Peritoneal metastases among Danish patients with colorectal cancer: Aspects of risk and patient-centred care

PhD dissertation

Sissel Ravn

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Health
Aarhus University
Department of Surgery, Aarhus University Hospital, Denmark

Supervisors

<u>Main supervisor</u>

Professor Lene Hjerrild Iversen, MD, PhD, DMSc

Department of Surgery

Aarhus University Hospital

Denmark

<u>Co-supervisors</u>

Henriette Vind Thaysen, RNSc, PhD

Department of Surgery

Aarhus University Hospital

Denmark

Professor Lene Seibaek

Department of Gynaecology and Obstetrics

Aarhus University Hospital

Denmark

Victor Jilbert Verwaal, MD, PhD

Department of Surgery

Aarhus University Hospital

Denmark

Evaluation committee

Professor, Senior Consultant of Gynaecological Cancer Pernille Tine Jensen (chairman)

Department of Gynaecology and Obstetrics

Aarhus University Hospital

Denmark

Professor of Gastrointestinal and Oncology Surgeon Pieter J. Tanis

Department of Surgery G6-254, Amsterdam University Medical Centres

The Netherlands

Professor, Consultant Oncologist Helle Pappot

Department of Oncology,

Rigshospitalet, Copenhagen

Denmark

Preface

When I was first involved in research at the end of medical school, honestly, the motivation was to break away from the books. I had no idea about the adventure I was facing.

First, a special thanks to *Sanne*; without you, I would not have had a position at the Surgical Research Department. I admire your drive and compassion, and I appreciate every piece of advice from you.

Lene, I was coincidentally placed in the corner of your office, and I must admit that my palms were sweating; and I felt performance anxiety creeping in. From the very start, I deeply admired your academic and clinical work. As I have been granted the opportunity to work with you, I have come to admire you even more for your persistence, your thorough considerations, your effort and attention to every detail, but most of all your personality. Thank you for providing me with this unique opportunity to do research; I could not have wished for anyone better to lead my path and educate me into the world of academia. I sincerely hope for future clinical and academic collaboration.

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My beloved *Laust*, thank you for your endless support, academic discussions and for carrying the burden of having my manuscripts proofread.

This PhD is based on following four publications

Paper I

Ravn S, Christian F. Christiansen, Rikke H. Hagemann-Madsen, Victor J. Verwaal, Lene H. Iversen.

The validity of registered synchronous peritoneal metastases from colorectal cancer in the Danish medical registries. *Clin Epidemiology* 2020; 12: 333-343

Paper II

Ravn S, Heide-Jørgensen U, Christiansen C.F , Verwaal V.J, Hagemann-Madsen R.H, Iversen L.H

A nationwide cohort study on the overall risk and risk factors for metachronous peritoneal metastases after colorectal cancer surgery. *BJS Open* 2020; 4: 284-292

Paper III

Ravn S, Thaysen H.V, HIPEC ePRO collaborative, Seibaek L, Verwaal V.J, Iversen L.H

Cancer follow-up supported by electronic patient-reported outcomes: Development and implementation. *Submitted to J Patient Rep Outcomes*, August 2020

Paper IV

Ravn S, Thaysen H.V, Verwaal V.J, HIPEC ePRO collaborative, Seibaek L, Iversen L.H

Cancer follow-up supported by Patient-reported outcomes in patients undergoing intended curatie complex surgery for advanced cancer. *Submitted to J Patient Rep Outcomes*, August 2020

Abbreviations

CCI	Charlson Comorbidity Index
CCR	Completeness of cytoreduction
ctDNA	Circulating tumour DNA
CI	Confidence interval
CIP	Cumulative incidence proportion
CRC	Colorectal cancer
CRS	Cytoreductive surgery
CT	Computed tomography
DCCG	Danish Colorectal Cancer Group
DNPR	Danish National Patient Registry
DNPatR	Danish National Pathology Registry
EMVI	Extramural venous invasion
EORTC	European Organisation for Research and Treatment of Cancer
ePRO	Electronically collected patient-reported outcomes
HIPEC	Hyperthermic intraperitoneal chemotherapy
HRQoL	Health-related quality of life
ICD	International Classification of Diseases
IQR	Interquartile range
OC	Ovarian cancer
MDT	Multidisciplinary team
MRI	Magnetic resonance imaging
M-PM	Metachronous peritoneal metastases
NOMESCO	Nordic Medico-Statistical Committee's Classification of Surgical Procedures
PAM	Patient activation measure
PCI	Peritoneal Cancer Index
PET	Positron emission tomography
PI	Patient involvement
PM	Peritoneal metastases
PPV	Positive predictive value
PRO	Patient-reported outcomes
RCT	Randomised clinical trial

RD   Risk difference

SNOMED   Systematized Nomenclature of Medicine

S-PM   Synchronous peritoneal metastases

TNM   Tumor, Node, Metastases

UICC   Union for International Cancer Control

Indholdsfortegnelse

1. Introduction

The past few years have seen advances in the treatment of metastatic cancer and therefore a growing number of cancer survivors. Curative treatment has become an option for selected patient groups with limited peritoneal metastases (PM) of gastrointestinal origin, wherefore growing of early detection attention is now being paid to low- and high-risk patients in general and investigation into strategies for PM in particular. Improvements in surgical and medical cancer treatment have been accompanied by a stronger focus on quality of patient care driven by patients, healthcare professionals and current healthcare policies alike. Patient-centred care has been introduced as a model of care that respects the patient's needs, values, experience and preferences in the delivery of care and hence as a means to improve the quality of care. Patient involvement (PI) is a strategy to achieve patient-centred care in the healthcare system, yet has barely been investigated in populations with advanced cancer treated with complex surgery. The present dissertation focuses on different aspects of PM including epidemiological aspects of risk and risk factors for PM following colorectal cancer (CRC) and aspects of patient-centred care for patients with PM.

2.0 Background

2.1 Colorectal cancer

CRC is the one of the most prevalent cancers in the industrialised part of the world [1,2]. The primary curative treatment option for this disease is surgery [3]. During the past 20 years, survival from CRC has improved significantly across all age groups [2,4,5]. These improvements are most likely attributable to improvements in early diagnosis, advancements in diagnostic methods (radiology and awareness), resort to multidisciplinary team-based treatment decision-making[6] and general improvements in treatment strategies[7]. Other explanatory factors include the introduction of total mesorectal[8-10] and mesocolic[11,12] resection, lymphadenectomy and central vascular ligation[12,13] improved oncological treatment[4,14] and better pathological evaluations[15,16]. Finally, specialisation and centralisation in regards to radiological diagnosis, oncological and surgical treatment and pathological evaluation have also improved the prognosis for patients with CRC[17-19]. Despite these improvements, metastatic disease still occurs in nearly 20-25% within 5 years after CRC surgery[20-23]. The prognosis differs according to the site of the metastatic spread[24]; yet the overall survival of patients with metastatic CRC has also improved, most likely due to the improvements outlined above [14,25-28].

2.1.1 Staging of colorectal cancer

Colorectal tumours are evaluated using the Tumor, Nodes, Metastases (TNM) classification of the Union for International Cancer Control (UICC)[29]. The T category describes the invasion depth of the primary tumour, the N category determines the degree of lymph node involvement and the M category describes the presence of distant metastases[30,31]. Based on the TNM assessment, a colorectal tumour is staged as I-IV based on the TNM categories[32].

2.2 Peritoneal metastases: Pathophysiology and diagnosis

PM are spread of malignant cells to the peritoneal surface, most often originate from various intra-abdominal organic sites, e.g. gastrointestinal cancers such as colorectal, appendiceal, gastric or pancreatic cancer, or gynaecological cancers such as ovarian tumours [33,34]. In some cases, PM occur from mucus-producing tumour cells affecting the peritoneum, referred to as pseudomyxoma peritonei[35,36]. Additionally, in rare cases, the cancer cells may develop in the peritoneum itself, in which case they are called malignant peritoneal mesothelioma or primary peritoneal cancer [37].

The term PM is often used interchangeably with peritoneal carcinomatosis. Throughout the present dissertation, the focus will be on peritoneal metastases originating primarily from CRC and to a much lesser extent from ovarian cancer. PM will be the preferred terminology.

Several pathogenic mechanisms are proposed to contribute to the spread of CRC cells into the intraperitoneal cavity. First, like other cancer cells, blood and lymphatic vessels are common metastatic pathways. Second, free tumour cells may either disseminate into the peritoneal cavity by direct transcoelomic growth or perforation of the primary tumour. Third, cancer cells can be seeded during resection of the tumour due to incomplete resection margins, iatrogenic perforation of the tumour or efflux of dissected blood and/or lymph vessels [38-42].

Anatomical and physiological features of the peritoneal cavity enhance the development of PM; these features include the extensive peritoneal area, the presence and transport of peritoneal fluid and the presence of adipose tissue with spots comprised of immune cells, stromal cells and capillary beds (e.g. the greater omentum) [39,43-46]. Finally, molecular and genomic pathways of CRC cells further predispose to PM[43,47].

2.2.1 Extent of peritoneal metastases and classification indices

The extent of PM can be assessed by different classification indices[48,49]. These indices include the Peritoneal Cancer Index (PCI)[50] or the Dutch 7 Region Count Score[51] (Figure 1). The PCI was introduced in the 1990s by Sugarbaker and combines tumour burden size and distribution[50]. The PCI divides the abdominal cavity into 13 regions (Figure 1). In each region, the largest tumour nodule is assessed. The PCI is a tool used to predict the prognosis, which is highly dependent on the score count [52,53]. In comparison, the Dutch 7 Region Count Score is simpler, divides the abdominal cavity into seven regions and takes absence or presence of PM into account[51]. The PCI is the most frequently used assessment[49].

Figure 1. *The extent of peritoneal involvement assessed by the Peritoneal Cancer Index (PCI) (left) and The Dutch 7 Region Count Score (right).*
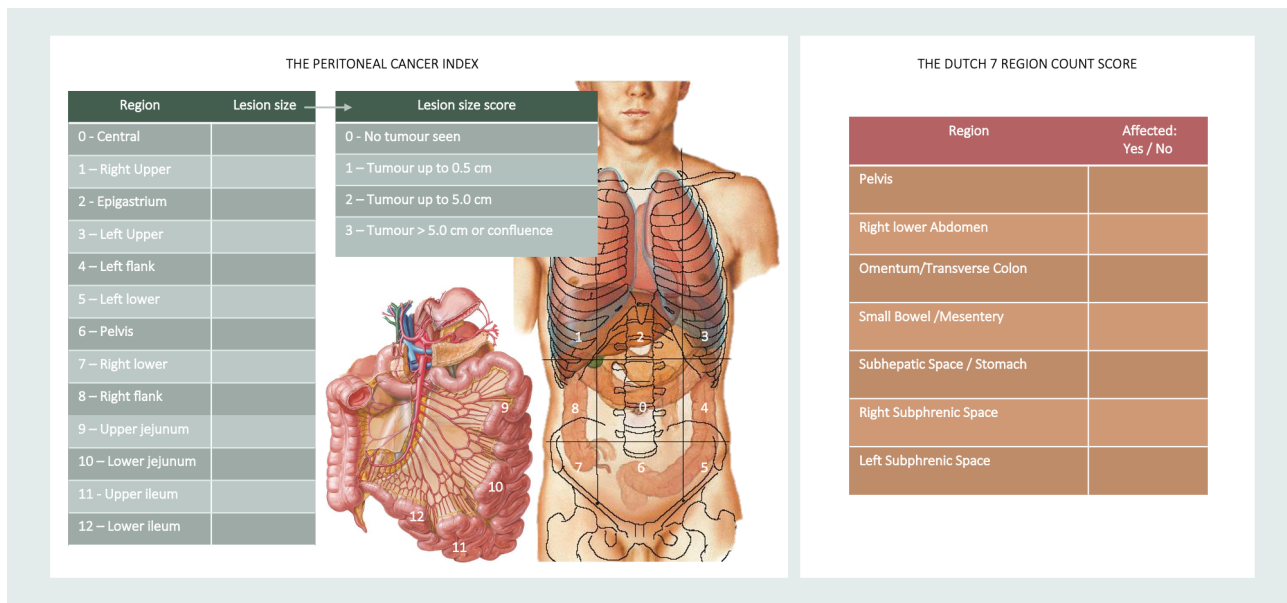
References:

[50] Jacquet P, Sugarbaker PH. Clinical research methodologies in diagnosis and staging of patients with peritoneal carcinomatosis. Cancer Treat Res. 1996;82:359-374

[51] Verwaal VJ, van Tinteren H, van Ruth S, Zoetmulder FA. Predicting the survival of patients with peritoneal carcinomatosis of colorectal origin treated by aggressive cytoreduction and hyperthermic intraperitoneal chemotherapy. Br J Surg. 2004;91(6):739-746.

2.2.2 Detection and diagnosis of PM

The diagnosis of PM and the evaluation of the peritoneal extent is challenging. Different imaging techniques, such as contrast-enhanced computed tomography (CT) and magnetic resonance imaging (MRI) are reported with a varying sensitivity. In a systematic review and meta-analysis from 2017, Laghi et al.[54] investigated the pooled sensitivity of CT and MRI in patients with PM of both gastrointestinal, gynaecological and other origins . The pooled sensitivity of CT was reported between 83% (95% confidence interval: 79-86%), whereas the pooled sensitivity of MR was reported to be 86% (95% confidence interval: 78-93%) [54]. In a review by Koumpa et al. from 2019, the sensitivity of CT to detect PM from CRC has been reported between 11-96%[55]. Both reviews found that the CT sensitivity differs according to region, e.g. a higher sensitivity in the epigastrium (region 2) and pelvis (region 6)), whereas regions like the upper jejunum (region 9), the small bowel and its mesenterium demonstrated a low sensitivity [54,55]. Several limitations complicate the generalisability of these imaging studies. First, the sensitivity measure of MRI is based on few

studies. Second, not all studies offered histopathological verification of the PM diagnosis. Third, differences were seen in imaging methodologies and variables, i.e. scanner and acquisition for protocols, MRI sequences and the investigating radiologist's experience[54]. It has been demonstrated that the CT estimation of the PCI significantly underestimates the surgical PCI[56], yet among the several imaging techniques available CT is recommended as the first choice to diagnose PM[57-60].

2.3 The epidemiology of peritoneal metastases
2.3.1 Terminology

Incidence

Incidence is a measure of the frequency of an outcome (i.e. disease, symptom or condition) and is expressed as the proportion of new cases of the outcome of interest occurring within a specified time period in a population initially free of the outcome[61]. Incidence is often reported as a proportion of diseased persons per time period (i.e. the cumulative incidence proportion (CIP), where each person contributes with a different observation time depending on the time of the event of interest and competing events.

Risk

The absolute risk is defined as the probability that an individual develops an event/outcome (i.e. disease), and the term is used interchangeably with incidence. Factors that increase the probability of the outcome are termed risk factors and can be characterised as modifiable/non-hereditary (e.g. dietary, lifestyle or obesity) or non-modifiable/hereditary (e.g. sex, age)[62]. To describe the attributable risk related to specific risk factor, the risk difference (i.e. subtraction of risks) is used as the measure of effect, whereas the relative risk (i.e. dividing of risks) describes the likelihood of disease among exposed relative to the non-exposed individuals[63].

