cancer with curative intent. *Health Technol Assess (Rockv)*. 2017;21(32):1-86.
12. Wille-Jørgensen P, Syk I, Smedh K, et al. Effect of more vs less frequent follow-up testing on overall and colorectal cancer-specific mortality in patients with stage II or III colorectal cancer: the COLOFOL randomized clinical trial. *JAMA*. 2018;319(20):2095-2103.
13. Lehmann K, Rickenbacher A, Weber A, Pestalozzi BC, Clavien PA. Chemotherapy before liver resection of colorectal metastases: friend or foe? *Ann Surg*. 2012;255(2):237-247.
14. Nordlinger B, Van Cutsem E, Rougier P, et al. Does chemotherapy prior to liver resection increase the potential for cure in patients with metastatic colorectal cancer? A report from the European Colorectal Metastases Treatment Group. *Eur J Cancer*. 2007;43(14):2037-2045.
15. Guerrera F, Mossetti C, Ceccarelli M, et al. Surgery of colorectal cancer lung metastases: analysis of survival, recurrence and re-surgery. *J Thorac Dis*. 2016;8(7):1764-1771.
16. Hansdotter P, Scherman P, Petersen SH, et al. Patterns and resectability of colorectal cancer recurrences: outcome study within the COLOFOL trial. *BJS Open*. 2021;5(4). https://doi.org/10.1093/bjsopen/zrab067

17. Osterman E, Hammarström K, Imam I, Osterlund E, Sjöblom T, Glimelius B. Recurrence risk after radical colorectal cancer surgery-less than before, but how high is it? *Cancers*. 2020;12(11):3308.
18. Procaccio L, Bergamo F, Manai C, et al. An overview on clinical, pathological and molecular features of lung metastases from colorectal cancer. *Expert Rev Respir Med*. 2019;13(7):635-644.
19. Taylor M, Abah U, Shah R. A review of interventional treatments for colorectal lung metastases: is it time for a change in practice? *Quant Imaging Med Surg*. 2020;10(6):1413-1417.
20. Macbeth F, Fallowfield L. The myth of pulmonary metastasectomy. *Br J Cancer*. 2020;123(4):499-500.
21. Pastorino U, Treasure T. A historical note on pulmonary metastasectomy. *J Thorac Oncol*. 2010;5(6):S132-S133.
22. Van Raemdonck D, Friedel G. The European Society of Thoracic Surgeons lung metastasectomy project. *J Thorac Oncol*. 2010;5(6):S127-S129.
23. Brandi G, Derenzini E, Falcone A, et al. Adjuvant systemic chemotherapy after putative curative resection of colorectal liver and lung metastases. *Clin Colorectal Cancer*. 2013;12(3):188-194.
24. Pfannschmidt J, Hoffmann H, Dienemann H. Reported outcome factors for pulmonary resection in metastatic colorectal cancer. *J Thorac Oncol*. 2010;5(6):S172-S178.
25. Welter S, Jacobs J, Krbek T, Krebs B, Stamatis G. Long-term survival after repeated resection of pulmonary metastases from colorectal cancer. *Ann Thorac Surg*. 2007;84(1):203-210.
26. Watanabe K, Nagai K, Kobayashi A, Sugito M, Saito N. Factors influencing survival after complete resection of pulmonary metastases from colorectal cancer. *Br J Surg*. 2009;96(9):1058-1065.
27. Forster C, Ojanguren A, Perentes JY, et al. Survival prognostic and recurrence risk factors after single pulmonary metastasectomy. *J Cardiothorac Surg*. 2021;16(1):357.
28. Tsukamoto S, Kinugasa Y, Yamaguchi T, Shiomi A. Survival after resection of liver and lung colorectal metastases in the era of modern multidisciplinary therapy. *Int J Colorectal Dis*. 2014;29(1):81-87.
29. Brouquet A, Vauthey JN, Contreras CM, et al. Improved survival after resection of liver and lung colorectal metastases compared with liver-only metastases: a study of 112 patients with limited lung metastatic disease. *J Am Coll Surg*. 2011;213(1):62-69.
30. Schüle S, Dittmar Y, Knösel T, et al. Long-term results and prognostic factors after resection of hepatic and pulmonary metastases of colorectal cancer. *Int J Colorectal Dis*. 2013;28(4):537-545.
31. Hansdotter Andersson P, et al. The COLOFOL trial: study design and comparison of the study population with the source cancer population. *Clin Epidemiol*. 2016;8:15-21.
32. Wille-Jørgensen P, Laurberg S, Påhlman L, et al. An interim analysis of recruitment to the COLOFOL trial. *Colorectal Dis*. 2009;11(7):756-758.
33. Kim HK, Cho JH, Lee HY, Lee J, Kim J. Pulmonary metastasectomy for colorectal cancer: how many nodules, how many times? *World J Gastroenterol*. 2014;20(20):6133-6145.
34. Saleh W, AlShammari A, Sarraj J, AlAshgar O, Ahmed MH, AlKattan K. Surgical treatment of pulmonary metastasis: report from a tertiary care center. *Asian Cardiovasc Thorac Ann*. 2018;26(4):296-301.
35. Milosevic M, Edwards J, Tsang D, et al. Pulmonary metastasectomy in colorectal cancer: updated analysis of 93 randomized patients-control survival is much better than previously assumed. *Colorectal Dis*. 2020;22(10):1314-1324.
36. Åberg T, Malmberg KÅ, Nilsson B, Nõu E. The effect of metastasectomy: fact or fiction? *Ann Thorac Surg*. 1980;30(4):378-384.
37. Ike H, Shimada H, Togo S, Yamaguchi S, Ichikawa Y, Tanaka K. Sequential resection of lung metastasis following partial hepatectomy for colorectal cancer. *Br J Surg*. 2002;89(9):1164-1168.
38. Kobayashi K, Kawamura M, Ishihara T. Surgical treatment for both pulmonary and hepatic metastases from colorectal cancer. *J Thorac Cardiovasc Surg*. 1999;118(6):1090-1096.
39. Shimizu K, Ohtaki Y, Okumura T, et al. Outcomes and prognostic factors after pulmonary metastasectomy in patients with colorectal cancer with previously resected hepatic metastases. *J Thorac Cardiovasc Surg*. 2019;157(5):2049-2057.
40. Yang Q, Liao F, Huang Y, et al. Longterm effects of palliative local treatment of incurable metastatic lesions in colorectal cancer patients. *Oncotarget*. 2016;7(15):21034-21045.
41. Riquet M, Foucault C, Cazes A, et al. Pulmonary resection for metastases of colorectal adenocarcinoma. *Ann Thorac Surg*. 2010;89(2):375-380.
42. Dudek W, Schreiner W, Hohenberger W, Klein P, Sirbu H. Forty-two years' experience with pulmonary resections of metastases from colorectal cancer. *Thorac Cardiovasc Surg*. 2017;65(7):560-566.
43. Pfannschmidt J, Dienemann H, Hoffmann H. Surgical resection of pulmonary metastases from colorectal cancer: a systematic review of published series. *Ann Thorac Surg*. 2007;84(1):324-338.
44. Gonzalez M, Ris HB, Krueger T, Gervaz P. Colorectal cancer and thoracic surgeons: close encounters of the third kind. *Expert Rev Anticancer Ther*. 2012;12(4):495-503.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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