Synchronous vs. metachronous peritoneal metastases from colorectal cancer

The presence of metastases at the time of diagnosis of primary CRC is referred to as synchronous CRC; the development of metastases after curative resection of primary CRC is referred to as metachronous CRC. Still, no international consensus definition exists [64,65] and the prognostic impact of this distinction remains unclear [65,66]. Regarding PM, synchronous PM (S-PM) is defined as metastases present at the time of diagnosis of primary CRC with a variance of up to 6 months reported throughout the literature, whereas metachronous PM (M-PM) is defined as recurrence in

the peritoneum diagnosed in the follow-up period after surgery for CRC [64,65]. The distinction between S-PM and M-PM in different studies is depicted in Figure 2.

Figure 2. *The reported distinction (days) between synchronous peritoneal metastases (S-PM) and metachronous peritoneal metastases (M-PM) following colorectal cancer (CRC). The time of CRC diagnosis is assessed as 0.*
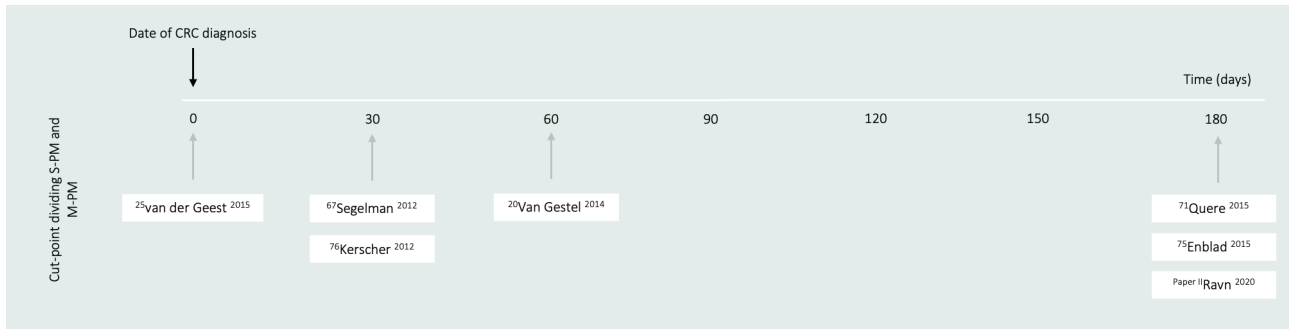
Throughout this dissertation, an interval of 6 months (180 days) is used to distinguish between S-PM and M-PM.

2.3.2 The prevalence of synchronous peritoneal metastases

The prevalence of S-PM has primarily been investigated in population-based studies and reported within a range of 4.2% [67]to 4.8% [68]. In some single-centre studies, a slightly higher prevalence of 8% has been reported[69].

2.3.3 The risk of metachronous peritoneal metastases

The incidence of M-PM has been described previously; however, the wide range in the reported incidence of M-PM may be attributed to the diversity of study methods and study populations. In population-based studies, incidences ranging between 3.5% [70] with a median follow-up time of 18 months from CRC to M-PM diagnosis, 4.2% with a median follow-up of 16 months and rising to 5.5% within 5 years[71] has been reported. In clinical trials, the risk of M-PM is reported to reach 19% of asymptomatic patients followed after curative CRC surgery[72,73]. In comparison, M-PM has been demonstrated at an incidence of 44% in patients curatively treated for CRC who became symptomatic in the follow-up period [72,74].

2.4 Risk factors for peritoneal metastases

Specific risk factors for PM have been investigated in both registry-based population studies [67,68,70,71,75], and prospective observational studies [69,76] as outlined in Table 1. Overall, population-based studies agree that several risk factors may exist simultaneously; advanced tumour and lymph node category, tumours located in the colon (mostly right-side colonic cancers), younger age (<60 years), emergency surgery due to perforation or obstruction, positive resection margins (R1/R2) and histological subtypes such as mucinous adenocarcinomas [67-71,75,76]. There is international disagreement as to whether the presence of synchronous ovarian metastases and synchronous PM should be considered a risk factor for PM [40,77]. Inversely, it has also been stated that these factors should not be considered risk factors for PM recurrence, but rather as indication of presence of S-PM and hence indication for curative treatment[78].

2.4.1 Methodological considerations

Several methodological differences should be taken into consideration in the comparison of risk factors. First, as listed in Table 1, the studies distinguish between S-PM and M-PM, which introduces potential misclassification bias. Second, the use of different inclusion criteria among patients subjected to investigation for M-PM leads to different incidences and risks of PM, which inhibits comparison. For example, Segelman et al. included patients with histopathologically uncertain radicality, tumour-involved resection margin with macroscopic radical surgery (R1) and non-microscopic resections (R2)[67]. Third, the diagnostic methods for establishing M-PM differ among the studies, resulting in different diagnostic sensitivities. Finally, risk factors are investigated in populations from different time periods, which may introduce actual differences due to improvements in diagnostic methods and treatment possibilities; however, it should be taken into consideration that definitions and classifications of investigated risk factors might have changed/developed, too.

2.5 Treatment of peritoneal metastases

The management of PM has evolved in recent decades [79,80]. Historically, PM has been considered an end-stage disease with a poor prognosis. However, the past decades have seen the introduction of curatively intended treatment of PM, which has improved long-term survival.

Treatment of patients with PM is categorised as follows: 1) no treatment, 2) symptom-directed surgery (palliative), 3) systemic chemotherapy with or without palliative surgery, 4) curatively

Table 1. *Prospective cohort studies and population-based studies investigating the prevalence of synchronous peritoneal metastases (S-PM), the incidence of metachronous peritoneal metastases (M-PM) and risk factors for both S-PM and M-PM.*

Author	Design and setting	Study population	Diagnosis of PM	Follow-up	[1] Definition [2] Risk (%)		Risk factors	
					Synchronous PM	Metachronous PM	Synchronous PM	Metachronous PM
Jayne [ref] 2002	- Singapore - Prospective single-centre study - 1989-1999	- CRC patients - Stage I-IV (n=2,756)	- Extracted from a departmental database Diagnostic method: - Macroscopy at laparotomy - CT (routine staging) - CT (symptomatic patients)	-Postoperative 3-monthly outpatient assessment -Postoperative routine CT at 1 year	[1] PM at initial presentation of CRC [2] 7.8 %	[1] PM > initial 'curative' CRC resection [2] 5.3%	NA	- Liver metastases - Tumour stage - Lymph node stage - Venous invasion - Perineural invasion
Lemmens [ref] 2011	-The Netherlands - Population-based cohort study -1995-2008	- CRC patients (n=18,738)	- Information extracted from Eindhoven Cancer registries	NA	[1] NA [2] 4.8%	NA	- <60 years -Right colon - T4-category -Increasing N-category -Poor/moderate differentiation -Mucinous adenocarcinoma	NA
Segelman [ref] 2012	- Sweden - Population-based cohort study - 1995-2007	- CRC patients (n=11,124) - Stage I-III -R0, R1 and R2 resection of primary CRC	-Information extracted from registries with data on follow-up and recurrence. Diagnostic method: -Macroscopy at surgery -Histopathology -CT	-Followed until death or 2010 - Median follow-up of 16 (1.4-142) months	[1] PM < 30 days from CRC [2] 4.3 %	[1] >30 days from CRC [2] 4.2 %	NA	- Colonic cancer (particularly right-side) - Advanced tumour category (T3 + T4) - Advanced lymph node category - Emergency surgery - Non-radical resections *(hazard ratios)*

			-Cytological examination of ascites					
Kerscher [ref] 2013	-Germany -Prospective single-centre study -1986-2009	-CRC patients (n=2,406) -Stage I-IV + unknown stage -	Diagnostic method: - Macroscopy at laparotomy - CT (routine staging) - CT (symptomatic patients)	-Followed until October 2010 -3-monthly outpatient assessment -CT 3 or 6 months after surgery, subsequently 1 year -Median follow-up: S-PM: 6.9 months M-PM: 28.0 months	[1] PM < 30 days from CRC [2] 4.8 %	[1] PM >30 days from CRC - symptomatic at follow-up [2] 5.9 %	NA	- age<62 years - T4-category - N2-category - Left colonic tumours - Appendix tumours (hazard ratios)
Van Gestel [ref] 2013	- The Netherlands - Population-based cohort study - 2003-2008 -	- CRC patients (n=5,671) - M0 disease - Curative resection (R0/R1/unknown)	Diagnostic method: -Histopathology -Imaging -Intraoperative -Clinical symptoms	-Follow-up in 2010-2011 -Median time to diagnosis: 18 months (range: 2.5-88)	[1] < 2 months from CRC [2] NA	[1] ≥ 2 months from CRC [2] 3.5 %	NA	- Colonic tumours - T4-category - Positive lymph node category - Primary mucinous adenocarcinoma - Positive resection margin (hazard ratios)
Quere P 2015	- France -Population-based cohort study - 1976-2011 - 1976-2007	-Total: CRC patients (n=9,148) -CRC patients at risk of M-PM (n=4410)		[1] Followed up to 5 years after CRC from 1976-2012 [2] Cumulative incidences at 1, 3 and 5 years [2] Regular surveys	[1] <6 months from CRC [2] 7% (n=626/9148)	[1] ≥ 6 months from CRC [2] 1-year: 1.2% 3-year: 4.5% 5-year: 5.5%	- Women - Mucinous adenocarcinoma - Obstruction or perforation	-TNM stage II and III -Macroscopic growth with infiltration or ulceroinfiltration -Mucinous adenocarcinoma -Obstruction or perforation
Enblad [ref] 2018	-Sweden -Population-based cohort study -2007-2015	-CRC and appendiceal cancer patients (n=35,120) (n=27,225)	-Information extracted from registries with data on follow-up and recurrence. Diagnostic method: -Macroscopy at surgery -Histopathology	Followed until M-PM, death or end of follow-up	[1] <6 months from CRC [2] 2.5%	[1] ≥ 6 months from CRC [2] 5-year cumulative incidence 2.0%	COLONIC TUMOURS - Female - <60 years - Right colon - T3- and T4-category - N1- and N2-category	COLONIC TUMOURS -Right colon -T4-category -N1- and N2-category -Venous invasion -Mucinous tumour

| | -Bowel resection (R0, R1-R2, R?, RX) -2007-2015 | -CT -Cytological examination of ascites | | - Perineural invasion - Vascular invasion - Mucinous tumour - Emergency surgery | -Emergency surgery |

intended treatment with cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC).

In a Dutch population-based study including 4,430 patients diagnosed with S-PM from CRC in the period from 2005-2012, treatment of patients with PM was distributed as followed: 25% were untreated, 23% received palliative surgery, 45% were treated with systemic chemotherapy with or without palliative surgery and 7% received CRS+HIPEC [80].

During the past decades, treatment with systemic chemotherapy has improved, and its application in the management of patients with PM has increased significantly[81]. Systemic chemotherapy is applied in the management of PM to prolong life and prevent aggressive progression[82-86].

PM resection alone is not considered a curative treatment of PM and is rarely applied [42,87]. However, resection is restricted to palliative or debulking (i.e. reduction of tumour volume) procedures, e.g. defunctioning stoma and/or bypass resection of obstructed intestines[88].

2.5.1 Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy

Currently, the only curative option is CRS and HIPEC. Both nationally and internationally, CRS+HIPEC is offered as a standard treatment to manage PM [89-91].

At most CRS+HIPEC centres, the preoperative assessment includes a CT scan of the thorax, abdomen and pelvis supplemented with a colonoscopy [90,92]. In Denmark, potential candidates are referred to the National CRS+HIPEC centre and evaluated at a multidisciplinary team (MDT) conference. At the MDT conference, surgical oncologists, radiologists, pathologists and oncologists, all specialised in CRS, decide on CRS+HIPEC treatment taking into account any patient characteristics and the preoperative assessment of the extent of PM.

The CRS procedure is initiated with a laparotomy and a thorough exploration of the peritoneal extension of the PM as measured by the PCI (a PCI $\geq$ 15 is considered a contraindication)[92]. It has been suggested that nearly 25% of patients subjected to CRS+HIPEC only receive an open-close procedure [93]. Obviously, the number of patients receiving such a procedure depends on the diagnostic and selection criteria applied. The principle of CRS is based on excision of all visible macroscopic tumour tissue, i.e. excision of the parietal peritoneum and resection of the visceral peritoneum-requiring organs[94]. Tumour elements of a maximum of 2.5 mm are allowed to be left in the intra-abdominal cavity, and after the CRS, the HIPEC is flushed. There are different chemotherapeutic agents for HIPEC, and the flushing time differs according to these[82,95].

Both neoadjuvant (preoperative) and adjuvant chemotherapy (postoperative) are often and widely used in patients undergoing CRS+HIPEC; yet evidence for the usefulness of this approach is limited to inconclusive observational studies [96]. To gain evidence-based knowledge on the topic, results from the randomised clinical trial (RCT) CAIRO-6 (Clinicaltrials.gov: NCT02758951) must be awaited. The CAIRO-6 trial investigates oncological outcomes (i.e. feasibility and safety, radiological and histopathological response and survival outcomes) of perioperative chemotherapy (neoadjuvant systemic therapy and adjuvant systemic therapy) and CRS+HIPEC versus upfront CRS+HIPEC alone[97].

A Dutch population-based study from 2016 has demonstrated that since the introduction of CRS+HIPEC in the period 2005-2009, the proportion of treated patients rose from 10% to 23% from 2010 to 2014[81]. The CRS+HIPEC procedure has been demonstrated to be cost-effective [98-100].

2.5.2 Postoperative morbidity and mortality

A number of factors, including the extensiveness of the CRS procedure[101] in combination with HIPEC, the expertise and experience of the institution[102], patient comorbidity and characteristics such as peritoneal extent[103], previous surgery and previous chemotherapy contributes to the postoperative morbidity[104]. Throughout the literature, morbidity has been reported to vary widely[73,105,106]. In a systematic review from 2016, Baratti et al. included one RCT and several cohort and comparative studies, reporting a high morbidity of 17.6-52.4%, i.e. a weighted average of 32.6%, however, specific complications were not detailed[73].

The mortality following CRS+HIPEC has been reported at different time points. The 30-day mortality has been investigated in different clinical trials and reported at around 1.6%, whereas the overall treatment-related 1-year mortality rate has been reported at 4.9%[107].

2.5.3 Patient selection, indications and contraindications

CRS+HIPEC is offered to patients with PM originating from CRC, appendix cancer (including goblet cell carcinoid), PM from small bowel cancer, pseudomyxoma peritonei and malignant peritoneal mesothelioma. CRS is performed if a complete cytoreduction leaving any remaining residual tumour < 2.5 mm is possible. Selection of potential candidates for this procedure is crucial to optimise and improve outcomes such as postoperative morbidity, mortality, recurrence and survival[108,109]. Patients are selected thoroughly based on following exclusion criteria's:

- Physiological age > 75 years
- ASA score $\geq$ IV (American Society of Anaesthesiologists)
- WHO performance status $\geq$ 2
- Disseminated disease
    - $\geq$ 4 non-curable liver metastases with a size > 3cm
    - >2 non-curable lung metastases
    - Other distant metastases (excluding abdominal wall metastases)
- PCI score $\geq$ 15, or $\geq$ 12 if curable liver metastases are present
- Dutch 7 region count score > 5
- PM involving caput pancreas
- Biliary obstruction

Currently, patients are selected based on a preoperative CT scan along with an MDT conference [110]. As described, no imaging technique has demonstrated its superiority. Therefore, a diagnostic laparoscopy may be used for direct visualisation of the peritoneal surface to determine the PCI and resectability. A diagnostic laparoscopy has been demonstrated to be safe and feasible for determining the PCI and surgical respectability, thereby avoiding unnecessary explorative laparotomies [55,111-114]. Critics of this approach have demonstrated an increased risk of port site metastasis following this procedure[115], indicating the increased risk of complications, and they have questioned the diagnostic accuracy compared to that of open surgery[116].

2.6 Survival of PM from CRC
Despite the introduction of CRS+HIPEC to a highly selected group of patients, many patients with PM remain untreated or are treated with systemic chemotherapy (with or without symptom-directed surgery)[81,117] .
Patients diagnosed with PM from CRC and left untreated are reported to have a median overall survival of around 5-6 months [83,117]. Evidence for systemic chemotherapy in the treatment of PM is sparse because patients in palliative treatment are rarely enrolled in such investigation [14,84].
Results from a database study including 10,553 patients with metastatic CRC enrolled from 14 RCTs investigating the effect of first-line systemic chemotherapy demonstrated that patients with PM have significantly shorter overall survival than those with other isolated sites of metastases, like the liver or the lungs; yet the presence of PM negatively impacts survival in patients with multiple

metastases[84] In summary, even with new, targeted chemotherapy, patients with PM have a poor overall survival[84].

Throughout the literature, existing evidence of a beneficial survival outcome from CRS+HIPEC is based on a single completed RCT [118], few well-designed case-control studies[119,120] and several case series[121]. As demonstrated in Figure 3, the RCT and the case-control studies report a beneficial overall survival effect of CRS+HIPEC compared with systemic chemotherapy. Results from these studies are displayed in Figure 3, and they demonstrate a median overall survival from CRS+HIPEC ranging from 22.2-62.7 months. In comparison, the median overall survival in the control groups in these trials is reported within a range of 12.6-23.9 months when patients were treated with systemic chemotherapy (Figure 3).

Although CRS+HIPEC is considered a well-established treatment for PM of gastrointestinal origin, the effect of HIPEC has not been analysed and standardisation of numerous of HIPEC modalities is lacking [122]. In a RCT (Clinicaltrial.gov: NCT00769405) published in abstract form in 2018[123], Quenet et al. compared 265 patients with CRC and isolated PM from 17 experienced institutions across France. Patients were randomised to CRS in combination with systemic chemotherapy or CRS+HIPEC. The trial demonstrated a median overall survival of 41.2 months (95% CI 35.1-49.7) in patients receiving CRS in combination with systemic chemotherapy, while patients receiving CRS+HIPEC experienced a median overall survival of 41.7 months (95% CI: 36.2-52.8) (hazard ratio = 1.00 (95% CI: 0.73-1.37))[123]. Quenet et al. performed a sensitivity analysis, demonstrating that overall survival and recurrence-free survival were significantly higher in the HIPEC group when considering patients with a PCI score between 11 and 15[123]. The trial has confirmed the use of CRS in the management of patients with PM, and initiated discussion of the role of HIPEC in the treatment of PM[123-125].

Figure 3. *Existing evidence of a survival outcome from cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) compared to systemic chemotherapy (SC). Following are listed from left to right: Author, treatment, median overall survival and methodological considerations.*
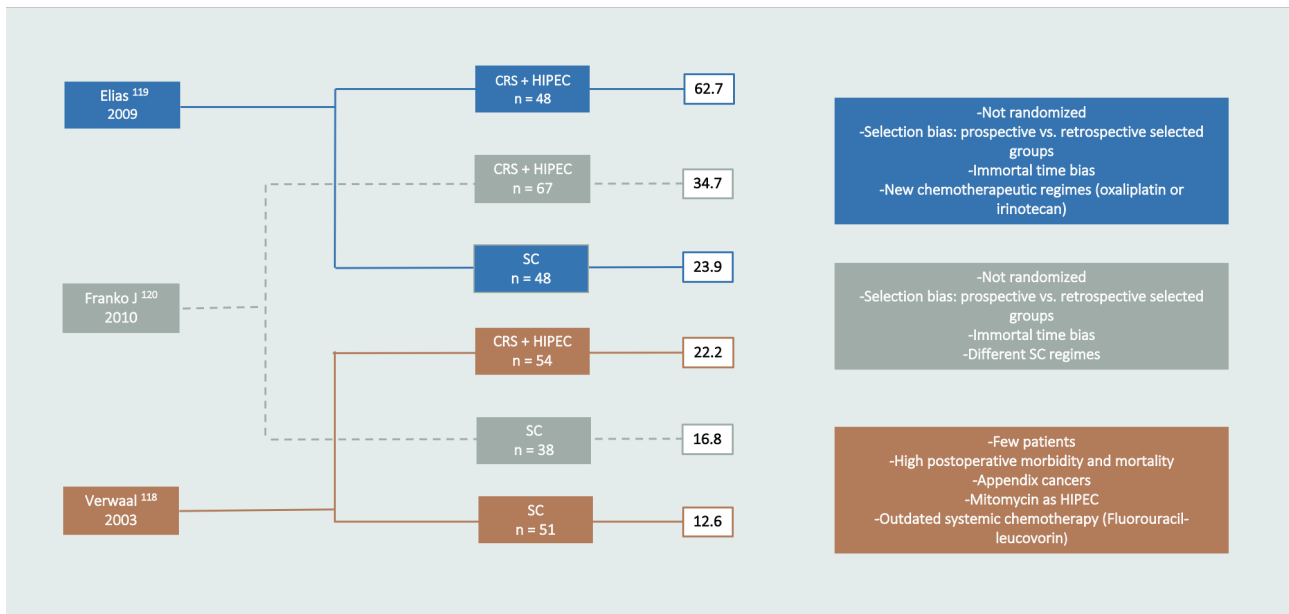
2.6.1 Methodological considerations regarding survival from CRS+HIPEC

Despite the results depicted in Figure 3 favouring CRS+HIPEC over systemic chemotherapy, several methodological differences complicate a direct comparison between the studies performed by Verwaal et al.[118], Elias et al.[119] and Franko et al[120]. As the studies were performed in different time periods, one of the primary differences is that the administration of different systemic chemotherapy regimens at that time was considered the best available treatment[105]. Developments and improvements in treatment options naturally introduce a bias that cannot be adjusted for, but these factors must be taken into account in the interpretation of the results [126].

Both Elias[119] and Franko[120] (performed case-control studies. In the nature of these study designs, groups were not randomised but selected. The selection was performed differently; in both studies, the HIPEC group was prospectively registered due to consecutive treatment, whereas the control group (systemic chemotherapy group) was retrospectively selected through registries. This introduces selection bias because patients selected for the study were diagnosed with resectable PM from CRC without any extraperitoneal disease. Finally, the survival analysis in both studies was initiated at the time of diagnosis of PM; yet the definition of the treatment groups (HIPEC vs. systemic chemotherapy) relies upon a future event (i.e. treatment) after the PM diagnosis. This

causes immortal time bias, consequently overestimating the survival benefit in the CRS+HIPEC group. To date, two RCTs have been performed investigating the effect of CRS+HIPEC [118,123]. Verwaal et al. conducted a well-designed RCT and demonstrated a significant survival in favour of CRS+HIPEC[118]. However, critics have argued that the RCT includes few patients, among whom nearly 20% had PM from appendiceal cancer, which has a better prognosis than CRC PM. Furthermore, it has been argued that the systemic chemotherapy applied was outdated compared to present-day treatments.

Results from the PRODIGE-7 trial have not yet been broadly introduced in the international clinical practice due to various points of criticism, both methodological[127] and HIPEC related[128] . First, it has been argued that the study sample was too small, creating an underpowered study unqualified to conclude on the stated aim (i.e. the role of HIPEC after CRS). Second, approximately 25% of the included patients had a PCI score > 16, which was demonstrated to be a poor prognostic factor after the study was set up. Finally, discussion of the HIPEC regimen has revolved around the efficacy of the chemotherapeutic drug, oxaliplatin, and its carrier solution, and potential adverse effects of the induced hyperthermia[128].

2.6.2 Prognosis following cytoreductive surgery and hyperthermic intraperitoneal chemotherapy

Two main factors are critical for the prognosis of patients treated with CRS+HIPEC; the extent of PM, which can be measures by the PCI ,and the completeness of cytoreduction (CCR)[129]. Several studies have demonstrated that survival differs with the PCI, i.e. a higher PCI has a negative impact on survival[48,53,130]. In a recent meta-analysis, Hallam et al.[129] demonstrated that a PCI score > 15 was associated with a significantly reduced overall survival. Furthermore, considering PCI as a continuous measure, the authors reported that each point increase was associated with reduced overall survival[129,131].

At the end of the CRS+HIPEC procedure, any residual intra-abdominal tumour nodules are classified using the CCR score. A CCR-0 indicates no visible residual tumour, whereas a CCR-1 score indicates tumour nodules of less than 2.5 mm. A CCR-2 demonstrates residual tumour nodules of a size between 2.5 mm and 2.5cm; finally, a CCR-3 score indicates residual tumour greater than 2.5 cm[132,133]. In the meta-analysis by Hallam et al., the pooling of seven eligible studies[134-141] demonstrated that a CCR > 0 was associated with a significant reduction in overall survival [129].

2.6.3 Strategies for patients with a high risk of PM

The extent of PM correlates directly with the results of CRS+HIPEC, as increased PCI is associated with poor survival[52,129,131,142]. To improve the prognosis of PM, early detection when PM is limited (and asymptomatic) is essential, hence a strategy such as second-look after curatively intended CRC surgery has been introduced. The second-look procedure can be followed by HIPEC with the aim to prevent the recurrence of PM. Two RCT studies have aimed to investigate the effect of second-look with HIPEC. Klaver et al. conducted the COLOPEC trial[143] (Clinicaltrials.gov: NCT02231086), which included 204 patients with T4N0–2M0 category tumours or perforated colon cancer. Patients were assigned to systemic chemotherapy (control group) or HIPEC (simultaneously during primary resection or 5-8 weeks later) *and* systemic chemotherapy (experimental group). In case of no evident sign of recurrence after 18 months, a diagnostic laparoscopy was performed in all patients. In the control group, 23% of the patients had PM (compared with 19% of patients in the experimental group). Goere et al. performed the PROPHYLOCHIP-PRODIGE 15 phase III trial[144] (Clinicaltrials.gov: NCT01226394), and included 150 patients with one (or more) of the following risk factors: synchronous and localized PM, ovarian metastases or perforated CRC tumour. At least six months after CRC resection and chemotherapy, patients without any sign of recurrence were randomized to surveillance (with CT) or second-look surgery with HIPEC. In total, 50/150 patients were diagnosed with PM recurrence, and these were equally distributed between groups.

Both studies confirmed that recurrence of PM is a concern in patients with high-risk factors, however, none of the studies demonstrated a significant reduction in peritoneal metastasis-free survival when patients were treated with HIPEC[143,144]. The definition of high-risk patients relies upon different factors in the two studies, and makes direct comparison difficult. There is still a need for exploration of high-risk patients, and a categorization of subgroups that might benefit from second-look in order to detect early PM and initiate treatment.

2.7 Follow-up after cancer

The scope and content of appropriate and sufficient cancer follow-up is debated [145-147]. Current advancements in cancer treatment have improved cancer survival rates[4], which requires evaluation of treatment follow-up. In general, an intensive follow-up programme after surgery is common, yet evidence of the effect of follow-up on survival is sparse[23,148]. For UICC stage I-III patients with CRC, a RCT has demonstrated that a high-intensity follow-up has no effect on survival or recurrence compared with a low-intensity follow-up[149]. These results demonstrated that patients

followed with a higher intensity experienced no increase in recurrence or in CRC-specific and overall mortality[149]. This underlines that a cancer follow-up programme should include identification of treatment-related (i.e. oncological, medical or surgical) side effects, physical and psychological symptoms and sequelae of any kind[146,150,151]. Yet both national and international investigations have demonstrated that advanced cancer survivors experience unmet needs in the follow-up period[152,153]. These unmet needs led the Danish National Board of Health to require that the national follow-up for cancer patients include detection of late side effects, rehabilitation, palliation and patient involvement (PI)[92,150]. These changes to the follow-up progamme aimed to improve the healthcare quality for cancer patients and changed the traditional disease-oriented approach to a more holistic approach where patient centeredness became an integral part of health care[154].

2.7.1 Follow-up after treatment of peritoneal metastases

Follow-up after CRS+HIPEC varies by country and by institution. A survey from 2018, including experts performing CRS+HIPEC in 19 countries[91], demonstrated that >75% of the experts agreed that routine follow-up should include > 2 visits/year in the first 2 years[91], encompassing a physical examination, blood samples and an abdominal-thoracic CT. The Danish guidelines mirror these recommendations[92].

2.7.2 Survivorship from PM

The research field of cancer survivorship care was established in an effort to identify and meet the diverse needs of patients who are surviving after a cancer diagnosis and to help them thrive and return to health or even better health and well-being than they had before being diagnosed with cancer. The National Coalition of Cancer Survivorship explains that the phrase cancer survivorship was created to describe this broad experience on the cancer continuum of living with, through and beyond a cancer diagnosis; and it defines survivorship as any patient living with cancer "from the time of diagnosis, through the balance of his or her life. Family members, friends and caregivers are also impacted and are therefore included in this definition"[155]. Therefore, survivorship includes issues related to follow-up care like screening, identification, evaluation and providing treatment recommendations for common consequences of cancer and cancer treatment[155].

The general health and well-being following CRS+HIPEC has been investigated, among others in some reviews including several heterogenic studies[156,157] which demonstrated the same tendency;

the majority of scores on health scales and overall health-related quality of life (HRQoL) decrease in the immediate period (3-4 months) after CRS+HIPEC; however, similar or better (than preoperative) levels are reached at 1 year.

Still, some prospective studies have demonstrated that long-term physical, functional and cognitive functions remain impaired after cancer therapy [158] and that cancer survivors have a high frequency of depressive symptoms[159].

2.7.2.1 Patient-centred care

Patient-centred care is a multidimensional concept that varies according to the setting and perspective applied [160-163]. Overall, patient-centred care is a refinement of the traditional disease-oriented approach and incorporates the patient's psychosocial situation and own perception of illness[154]. It also ensures that while assisted by healthcare professionals, the patient maintains the primary responsibility for his or her own care[162]. In the present thesis, we consider patient-centred care as "providing care that is respectful of, and responsive to, individual patient preferences, needs and values, and ensuring that patient values guide all clinical decisions" defined by the Institute of Medicine [164].

2.7.2.2 Patient involvement

PI represents a strategy to obtain patient-centred care. PI was initially suggested as a means to manage the growing population of patients with chronic diseases (i.e. diabetes, heart disease, rheumatic diseases and asthma) in order to prevent overloading of the healthcare system and to restore the patient to a central position in his or her own life [165]. By involving and committing patients to treatment, benefits of PI are expected to include better patient health outcomes, improved symptom and disease control, greater patient satisfaction and reduced health costs [165,166]. The described benefits are primarily based on the implementation of PI in chronic care[167-171]. However, with the growing number of cancer survivors, cancer may be considered a chronic disease[172].

The benefit of PI in vulnerable patients undergoing extensive surgery for advanced cancer has barely been investigated, and PI in such setting has been only sparsely discussed [173]. In the present dissertation, PI refers "specifically to the rights and benefits of patients to have a central position in the healthcare process"[174]

In a clinical setting, individual PI entails elements such as identification of patients' needs and preferences, shared decision making, self-management support and improvements in communication between patients and clinicians [175-178].

Self-management support is a portfolio of techniques performed by the healthcare professionals and healthcare system aiming to support the patient's knowledge, skills and confidence to manage long-term conditions effectively[176]. Interventions aiming to improve elements of PI are by the very nature of the phenomenon complex and affected by several factors as demonstrated in Figure 4[179].

Several RCTs[172,180-183] have investigated the effect of interventions with patient-involving, a summary of these studies is listed in Table 2. In general, all studies find positive associations between the intervention and one (or more) patient-associated outcome(s). However, as demonstrated in Table 2, the cancer populations subjected to patient-involving interventions are heterogeneous, the interventions serve several aims and the studies apply heterogeneous measurements of outcomes. Naturally, this limits an unambiguous conclusion.

Figure 4. *Factors influencing patient involvement in a clinical setting. The clinical setting could can be any situation during a disease course. In this Figure, the setting is the follow-up period after a diagnosis.*
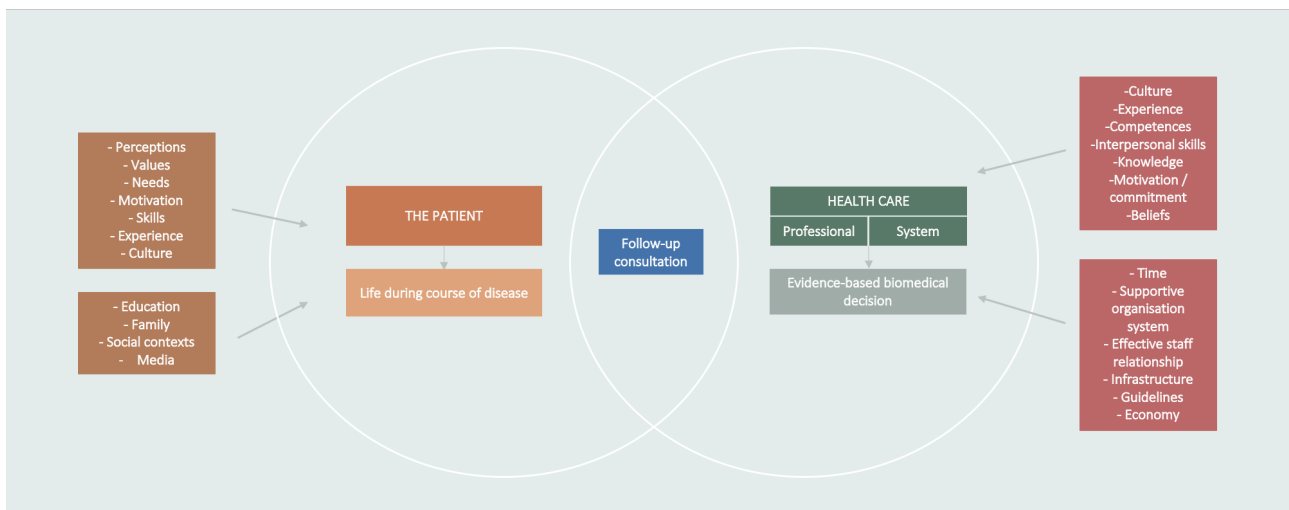
2.7.2.3 Measurements of patient involvement

As outlined in section 3.3.2, the benefits of PI are expected to be several, for which reason multiple outcome measurements exist[184]. As demonstrated in Figure 4, the patient, healthcare professionals and the healthcare system may interact and influence each other, and outcomes can therefore be measured at different levels[185]. Applied in a clinical setting, outcomes can be measured objectively

Table 2. Randomised Clinical Trials (RCT) investigating the effect of patient involving elements

Author	Design and setting	Study population		Aim	Intervention	Outcome	Results
		Patients	**Health care**				
Velikova[182] 2004	- Leeds, England - Prospective RCT - Outpatient clinical cancer setting - 2000-2001	- Patients with various cancers (breast, gynaecological, renal, bladder, sarcoma and melanoma) -Receiving active oncological treatment (n=286)	- Oncology consultants and physical trainees (n=28)	- Examine the effect of regular, repeated collection and feedback of health-related quality of life (HRQoL) questionnaires	Description: Completion of HRQoL questionnaires prior to consultation. Clinicians used the HRQoL during all intervention consultations. Intervention group: Completion of HRQoL measurement + feedback from clinician Attention-control group: Completion of HRQoL measurement, no feedback from clinician Control group: No HRQoL measurement before clinic encounters, no feedback from clinician	Primary: - Patients' well-being measured as HRQoL - Process of care: Discussion of HRQoL issues, medical and nonmedical actions and length of consultations	- Intervention and attention group had better HRQoL - A positive effect on emotional well-being was associated with feedback - Nonspecific chronic symptoms were more frequently discussed in the intervention group
Boyes[183] 2006	-Australia -Prospective RCT (Pilot study) -Medical oncology outpatient clinic -Single major public cancer treatment centre	-Patients with various cancers (colorectal, breast, lung, lymphoma, melanoma) (n=80) -Receiving active oncological treatment	-Medical oncologists (n=4)	-Examine the effect of repeated collection of patient-reported outcomes with immediate real-time feedback	Description: Completion of an electronic survey immediately before follow-up at their oncologist + graphical summary and real-time feedback from oncologist Intervention group: Completion of survey + graphical presentation of symptoms and care needs + real-time feedback from the oncologist (n=42) Control group: Completion of survey (n=38)	Primary: - Reduce patients' levels of anxiety, depression, perceived needs and physical symptoms Secondary: Medical oncologists' and patients' acceptability of the	-Significant reduction in patients' debilitating symptoms over time in the intervention group -No difference in reduction of anxiety, depression and perceived needs among intervention and control group -The majority of oncologists and patients found the survey easy to apply.

						intervention (applicability, usefulness and impact)	- Half of the medical oncologists found the survey to be useful with impact -Very few intervention patients had the feedback report discussed
Berry[180] 2011	- USA - Prospective RCT - Outpatient clinical cancer setting - 2005-2007	-Various cancer diagnoses (breast, gastrointestinal, genitourinary, gynaecological, head and neck, haematological) - In medical or radiation treatment (n=660)	- Clinicians of different positions and specialities (n=262)	- Determine the effect of an electronic self-reported cancer assessment on the likelihood of symptoms and health-related quality of life (HRQoL) issues being discussed between patient and clinician	Description: Patients electronically reported symptoms and HRQoL which was summarised in coloured graphics and presented to the clinician Intervention group: Graphical summary presented in the clinical consultation (n=327) Control group: No graphical summary presented to the clinician(n=333)	Primary: Discussion of symptoms and HRQoL issues measured by audio recordings Secondary: -Duration of outpatient visits -Clinician evaluation	-The intervention promoted discussion of troublesome symptoms and HRQoL -No difference in duration of consultations -The majority of clinicians reported the intervention as useful
Ruland[181] 2010	- Norway - Prospective RCT - One specialised hospital - Inpatient and outpatient clinical cancer setting	-Patients with haematological cancers -Starting active oncological treatment (n=145)	-NA	- Examine the effect of a computer-assisted, interactive, tailored patient assessment of symptoms, problems, distress and needs	Description: Prior to inpatient and outpatient contact, all patients completed the interactive, tailored patient assessment tool. Intervention group: Assessment summaries available to clinicians and nurses Control group: Assessment summaries not available to the clinician at any time	Primary: - Number of symptoms and problems addressed by clinicians and nurses - Changes in symptom distress - Changes in patients' need for symptom management support over time	-Significantly more symptoms discussed in intervention group -Significant decrease in symptom distress in intervention group - Reduced need for symptom management support in intervention group
Van der Hout[172]	-Netherlands	-Survivors from head and neck, colorectal and	-NA	-Support survivors in self-management, reduce symptom	Description: An electronic health self-management application, Oncokompas, consists of three components: Measure, Lean	Primary: - Improve knowledge, skills and confidence for self-management	Primary:

| 2020 | -Non-blinded RCT with block randomisation -Electronically based evaluations -Included from 14 Hospitals -2016-2018 | breast cancer and lymphoma (n=625) -Invited by electronic survey | | burden and improve HRQoL | and Act. Oncokompas provides feedback and information on patients' scores provides a personalised overview of supportive care options (e.g. self-help interventions or contact to medical specialists)

Intervention group: Direct access to Oncokompas (n=320)
Control group: Waiting group – access to Oncokompas after 6 months (n=305) | measured by the Patient Activation Measurement (PAM) measured at inclusion and at 3 and 6 months of follow-up
Secondary:
-Impact on HRQoL and tumour-specific symptoms
-Mental adjustments, supportive care needs, self-efficacy, personal control and patient-physician interaction | - No difference in PAM scores between the intervention group and the control group over time

-HRQoL was significantly better in the intervention group over time -No difference in mental adjustments, supportive care needs, self-efficacy, personal control and patient-physician interaction between groups |

(i.e. access to care, care availability, financial burden or audiotaped consultations) and subjectively by the patient him or herself, i.e. patient-reported outcome (PRO).

2.7.3 Patient-reported outcomes

PRO is defined as 'any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else'[186]. PROs directly reflect delimited areas of the impact of disease and its treatment from the patient's perspective, and can measure the trade-off between efficacy of a given treatment and what the patient is willing to tolerate[187]. The purposes of PRO are multiple, and besides measurement of HRQoL and symptoms, PROs reflect the patient's perspective and harbour the potential to facilitate PI, support treatment decision-making and provide guidance for healthcare decisions. Hence, the use of PRO data in clinical practice has been suggested to improve patients' HRQoL by facilitating discussions regarding unspecific symptoms or health-related problems [182,188-192]. A PRO is a clinical measure that cannot be verified physically[193]. Therefore, in clinical practice, the validity of PROs is evaluated in terms of contents (i.e. measurement of all dimensions in each scale), criterion (i.e. prediction of observable scales) and construct (i.e. accurate measurement of the theoretical construct it is designed to measure). Furthermore, terms such as reliability (i.e. precision) and responsiveness (sensitivity to changes in clinical conditions) are used to evaluate the performance of a PRO measure[187,193,194].

3.0 Summary and gap

Improvements in diagnostics, treatment and survival of patients with CRC are mirrored in patients with metastatic CRC. This development has gained pace with the introduction of CRS+HIPEC, which has improved survival and prognosis for a selective group of patients with PM. Furthermore, investigations of high risk and early detection of PM are being explored[143,144,195]. The inclusion of high-risk patients in these studies is based on previous register-based and prospective studies, including populations subjected to surgery prior to the general improvements observed in the up-to-date management of patients with CRC. It is of interest to investigate if these improvements have affected the overall risk and risk factors for PM. Registries contain large comprehensive data, providing clinicians and researchers with the possibility to monitor prevalence, incidence, mortality and prognosis of a disease on the assumption that data are valid. In general, the validity of metastases registered in medical registries is debated[196-198]. Little is known about the validity of PM registrations.

Survival and prognosis of patients undergoing CRS+HIPEC have been described in detail; yet other aspects of treatment such as optimal patient-centred follow-up are sparsely described. Patient involvement is a preferred strategy for facilitating patient-centred care. The beneficial outcomes of this approach show in better HRQoL and emotional well-being [172,182], increased discussion of symptoms[180-182] and fewer symptoms[181,183] both in chronic diseases and following cancer. However, PI has barely been investigated in populations with advanced cancer treated with complex surgery. Therefore, four studies were performed to address the hypotheses and aims presented in the next chapter.

Paper I

Hypothesis: Registration of CRC metastases at a specific anatomical location is underreported.

Aim: To evaluate the completeness and positive predictive value (PPV) of S-PM registered in Danish medical registries.

Paper II

Hypothesis: Following improvements in the treatment of CRC, the risk and risk factors for PM have changed.

Aim:

- To describe the overall risk of M-PM within 5 years in patients undergoing intended curative surgery for CRC
- Identification of risk factors for M-PM within 5 years after intended curative CRC surgery.

Paper III

Hypothesis: Is use of electronically collected PRO (ePRO) possible in an outpatient clinical cancer setting with highly specialised surgeons following patients surgically treated for advanced cancer

Aim:

- To describe the development of an ePRO used in the follow-up after complex cancer surgery
- To evaluate the implementation of an ePRO-based follow-up after complex cancer surgery

Paper IV

Hypothesis: A patient-centred follow-up supported by ePRO increases PI and patient activation

Aim: To evaluate if follow-up based on e-PRO is associated with increased levels of:

- PI measured by five generic questions
- Patient activation

5.0 Methods

This section gives an overview of the methods used in each paper. For details, please see each paper in the Appendix.

5.1 Setting and data sources

<u>Paper I and paper II</u>

Denmark is a country with approximately 5.8 million inhabitants, in which all Danish citizens have access to a tax-supported primary and secondary healthcare system offering equal access to all types of treatment[199]. All Danish citizens are assigned with a unique 10-digit civil personal registration number, enabling unambiguous individual-level record linkage between registers[200]. The following registries are used as data sources in the present dissertation (Paper I and II):

The Danish Colorectal Cancer Group database (DCCG)

The Danish Colorectal Cancer Group database contains information on all first-time patients with CRC since 2001. Patient completeness is above 95% [201]. The database contains information regarding patient characteristics, radiological evaluation, surgical and oncological treatment, pathology reporting and postoperative course for the first 30 days after surgery. Prior to March 2014, symptoms led to a medical investigation and CRC diagnosis, whereas from March 2014 the implementation of national screening led to diagnoses of both symptomatic and asymptomatic CRC, all of which are registered in the DCCG database.

The Danish National Patient Registry (DNPR)

The Danish National Patient Registry provides longitudinal data as from 1977 regarding administrative and clinical information including information about patient time and reason for contact with the healthcare system. One primary and potentially several secondary diagnoses are recorded at each contact with the hospital[202]. Diagnoses have been recorded by using the International Classification of Diseases 10th revision (ICD-10) codes from 1994, while treatment and procedures are registered by using a Danish version of the Nordic Medico-Statistical Committee's Classification of Surgical Procedures (NOMESCO).
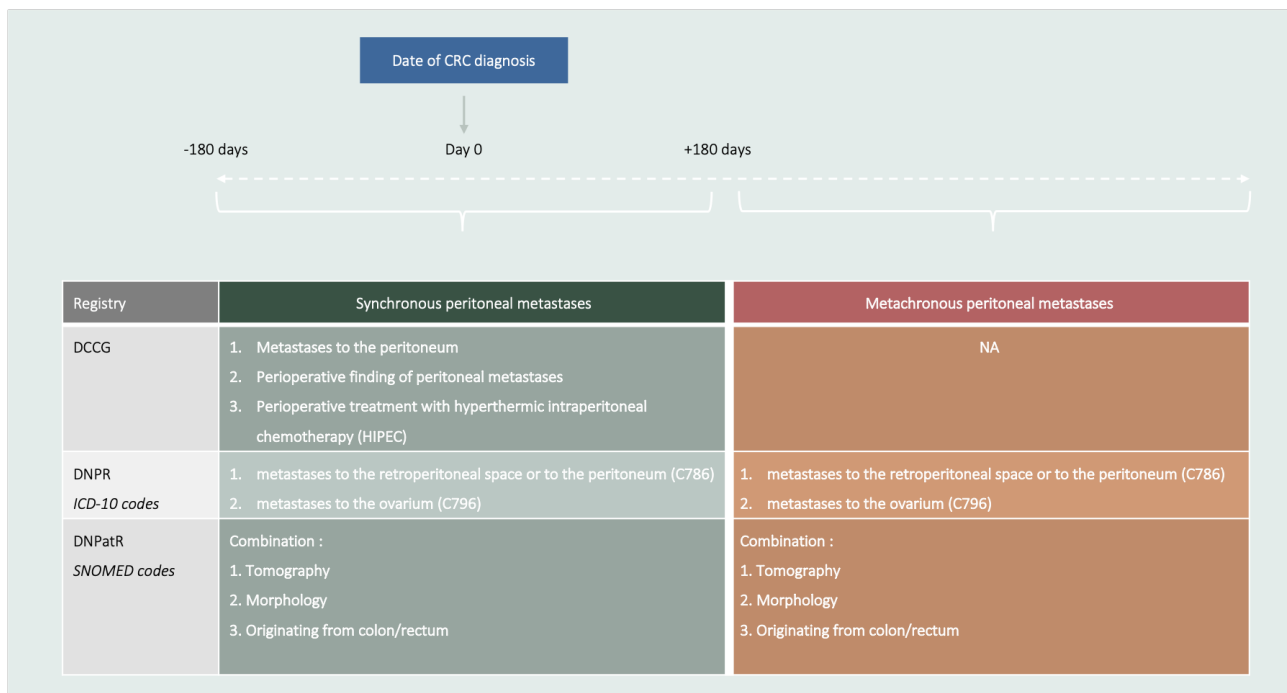
The Danish National Pathology Registry (DNPatR)

The Danish National Pathology Registry was established in 1997, and all pathological examinations performed in Denmark are registered according to a uniform guideline[203]. Each specimen is linked to the civil personal registration number, the hospital department responsible for treatment, the date of request, the specific Danish Systematized Nomenclature of Medicine (SNOMED) codes and other sources of data[203].

The Danish Civil Registration System

The Danish Civil Registration System is an administrative register established in 1968 recording information about residency and vital status of all Danish citizens. The register is updated daily and has a high accuracy, allowing for complete long-term follow-up[200].

Figure 5. *Information from following registries The Danish Colorectal Cancer Group database (DCCG), The Danish National Patient Registry (DNPR), The Danish National Pathology Registry (DNPatR)were applied to define and distinguish between Synchronous peritoneal metastases (S-PM) and metachronous peritoneal metastases (M-PM). Day 0 is considered as the date of colorectal cancer diagnosis (CRC).*

Registry	Synchronous peritoneal metastases	Metachronous peritoneal metastases
DCCG	1. Metastases to the peritoneum 2. Perioperative finding of peritoneal metastases 3. Perioperative treatment with hyperthermic intraperitoneal chemotherapy (HIPEC)	NA
DNPR *ICD-10 codes*	1. metastases to the retroperitoneal space or to the peritoneum (C786) 2. metastases to the ovarium (C796)	1. metastases to the retroperitoneal space or to the peritoneum (C786) 2. metastases to the ovarium (C796)
DNPatR *SNOMED codes*	Combination : 1. Tomography 2. Morphology 3. Originating from colon/rectum	Combination : 1. Tomography 2. Morphology 3. Originating from colon/rectum

Paper III and paper IV

CRS+HIPEC is performed at Aarhus University Hospital as the only hospital in Denmark. Treatment is performed at two different departments, as a routine at the Department of Surgery and as part of an experimental clinical trial at the Department of Gynaecology[204]. At the Department of

Surgery, patients were offered follow-up in the outpatient clinic at 3, 6, 12, 18, 24, 36, 48 and 60 months postoperatively. Each follow-up visit (i.e. consultation) was preceded by a CT scan of the thorax, abdomen and pelvis[92]. All consultations were performed by experienced surgeons who all performed CRS+HIPEC. The consultation included a clinical examination and a description of the performed CT scan.

At the Department of Gynaecology, patients were offered follow-up at 1, 3, 6, 12, 18, 24, 36, 48 and 60 months postoperatively[204]. The consultation was preceded by a CA 125 blood sample, and the follow-up consultation included a clinical examination and a vaginal ultrasonic examination. In case of suspicion of recurrence, a CT scan was performed[204].

## 5.2 Study design and study population

Paper I

Paper I was designed as a nationwide population-based prevalence study including all Danish patients registered with primary CRC in the DCCG database between 1 January 2014 and 31 December 2015. S-PM was identified using the DCCG, the DNPR and the DNPatR; yet the DCCG was used as the reference since S-PM was routinely registered here.

Paper II

Paper II was conducted as a nationwide, registry-based cohort study. The study included all patients diagnosed with CRC in the DCCG database between 2006 and 2015. M-PM and vital status were obtained from the DNPR (diagnostic coding of PM), the DNPatR (histologically proven PM) and the Danish Civil Registration System (vital status).

Patients were excluded in case of death, non-CRC, S-PM and non-curative resections within 180 days from CRC diagnosis. See Figure x.

Figure 6. *Inclusion and exclusion of patients.*
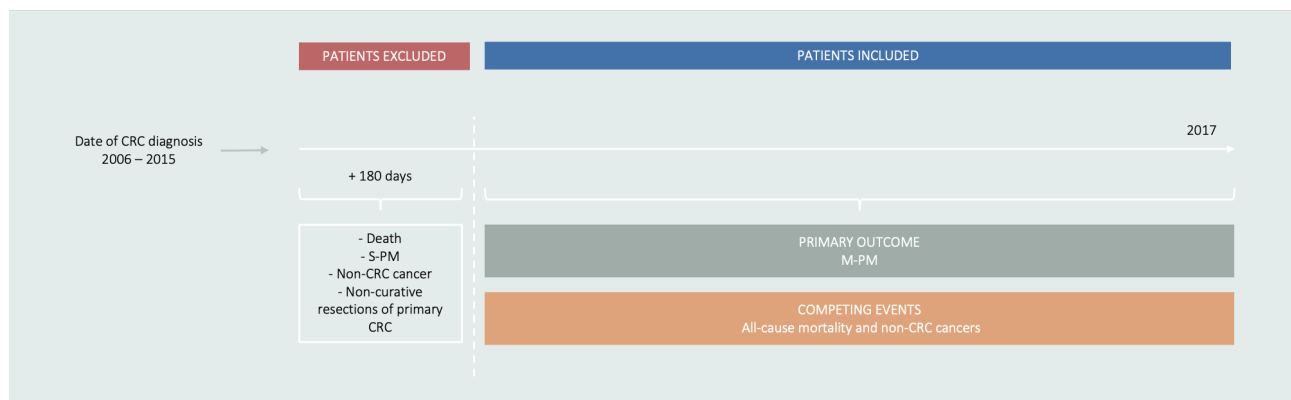
Abbrevations: CRC: Colorectal cancer; S-PM : Synchronous peritoneal metastases.

Paper III

Paper III was carried out as an explorative study aiming to develop and implement an intervention with the purpose to promote patient-centred follow-up after CRS+HIPEC. The intervention consisted of electronic Patient-Reported Outcomes (ePRO) supporting follow-up after CRS+HIPEC. The ePRO was a tool to facilitate dialogue in the follow-up consultation. The ePRO was set up using an Ambuflex system[205,206] , integrated and assessed through patients' electronic medical records. A graphical presentation of the ePRO was available for the clinician to facilitate flagging of important symptoms. The study included patients treated with CRS+HIPEC and followed in the outpatient clinic at the Department of Surgery and the Department of Gynaecology at Aarhus University Hospital in the period from February 2017 to January 2019. Patients were included continuously prior to a consultation in the outpatient clinic (i.e. patients could be included at any time during their follow-up period).

Paper IV

Paper IV was carried out as a prospective, descriptive cohort study aiming to evaluate the effect of a follow-up based on ePRO. The study inclusion was performed like described in study III.

5.3 Outcome measurements

Paper I

The data quality of registered S-PM in the DNPR and the DNPatR was assessed as completeness and PPV, using the DCCG database as reference.

Completeness:

The sensitivity describes the ability of a diagnostic test to correctly identify actual positives. In epidemiological research, the sensitivity can be used as a measure of completeness, viz. the proportion of individuals in the target population correctly classified in the data source (i.e. registry) [202,207,208]. To determine the sensitivity, the number of identified positives should be compared to a data source containing the "true" number of diseased individuals, also referred to as the "golden standard". Factors such as demographic features, disease severity and prevalence in the population subjected to the test may potentially impact the sensitivity[209]

Positive predictive value:

While the sensitivity describes the characteristics of a test, the predictive value describes its clinical relevance (i.e. registration in a registry) and refers to the probability of a disease being present in case of a positive test[208,210]. The predictive value is affected by the prevalence of a given disease in the investigated population. The validity describes the extent to which the diagnostic test measures what it intends to measure[208].

<u>Paper II</u>

The primary outcome of interest was the CIP and risk factors for M-PM. The identification and definition of M-PM are outlined in Figure x. M-PM was identified in the follow-up period, which started on the date of CRC diagnosis plus 180 days. Patients were followed until the M-PM event, death, non-CRC cancer or end of follow-up, which ever came first.

Secondary outcomes were risk factors for M-PM. Potential risk factors were age (<60 years, 60–75 years and >75 years), sex, tumour localisation, priority of surgery, perforation of the tumour as assessed intraoperatively by the surgeon, pathologically assessed T-category and N-category, tumour histology, extramural venous invasion (EMVI), the pathologically assessed radicality of the bowel (R0, R1) and administered systemic chemotherapy (yes, no).

<u>Paper III</u>

The outcome of interest was development and implementation of a patient-centred follow-up based on ePRO (i.e. intervention). The ePRO had the purpose to facilitate dialogue in the follow-up consultation.

The development process consisted of different elements, which is outlined briefly in Figure 7, but described in details in paper III in the manuscript.

Figure 7. *The development process consisted of different elements: 1) Selection of ePROs. 2) Development of ePRO response algorithm. 3) Patient's feedback by interview 4) Revision of ePRO. 5) Clinician's feedback.*
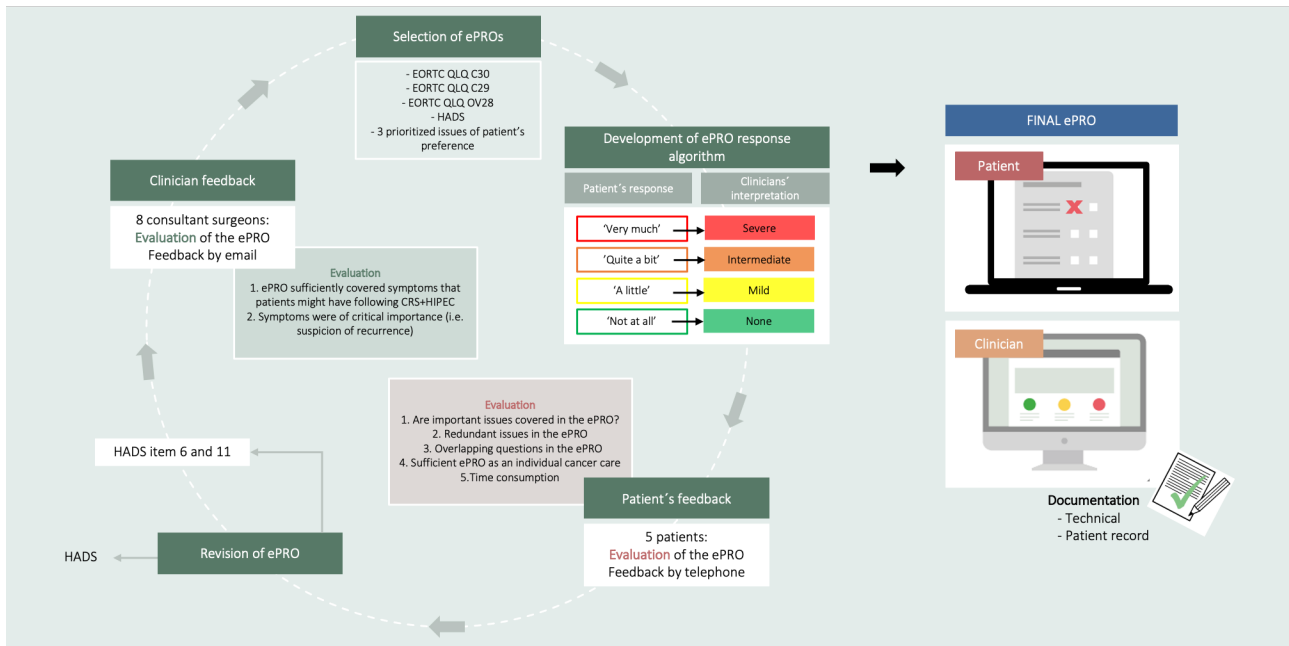
The implementation was assessed by the following:

Handling of the ePRO

- Patients' response rate to e-PRO
- Number of e-PROs used by the clinician
- Patients' prioritised issues prior to the consultation (refined to 'yes' / 'no'), stratified by time since surgery (<6 (+1 month) months/ >6 (+ 1 month) months) and gender (male/female)).
- Patients' prioritised issues prior to the consultation categorized into thematic topics:

Patients' evaluation

- Purpose and need of follow-up visit
- Time allocated for follow-up visit.
- Support provided during follow-up

Paper IV

The outcome of interest was patient activation and PI following a patient-centred follow-up based on ePROs. These outcomes were measured using an electronic questionnaire sent out 2-4 days after the follow-up visit.

Patient activation was measured using the 13-item Patient Activation Measure (PAM) survey, which was developed and validated by Hibbard et al. [211]. The PAM is a PRO instrument that

measures a patient's amount of knowledge, skills and confidence for self-management; the measure scores from 0-100, where a higher score indicates a higher level of activation.

PI was considered a feasibility measure and was monitored in each consultation. PI was measured by five questions developed and tested as PI indicator targets by DEFACTUM, an institution hosted by the Central Denmark Region focused on applied social, health and labour market research[212]. The following five themes were explored: 1) The healthcare provider asked about my own experiences with my illness / condition, 2) I talked to the healthcare provider about the questions or concerns I had, 3) The healthcare professional encouraged me to ask questions or talk about concerns, 4) I received advice when deciding what was going to happen and 5) I have had appropriate conversations with healthcare professionals about how to best manage my illness / condition.

5.4 Statistical analysis

All statistical analyses were performed using STATA statistical software (STATA, release IC15, STATACorp, Texas, USA

Descriptive data

For all papers (Paper I-IV), descriptive data on patient characteristics are presented as medians with ranges or interquartile ranges (IQR) for continuous variables, whereas categorical variables are presented as frequencies with percentages.

Paper I

The algorithm applied to identify patients with S-PM included the identification of a PM diagnosis registered in at least one of the three registries (the DCCG database, the DNPR and the DNPatR) within 180 days after the date of CRC diagnosis. To validate the registration of the ICD-10 codes in the DNRP and SNOMED codes in the DNPatR, we used registrations in the DCCG as reference. Completeness was estimated for each registry (DNPR and DNPatR) and for the registries in combination (DNPR/DNPatR). Completeness was estimated by following sensitivity formula:

1 (DNPR), 2 (DNPatR) or 3 (DNPR/DNPatR) should include the number of patients (n) with a PM diagnosis in the registry of interest

$$\frac{\begin{array}{l}\text{1. DNPR}\\\text{2. DNPatR}\\\text{3. DNPR/DNPatR}\end{array} + \text{DCCG}}{\text{DCCG}}$$

The PPV was estimated for each registry (DNPR and DNPatR) and for the registries in combination (DNPR/DNPatR). The PPV was defined as:

1 (DNPR), 2 (DNPatR) or 3 (DNPR/DNPatR) should include the number of patients (n) with a PM diagnosis in the registry of interest

$$\frac{\begin{array}{l}\text{1. DNPR}\\\text{2. DNPatR}\\\text{3. DNPR/DNPatR}\end{array} + \text{DCCG}}{\begin{array}{l}\text{1. DNPR}\\\text{2. DNPatR}\\\text{3. DNPR/DNPatR}\end{array}}$$

The coding quality was evaluated in the DNPR/DNPatR within clinically relevant subgroups that were stratified by age ($\leq$60, 60-69, 70-74, 75-80 and $\geq$80 years), sex, WHO performance status, tumour location and distant metastases to the liver and/or the lungs (yes/no).

Paper II

According to Figure 6, patients were followed from +180 days after having received a CRC diagnosis until the date of diagnosis of M-PM or another cancer, death or end of follow-up (25 January 2017), whichever came first. A cumulative incidence (risk) curve of M-PM considering all-cause mortality and diagnosis of non-CRC as competing risk was performed.

To analyse potential risk factors, a multivariate absolute risk regression model considering death and non-CRC as competing risks was performed. The analysis was performed as a complete case analysis. Each risk factor for M-PM was presented as a 1-, 3- and 5-year risk difference (RD) with a 95% confidence interval (CI.) The multivariate absolute risk regression model included all risk factors (except radicality and EMVI). The analysis was adjusted for time of CRC diagnosis (year)

and we included comorbidity assessed by the Charlson Comorbidity Index (CCI) (categorised as low (score 0), medium (score 1–2) or high (score > 2)). We considered death and non-CRC as competing risks

Some potential risk factors (radicality (R1) and EMVI) were not available throughout the whole study period. These risk factors were therefore investigated in subgroups of the cohort restricted to relevant calendar periods, using models adjusted only for age, sex and comorbidity (CCI) due to few M-PM cases.

Paper III

Results are descriptive and presented as medians with ranges or IQR for continuous variables, whereas categorical variables are presented as frequencies with percentages.

Patients' prioritized issues prior to the consultation were presented as refined to 'yes' / 'no'. A sensitivity analysis stratified by time since surgery (<6 (+1 month) months/ >6 (+ 1 month) months) and gender (male/female)).

Patients' prioritized issues were further thematic categorized by the first author. Each free form sentence/word was converted to a spreadsheet, and the thematic categorization was performed based on 1) the subscales from the European Organization for Research and Treatment of Cancer (EORTC QLQ-C30)[213] (gastrointestinal, mental, somatic, pain cognitive, mental), 2) issues related to the CRS+HIPEC course (disease and treatment related, general sequelae, status of the CT scan, future follow-up, future prognosis, elaborative conversation, treatment of recurrence), 3) concerns regarding body image, 4) practical concerns and 5) other issues. The author group discussed the categorization in plenum.

Paper IV

Patients were divided into two groups based on the type of follow-up. Patients who only completed the routine follow-up without e-PRO were referred to as '-e-PRO', whereas patients who participated in the intervention were referred to as '+ePRO'. Patients receiving a routine and interventional follow-up were included in the '-/+ePRO' group.

Since the five questions regarding PI were used to monitor PI in the follow-up consultation, each response was considered independent and stratified by routine (-ePRO) and interventional (+ePRO) follow-up. Therefore, it should be noticed that some patients occur with repeated measurements.

Both a median and a mean PAM score along with 95% CIs were presented for 1st, 2nd and 3rd response in each period (-ePRO period and +ePRO period).

In a stratified analysis, we investigated the correlation between the PAM score and the time since surgery.

6.0 Results

In this section, the main results of each paper are presented. For detailed information on the remaining results, please see each paper in the Appendix.

6.1 Paper I

Using the algorithm to combine data from the DCCG, the DNPR and the DNPatR, 468 of a total of 9,142 (5%) patients were registered with S-PM. The number of patients identified with S-PM in each registry as well as the completeness and PPV for each registry and the registries in combination are outlined in Table 3.

Table 3. *The number of patients identified in each registry and the following completeness and positive predictive value (PPV) using the DCCG as reference.*
Paper I, Published as:
Ravn S, Christian F. Christiansen, Rikke H. Hagemann-Madsen, Victor J. Verwaal, Lene H. Iversen. The validity of registered synchronous peritoneal metastases from colorectal cancer in the Danish medical registries. Clin Epidemiology 2020; 12: 333-343

	DCCG n = 366		Total	Completeness	PPV
Registry	+	-			
DNPR and/or DNPatR	153	102	255	42 (37-47)	60 (54-66)
DNPR	118	89	207	32 (27-37)	57 (50-64)
DNPatR	71	22	93	19 (15-23)	76 (68-85)
	DCCG: The Danish Colorectal Cancer Group DNPR: The Danish National Patient Registry DNPatR: The Danish National Pathology Registry PPV: Positive predictive value				

In the stratified analysis, patients who are potential candidates for curative treatment (patients aged <60 years, patients with WHO performance status and patients with no distant metastases) are registered with a higher completeness (see Paper I in the Appendix)

6.2 Paper II

Among 42,250 CRC patients identified in the DCCG database, 22,586 were included in the analysis in this paper.

<u>The cumulative incidence proportion</u>

We found an overall risk of M-PM as follows: 1-year: 0.9% [95% CI: 0.8; 1.0], 3-year: 1.9% [1.8; 2.1], 5-year: 2.2% [2.0; 2.4]. The risk of M-PM is presented graphically in Figure 8. Death and another cancer than CRC were major competing risks (Figure 8).

Figure 8. *The cumulative incidence proportion of metachronous peritoneal metastases considering overall mortality and other cancers as competing risks.*

*Paper II, published as **Ravn S**, Heide-Jørgensen U, Christiansen C.F, Verwaal V.J, Hagemann-Madsen R.H, Iversen L.H, A nationwide cohort study on the overall risk and risk factors for metachronous peritoneal metastases after colorectal cancer surgery. BJS Open 2020; 4: 284-292*
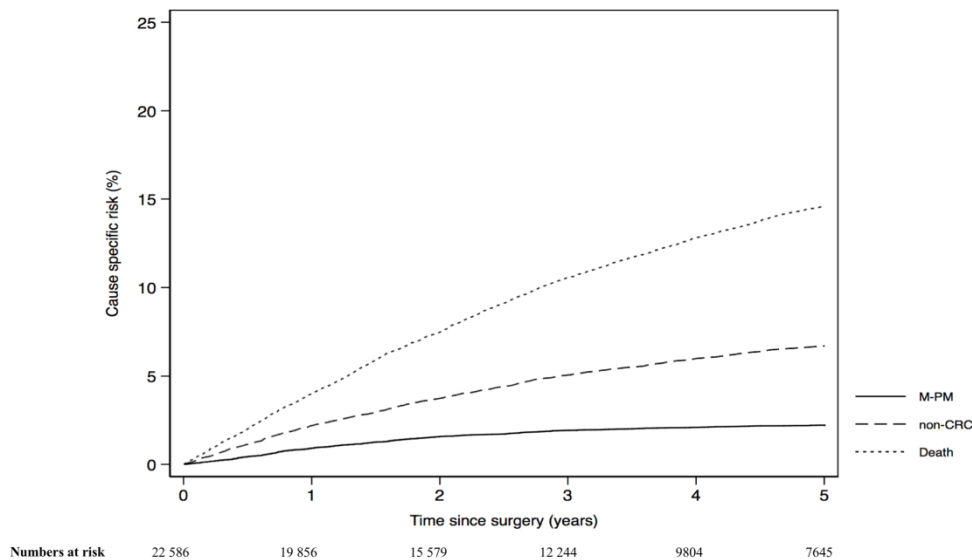
Potential risk factors are presented in Table 4

4.1.3 According to the analysis depicted in Table x, the baseline risk of M-PM for a reference person, i.e. the risk of someone who takes on the reference value for all covariates, is 0.6% [95% CI: 0; 1.5] after 3 years (Table 4). The absolute RD for each potential risk factor should be added to the baseline risk to obtain the predictive risk of M-PM for a specific patient. For example, a person with a (y)pT3N1 rectal cancer undergoing elective surgery has an estimated total risk of M-PM of 2.2% after 3 years [0.6% (overall risk) - 0.3% (rectal cancer) + 0.6% ((y)pT3) + 1.3% ((y)pN1) + 0% (elective surgery)].

In contrast, a person with a right colonic tumour, pathologically assessed (y)pT4N2, undergoing emergency surgery has an estimated risk of M-PM of 13.4% [0.6% (overall risk) + 0.6% (right

colonic cancer) + 6% ((y)pT4) + 4.3% ((y)pN2) + 1.9% (emergency surgery)] 3 years after curatively intended surgery. EMVI and radicality were not adjusted for in multivariate analysis; thus, the estimated RDs associated with these variables should be interpreted with caution.

Table 4. *Multivariate absolute risk differences (%) for metachronous peritoneal metastases (M-PM) 1 and 3 years after intended curative colorectal cancer surgery, treating death and non-colorectal cancers as competing risks. Presented with 95% confidence intervals.*

*Paper II, published as **Ravn S**, Heide-Jørgensen U, Christiansen C.F , Verwaal V.J, Hagemann-Madsen R.H, Iversen L.H, A nationwide cohort study on the overall risk and risk factors for metachronous peritoneal metastases after colorectal cancer surgery. BJS Open 2020; 4: 284-292*

Table 4. *Multivariate absolute risk differences (%) for metachronous peritoneal metastases (M-PM) 1 and 3 years after intended curative colorectal cancer surgery, treating death and non-colorectal cancers as competing risks. Presented with 95% confidence intervals.*
Paper II, published as Ravn S, Heide-Jørgensen U, Christiansen C.F , Verwaal V.J, Hagemann-Madsen R.H, Iversen L.H, A nationwide cohort study on the overall risk and risk factors for metachronous peritoneal metastases after colorectal cancer surgery. BJS Open 2020; 4: 284-292

Patient Characteristic *Potential risk factors - covariates*	*Multivariate adjusted[1]* *1-year absolute risk difference (%) (95% confidence interval) of metachronous peritoneal metastases* The risk of M-PM for a person of reference: 0.2 % (0^2, 0.7)	*Multivariate adjusted[1]* *3-year absolute risk difference (%) (95% confidence interval) of metachronous peritoneal metastases* The risk of M-PM for a person of reference: 0.6 % (0^2, 1.5)
Age at the time of colorectal cancer diagnosis.		
<60	Reference (0)	Reference (0)
60-75	-0.2 (-0.6, 0.2)	-0.5 (-1.1, 0.2)
>75	-0.5 (-0.9, 0.0)	-1.0 (-1.7, -0.4)
Gender		
Female	Reference (0)	Reference (0)
Male	0.1 (-0.2, 0.4)	0.3 (-0.1, 0.7)
Localisation		
Left colon	Reference (0)	Reference (0)
Left colonic flexure	0.6 (-0.5, 1.6)	0.6 (-0.9, 2.2)
Transverse Colon	0.2 (-0.5, 0.9)	0.2 (-0.9, 1.3)
Right colonic flexure	0.1 (-0.6, 0.7)	-0.2 (-1.2, 0.9)
Right colon	0.5 (0.1, 0.9)	0.6 (0.0, 1.3)
Rectum	-0.1 (-0.4, 0.2)	-0.3 (-0.8, 0.1)
Priority of surgery		
Elective	Reference (0)	Reference (0)
Emergency	0.9 (-0.1, 1.9)	1.9 (0.5, 3.4)
Tumour perforation		
No	Reference (0)	Reference (0)
Yes, encapsulated	-1.0 (-2.1, 0.1)	-0.3 (-2.5, 1.9)
Yes, freely to peritoneum	-0.1 (-2.2, 2.0)	-0.2 (-3.4, 3.1)
Pathological (y)pT-category		
T1	Reference (0)	Reference (0)
T2	-0.1 (-0.3, 0.2)	0.0 (-0.4, 0.4)

T3	0.1 (-0.2, 0.3)	0.6 (0.2, 1.0)
T4	2.9 (2.1, 3.7)	6.0 (4.9, 7.2)
Pathological (y)pN-category		
N0	Reference (0)	Reference (0)
N1	0.5 (0.1, 0.9)	1.3 (0.7, 2.0)
N2	2.5 (1.8, 3.2)	4.3 (3.2, 5.3)
Tumour histology		
Adenokarcinom	Reference (0)	Reference (0)
Other	0.2 (-0.6, 0.9)	0.4 (-0.8, 1.5)
Postoperative chemotherapy within 180 days after diagnosis of colorectal		
No	Reference (0)	Reference (0)
Yes	0.0 (-0.4, 0.4)	-0.2 (-0.8, 0.5)
Extramural venous invasion[3]		
No	Reference (0)	Reference (0)
Yes	2.3 (1.7, 3.0)	3.4 (2.5, 4.4)
Radicality of surgery [4]		
R0	Reference (0)	Reference (0)
R1	3.9 (1.6, 6.2)	5.9 (2.6, 9.3)

[1] In total, n=21 581 complete cases are included in the multivariate analysis, adjusted for all risk factors above including year of diagnosis and comorbidity (Charlson Comorbidity Index).

[2] The statistical lower boundary is negative. In accordance to reality, we made the intercept for the risk 0.

[3] Available from 2009; only adjusted for age, sex and comorbidity. In total, n=13 222 (patients with complete cases in the multivariate analysis and complete information of EMVI) were included in the analysis restricted for a group of the cohort

[4] Available from 2014, only adjusted for age, sex and comorbidity. In total, n=5 861 (patients with complete cases in the multivariate analysis and complete information of R1 resection available from 2014 and 2015) were included in the analysis restricted for a group of the cohort.

t

6.3 Paper III

Development: Patient interview

During the development process, the five interviewed patients (3 females, 2 males, a median age of 57 (range: 41-64) with a median of 19.5 months (range: 3.1-80.7) since CRS+HIPEC) evaluated the ePRO to be sufficient and sensitive with an appropriate consumption of time varying from 5-7 minutes.

Initially the ePRO included questionnaires were the generic Survey, the EORTC QLQ-C30[213], the EORTC validated for colorectal respective ovarian cancer patients (EORTC CR-29/38[214] and EORTC OV28[215] and the Hospital Anxiety and Depression Scale (HADS) [216].

Based on the patient interviews, the majority of questions in the HADS (screening for anxiety and depression) were assessed redundant, as they were sufficiently covered by the EORTC QLQ-C30 (q20-q25)- Consequently, as a consequence, only two items form the HADS (item 6 and item 11) were included in the ePRO (Figure 7). The ePRO ended up with included 67 items + 3 prioritized issues of patient's own preference for Dep A, and 52 items + 3 prioritized issues of patient's own preference at Dep. B. B.
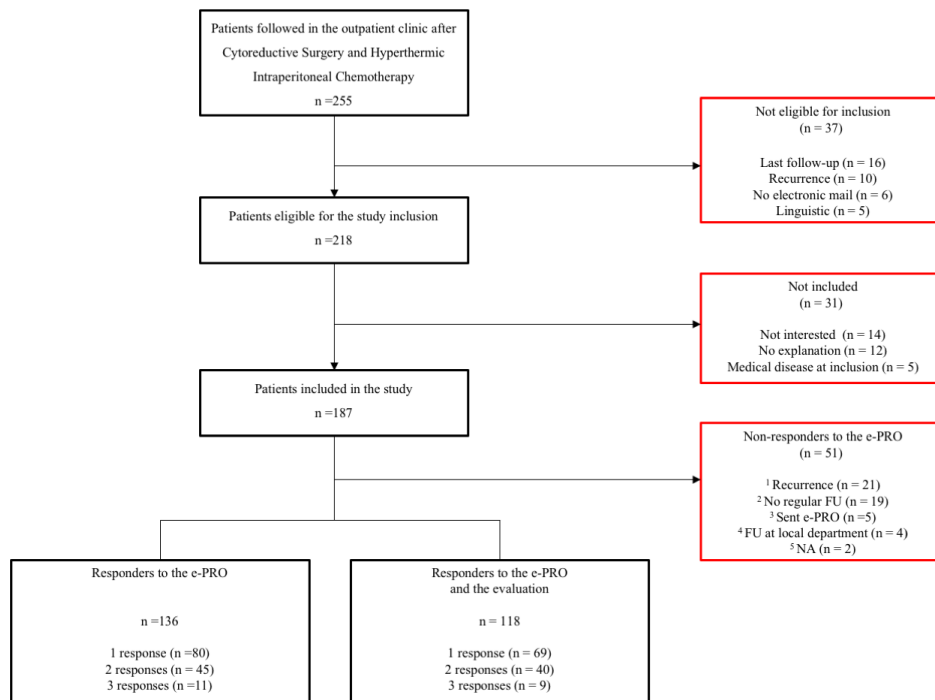
 None of the surgeons had any suggestions for additions to the ePRO.

Implementation

Patient and clinician participation

In total, 187 patients were included in the study of whom 73% (n=136/187) responded to the ePRO and participated in a patient-centred follow-up (Figure 9).

Figure 9. *Patient inclusion.*

Among the 203 ePRO-based consultations, 42 (21%) were not documented in the Ambuflex system or the medical record. These 42 ePRO consultations were equally distributed throughout the study period with ePRO-based consultations (data not shown).

Prioritised issues of patient preference

Overall, 203 ePRO consultations were performed. This produced a total of 609 prioritised patient preference issues (203 consultations x 3 prioritised issues among patients' preferences).

In total, 139/609 (23%) of the prioritised issues did not include a response; among these, the majority (80%) of consultations were performed > 6 months since CRS+HIPEC.

The primary issues prioritised by patients were gastrointestinal symptoms, explanation of the CT scan and concerns regarding prognosis (i.e. risk of recurrence) and follow-up (Figure 10).

Figure 10. *Patient-prioritized issues for follow-up categorized into themes.*
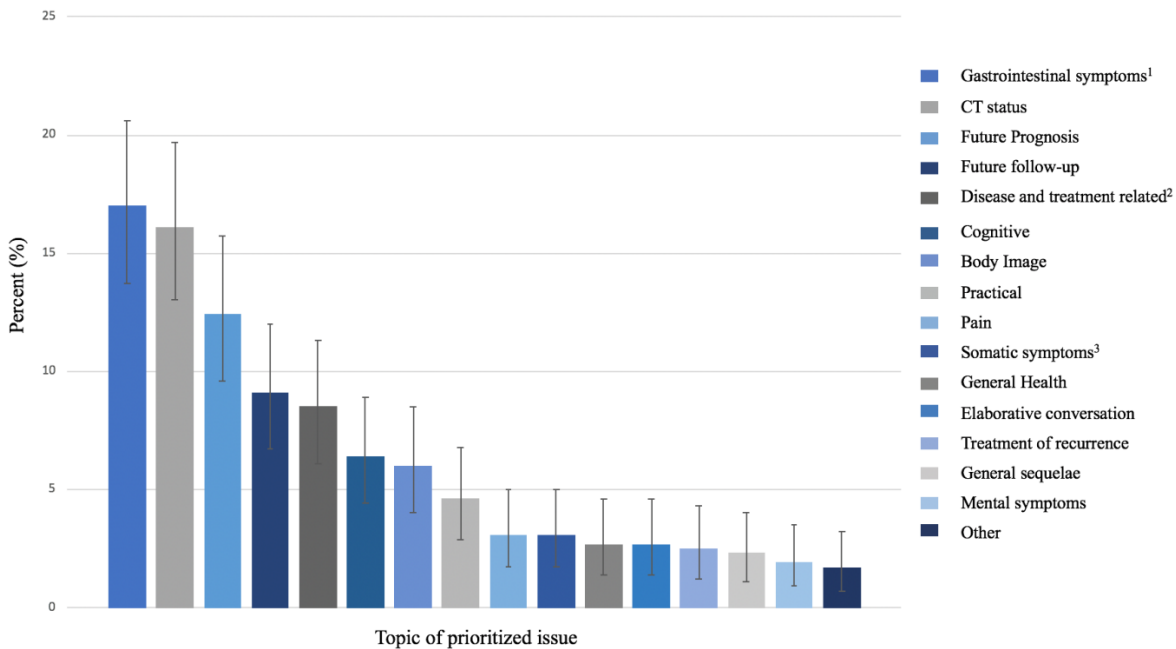
[1]Included problems related to ostomies and hernias

[2]Including treatment related side-effects

[3]Included symptoms related to sexual dysfunction

Purpose and need of follow-up visit

In total, 118 patients filled out an ePRO and then evaluation of the follow-up consultation (Figure 9) thus a number of 176 evaluations are applied in the analyses below.

Among the 176 evaluations, 127 (72 %) patients evaluated the follow-up to be necessary in order to discuss the outcome of the CT scan, symptoms, and/or prioritized issues (answer: "It was necessary so I could get explanations to my CT scan AND talk about my other problems"). Patients found the follow-up necessary to discuss only the result of the CT scan in 33/176 (19%) (answer: "It was necessary so I could get explanations to my CT scan AND nothing else") of the evaluations. Further, 4.5% of the consultations were assessed as not necessary ("It seemed unnecessary, but it was nice to get explanations to my CT scan" (3.4%) or "It seemed unnecessary, I could have done without it" (1.1%)). In total, 4.5% did not respond to the evaluation questions. Concerning the timeframe of the follow-up consultation, 88% of the patients found the timeframe appropriate, while 8% thought it was too sparse. Further, 4% did not respond.

Time allocated for follow-up visit.

Among the 176 evaluations, 127 (72 %) patients evaluated the follow-up to be necessary in order to discuss the outcome of the CT scan, symptoms, and/or prioritized issues. Patients found the follow-up necessary to discuss the result of the CT scan in 33/176 (19%) of the evaluations. Further, 4% of the consultations were assessed as not necessary. In total, 5% did not respond to the evaluation questions. Concerning the timeframe of the follow-up consultation, 88% of the patients found the timeframe appropriate, while 8% thought it was too sparse. Further, 4% did not respond.

Support provided during follow-up

The majority of follow-up visits (range: 19.3 – 56.3%) were evaluated to be supportive in terms of physical (42%), mental (56.3%), sexual (19.3%) or dietary (26.7%) issues raised. Further, a range from 34 – 60% of the patients reported that they did not need support related to these issues. Still, a range from 7.4 - 15.9% of the follow-up were not assessed to provide sufficient support regarding physical (12.5%), mental (7.4%), sexual (15.9%) or dietary (14.2%) issues. Sub-analyses stratified by time since surgery (<6 months and > 6 months) and gender, revealed no clear difference in the assessments of the support provided at the follow-up visit (data not shown).

6.4 Paper IV

In Paper IV, 255 patients were followed in the outpatient clinic in the study period from 2017 to 2019. Among these patients, 218 were eligible for inclusion and 187 (86%) accepted study participation. Patients were grouped according to the type of follow-up. In total, 48 patients were in the -ePRO, 57 patients in the -/+ePRO and 82 patients in the +ePRO. For baseline characteristics, please see the draft of Paper IV in the Appendix.

Patient activation

Overall, no differences in the mean PAM scores between the groups were observed (Figure 11). Considering the -/+ePRO group, i.e. patients subjected both to –ePRO and +ePRO, patients tended to report a statistically non-significant higher mean PAM score in the +ePRO period.

Figure 11. *Mean PAM score at 1ˢᵗ, 2ⁿᵈ and 3ʳᵈ response for patients receiving -ePRO or +ePRO follow-up (a), and mean PAM score at 1ˢᵗ, 2ⁿᵈ and 3ʳᵈ response for the -/+ePRO group (b).*
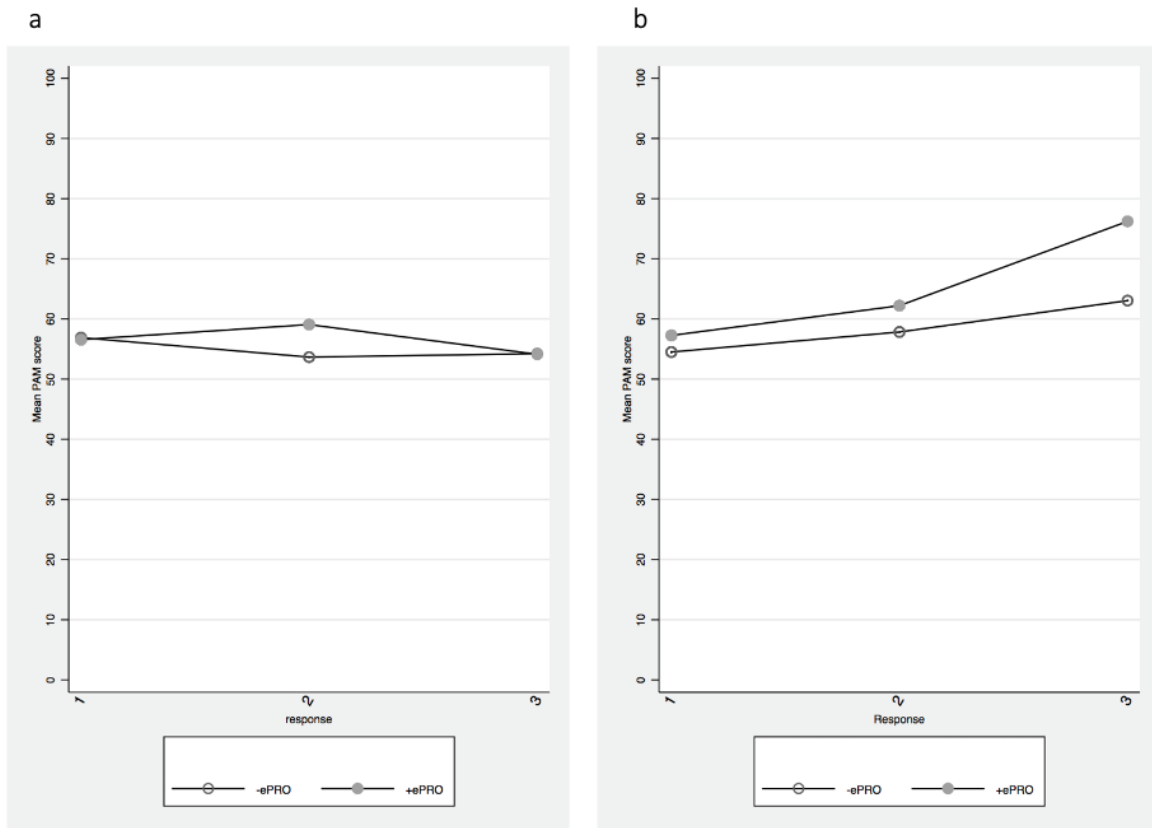
Patient involvement

Patients' assessment of PI in the consultation is presented in Figure 13. Irrespective of the question (I-V), a larger proportion of patients in the +ePRO group evaluated themselves as "much" involved in the consultation (Figure 12).
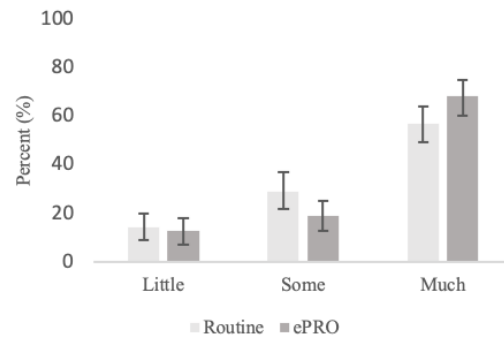
Figure 12. *Patient´s assessment of patient involvement stratified by groups (ePRO+/-).*

Q1. The healthcare provider asked about my own experiences with my illness / condition
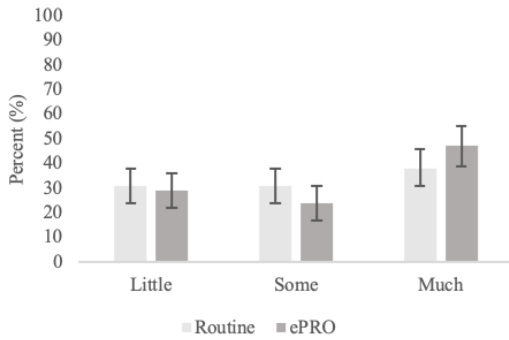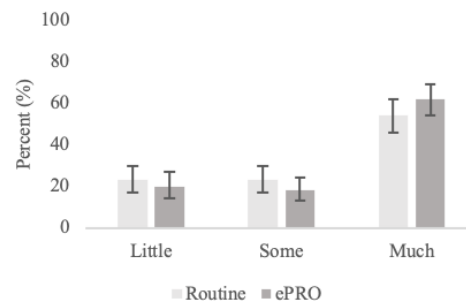

Q2. I talked to the healthcare provider about the questions or concerns I had
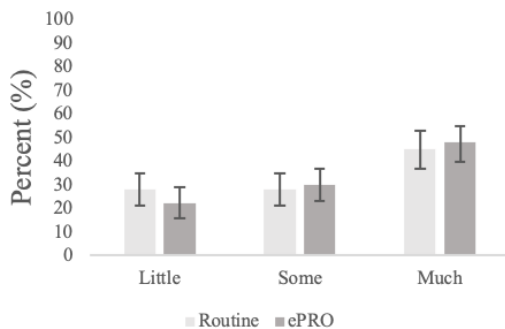

Q3. The healthcare professional encouraged me to ask questions or talk about concerns
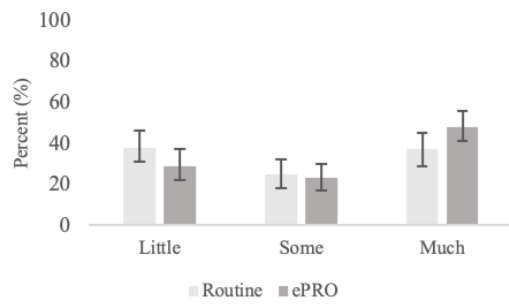
Q4. I received advice when deciding what was going to happen

Q5. I have had appropriate conversations with healthcare professionals about how to best manage my illness / condition

7. Discussion

This section discusses the main findings of Paper I-IV by considering aspects of internal and external validity, and it places our results in the context of the existing international literature. Paper I and II will focus on aspects of S-PM and M-PM along with early detection of PM and selection of high-risk patients. The discussion of Paper III and IV will primarily address aspects of PRO as a patient-involving tool and outcome measurement tool, and it will offer a general review of PI as a strategy to achieve patient-centred care within this population treated with complex surgery for advanced cancer.

7.1 Main findings
7.1.1 Paper I and II

Using our algorithm combining data from the Danish medical registries (DCCG, DNPR and DNPatR), we identified 5% of patients with CRC with S-PM. This percentage corresponds to international findings based on registry data [67,68,71,75]. We found that the DNPR and the DNPatR capture fewer than half of patients with S-PM. However, potential candidates for curative treatment are registered with a higher completeness than the rest of the PM population. It should be noted that this was demonstrated for patients with S-PM and therefore does not necessarily apply to patients with M-PM. This reservation should be considered when using data from these registries. In Paper II, we found an overall low risk of M-PM of 2.2% after 5 years considering all-cause mortality as a competing risk. In accordance with international literature (Table 1), we found that the primary risk factors for M-PM are advanced T and N category, which alone, according to our data, can increase the absolute risk by up to 10.3% 3 years after intended curative CRC surgery. Furthermore, we found that factors such as right-sided colonic tumours, emergency surgery, extramural venous invasion and surgical radicality (R1) independently increased the risk of M-PM.

7.1.2 Paper III and IV

To facilitate patient-centred care, we developed an intervention aiming to involve patients in their follow-up after complex surgery for advanced cancer. The intervention consisted of e-PROs and prioritised issues among patients' preferences as a supplement to the routine follow-up consultations. The ePRO was developed in collaboration with patients, clinicians and researchers, who all found it to be sensitive and sufficient to cover patients' need in the follow-up period after CRS+HIPEC. The primary issues prioritised by patients in the follow-up consultation were

gastrointestinal symptoms (including problems related to ostomies and hernias), explanation of the CT scan (i.e. potential recurrence) and future concerns regarding prognosis and follow-up.

In 21% of the ePRO consultations, the surgeon did not take the ePRO into consideration. Yet, patients found that the ePRO follow-up consultations had a higher degree of PI as measured by five specific questions on that topic [212] and that the consultations tended to encourage and facilitate conversations about questions and concerns and furthered conversation about patients' own experience with their disease/illness. Furthermore, patients with an ePRO consultation tended to assess themselves as being more involved in the decision-making process than patients with -ePRO consultations (Figure 12). Patients with an ePRO consultation did not report a higher degree of patient activation.

7.2 Critical methodological considerations

The internal validity is the degree to which the results of the papers are correct or if they are prone to *random* or *systematic* error[217]. The effect of a *random* error on the estimate increases with decreasing sample size, whereas the impact of a *systematic* error is due to study design and (often) unaffected by sample size. Systematic errors may be categorised intro selection bias, information bias and confounding[217].

7.2.1 Selection bias

In Paper I, we did not use medical journals as a gold standard, which is usually done in traditional validation studies. The quality of medical journals as far as validation of registered metastases is concerned has been questioned[196,218], mainly because medical charts themselves may be incomplete. This incompleteness may concern the presence, the exact number and (any) location of single or multiple metastases. In the DCCG, dedicated CRC surgeons have been required to register the presence or absence of PM since 2014. We therefore expect that these data have a high degree of completeness, and we used these data as the validation source/gold standard.

The primary selection bias of concern is loss of subjects during the study period, which will prevent direct comparison of average estimates between groups because the outcome is unknown for lost subjects. In a registry-based cohort study, such as Paper II, potential selection bias due to loss to follow-up is not a major problem since the DCCG [201] and the DNPR have a high degree of completeness[219]. Yet, other aspects of selection bias must also be considered. A special type of selection bias may be referred to as survivor bias, which occurs due to differential competing risks.

Survivor bias may exist in Paper II where we considered both mortality and other cancers as competing risks. We found a high mortality rate in the population, reaching nearly 15% after five years (Figure 8). Potentially, mortality was more substantial among the high-risk population; thus, these subjects were censored in the statistical analysis. The implications of the presence of survivor bias would be that the true incidence and hence the magnitude of each risk factor would be underestimated.

In Paper IV, the loss of subjects could be due to non-responders for both ePRO and outcome. The reason for non-response is unknown, and its impact depends on the reason for non-response. Responders may potentially be healthier participants because it required mental and physical resources to answer the questionnaire. On the other hand, in theory, healthier participants might be prone not to assess the ePRO because they feel healthy and find it unnecessary to participate. In both cases, the effect depends on the outcome measurement of interest. For example, in the case of healthier participants, hypothetically, an outcome like PI may be reported to be higher in this group of patients because they had more mental and physical resources; thus, the estimate of PI would overestimate the potential effect of an intervention. On the other hand, one could hypothesize that the potential for change (with a patient-involving intervention) is less in this group (i.e. healthier participants)[172,220,221]. Thus, the average estimate of PI would underestimate the potential effect of an intervention. To investigate the magnitude of a potential selection bias, the demographic characteristics of responders, non-responders and non-participants should be analysed in a sensitivity analysis.

7.2.2 Information bias

Information bias occurs when random or systematic inaccuracy affects the measurement of important variables (exposure or outcome). In general, misclassification (i.e. exposure, disease / outcome) can be categorised into *differential* and *non-differential misclassification*. The former depends on the value of other variables, whereas the latter is independent of the value of other variables [217].

We investigated the completeness of PM registered in the Danish medical registries to assess the magnitude of potential information bias (i.e. misclassification) affecting exposure or outcome in future studies. Overall, the completeness of registered S-PM was low; however, conducting a stratified analysis, we demonstrated that potential candidates for curative treatment were registered with a higher completeness in the DNPR than the remaining S-PM population. This potentially

introduces differential misclassification in the registration of PM, i.e. the registration of S-PM depends on age, WHO performance status and metastatic status.

The low completeness of PM registrations was investigated for S-PM and not for M-PM; however, one could assume that the same was valid for M-PM. This should be taken into consideration if the registry-based information on PM is used in future studies (both as exposure and outcome). Thus, if underreporting is due to non-differential misclassification, measurements of overall risk and RDs would be based on a disease variable with a low completeness (i.e. outcome in Paper II), thereby underestimating the true overall risk and the impact of each risk factor. The differential misclassification bias described in Paper I introduces another type of bias called sampling bias. In the case of a higher registration of potential candidates for curative treatment (i.e. a healthier population), these patients are sampled differently than the rest of the population. The impact of this is particularly important to consider in the analysis of survival, as the consequence would be an overestimation of the survival and prognosis for these patients.

Considering PRO, another type of information bias, i.e. recall bias, is important. In Paper IV, all measurements (intervention and outcome) could be affected by recall bias. The impact of any recall bias is difficult to predict. In Paper IV, recall bias regarding the ePRO would not affect any estimate, because it was used as a tool to facilitate PI. However, the outcome measurements (measured 2-4 days after the follow-up consultation) could be affected by recall bias dependent on the experience at the follow-up consultation (i.e. differential misclassification).

7.2.3. Confounding

Confounding occurs in cohort studies, especially in investigation of the association between exposure and outcome [217]. Thus, in the present thesis, this is relevant only for Paper II and IV. Confounding can simply be explained as the "confusion of effects". Thus, an observed risk association between exposure and outcome may be misinterpreted as the effect of the exposure although it is actually caused by the confounder. Confounding can be adjusted for in the study design (e.g. randomisation, restriction, matching) or analyses (e.g. matching, stratification, statistical adjustments (simple or multivariable) or sensitivity analysis), whereas statistical analyses rarely adjust for substantial design flaws, i.e. selection and information bias. The magnitude of these flaws must be investigated in sensitivity analyses[217].

Paper II
We performed a multivariable risk regression analysis to adjust for potential confounding.

Paper IV

Paper IV was performed as a descriptive intervention study. We therefore did not perform multivariable adjustment analysis of the outcome estimates, since the study was underpowered for this purpose. In general, a well-designed, carefully executed study usually gives results that are obvious without a formal analysis; and if there are substantial flaws in design and execution, a formal analysis will not help[222]. Therefore, our results may be affected by several potentially confounding effects; disease, comorbidity, gender, etc. Furthermore, certain factors are difficult to measure and consequently cannot be adjusted for. These unmeasured factors, e.g. the patient-clinician relationship, may affect the results to a variable, unknown degree. To investigate the magnitude of the patient-clinician relationship, stratification for the clinician at each visit could have been performed.

Finally, as the study was performed over a 2-year period, both potentially confounding covariates, i.e. ePRO responses and outcome measurement, were time-dependent and may thus have been affected by time.

7.2.4 External validity

To offer a convincing conclusion, it is necessary and important to ensure study replicability, i.e. establish the external validity of the study. Assessment of the replicability of Paper I is possible because clinical variables, ICD-10 codes and SNOMED codes are specified (see Appendix I). The combination of codes is simple and reproducible (i.e. we combined three variables from the DCCG, two ICD-10 codes and several SNOMED codes), enabling a potential external validation. However, at a national level, a validation would not be possible, simply because no other data sources are available against which to validate our algorithm. An external validation using international data sources could theoretically be possible by comparing the completeness of S-PM data registered in databases such as Surveillance, Epidemiology and End Results (SEER-Medicare) and/or the American National Cancer Database (NCDB) with data obtained from a clinical database.

In Paper II, we included patients who were free of other cancer, S-PM and other metastases, and who received radical or microradical surgery. Due to this strict inclusion, only 53% of the study population was included in the analysis for risk and risk factors for M-PM (Appendix 1), and potentially introduces intentional selection bias. The implication of our strict inclusion criteria's is a population with an a priori low risk of M-PM, which affects our external validity and should be taken into consideration when generalising our results to other populations.

7.3 Synchronous peritoneal metastases

Synchronous peritoneal metastases have been reported at a prevalence of around 5% in patients at the time of CRC presentation [67,68], which correlates with our findings in Paper I. Characteristics observed in the majority of patients with CRC and S-PM include advanced tumour features (i.e. T4 tumours and lymph node involvement), age and poor performance status [68]. A particular challenge that must be addressed in this group is disease dissemination at the time of CRC diagnosis, which limits treatment options[223,224]. This is supported by our findings in Paper I, where 52% of the S-PM population presented with liver and/or lung metastases. For patients with S-PM, depending on the extent of the peritoneal disease, patient performance and preferences and the institutional capability, treatment options vary among none/supportive care, systemic chemotherapy, palliative resections, surgical procedures with resection of the primary tumour (open or laparoscopic), debulking/cytoreduction alone or CRS in combination with HIPEC[225].

Previous studies have demonstrated that treatment strategies are diverse, both on a national and an international level[71,226,227], reflecting the heterogeneity of the population with S-PM. Current guidelines[60] recommend that CRS+HIPEC is considered if the PCI allows it. The PCI is the most compelling prognostic factor[228], and it has been demonstrated that a PCI > 15 significantly reduces survival; hence, this is considered as a contraindication[228]. Despite these recommendations, there may be situations in which CRS+HIPEC is not an option. For example, some patients debut with intestinal obstruction (or perforation) of the CRC due to S-PM, which requires emergency treatment of the primary tumour. The selected emergency treatment could be resection of the primary tumour, diverting stoma or self-expanding metallic stent [229]. There may also be situations in which the peritoneal involvement goes unnoticed perioperatively and is discovered during the histological examination of the bowel specimen. Regardless of the situation, resection of S-PM without CRS+HIPEC is associated with a high recurrence rate [42,195] and potentially conflicts with the opportunities for treatment with CRS+HIPEC for several reasons. First, small tumour cells will be captured into fibrosis and adherences during the primary resection which hampers perfusion of the HIPEC into the tissue[230]. Second, the possibility of CRS+HIPEC may be delayed for up to 3-6 months in case of a primary open surgery with resection of the primary tumour [92](. In case of S-PM and a PCI <15, CRS+HIPEC along with resection of the primary tumour should be considered as the most optimal treatment [231].

Dutch data from the past two decades testify to a general increase in some treatment modalities (i.e. systemic therapy, CRS+HIPEC and resection of lymphatic or haematogenous metastases) offered to patients with S-PM. Specifically, Dutch data show that from 2005-2009, 10% of patients with S-PM were treated with CRS+HIPEC. This percentage rose to 23% from 2010-2014. Additionally, a significant increase in overall median survival in the total population of patients with S-PM has been observed, increasing from 6 months in 1995-2000 to 12.5 months in 2010-2014[80,81]. Simultaneously, other advancements in the treatment of CRC metastases have been seen. For example, treatment with CRS+HIPEC and concurrent treatment of liver metastases has been investigated and proven to be safe and feasible [139]with a beneficial survival effect compared with systemic chemotherapy [232-234].

Despite the growing number of treatment options and beneficial survival effects for metastatic CRC, the presence of S-PM continues to represent a clinical problem. Therefore, to decrease the incidence of CRC and synchronous metastases and to improve overall survival for these patients, early detection (i.e. screening programmes) of CRC and removal of pre-malignant polyps have been prioritised [1]. The introduction of CRC screening has stabilised or decreased the incidence of CRC[1], and early detection of CRC is expected to decrease the incidence of CRC metastases and lower mortality[235,236]. Despite the introduction of screening, the overall participant rate in Denmark has been reported to be 67.2%[237], and some will debut with CRC at an advanced stage, hence the presence of S-PM continues to represent a clinical problem.

7.4 Metachronous peritoneal metastases

As demonstrated in Table 1, registry-based studies from Sweden[67] and The Netherlands[68,70] report incidences comparable with ours, while some clinical trials have demonstrated incidences of PM reaching 56% in asymptomatic patients a year after CRC surgery[195]. In general, a risk is a probability that takes a value conditional on specific selected pieces of information and may be higher or lower than that value if we condition on other relevant information. Therefore, the assignment of a given risk merely reflects the particular grouping. This is especially relevant when considering the literature regarding the incidence of PM among patients with CRC, where reported incidences fall in the range 3-56%[72,195]. In Paper II, we found an overall risk of 2.2% [2.0; 2.4] after 5 years. We did expect that the incidence of M-PM would have decreased due to improvements in surgical and oncological treatment [4] compared to previous registry-based studies[67,68]. The incidence of M-PM reflects the surveillance and diagnostics of recurrence after curative CRC. In Denmark,

follow-up is conducted according to national guidelines recommending that patients with CRC, as a minimum, undergo a CT of the thorax and abdomen at 12 and 36 months after surgery and a colonoscopy every fifth year until the age 75 years (DCCG – opfoelgning). No optimal surveillance is available, and as outlined in section 2.2.2, the sensitivity of CT to detect PM is limited. Registry-based data of PM is aggregated on this basis, which should be taken into consideration when interpreting incidences and risk factors based on such data. Paper I, demonstrates that < half of patients with S-PM are registered in the Danish Medical Registries. Even though we have not investigated the validity of M-PM registration, one could hypothesis that similar registration is current for M-PM. In Table 1, some of the exsisting international registry-based data is listed. These data have founded the basis for definition of high-risk patients, without a description of the validity. These high-risk patients have been included in the COLOPEC trial[143] and the PROHYLOCHIP[144] trial. The PROHYLOCHIP trial demonstrates, that despite no sign of recurrence by standard imaging (6 months after CRC surgery), still, 37 patients out of 71 patients in the experimental arm had PM at the second-look. Furthermore, the aetiological patterns underlying recurrence remain unknown/speculative; hence, the anatomical site of recurrence (some with PM, some with liver and/or lung metastases) may vary although patients have largely the same TNM stage; some patients develop metastases in the early follow-up period, others later[143,144]. Both trials have demonstrated the major clinical problem with recurrence in the peritoneum for particular high-risk patients, and confirmed that no standard imaging technique can assist in the early detection.

In Paper II, we described a low risk of PM among a population considered to be at low risk (i.e. patients undergoing R0 or R1 resections, and patients free of other cancers and metastases 180 days after CRC surgery); yet, the incidence of M-PM continued to increase during a 3-year period. Our results suggest that recurrence in the peritoneum remains a problem even in a low-risk population. We identified T- and N-category as the major risk factors driving this increase in risk; yet, other independent risk factors included venous invasion, microradical surgery (R1), emergency surgery and right colonic cancers. Our results are consistent with the described high-risk populations identified in the international literature (Table 1), and underlines that patients with T4 category and N2 category tumours require thorough surveillance. Besides these well-known major risk factors, other risk factors are described only sparsely [229]. Therefore, the risk factors (right colonic cancers, emergency surgery, R1, EMVI) identified in Paper II could contribute with additional detailed information on which patients (among those with T4 tumours) require extra attention during the surveillance period. There is an inconsistency in the definition of high-risk patients. For example,

around half of the patients in the PROPHYLOCHIP trial had localized S-PM or synchronous ovarian metastases, which should be considered as signs of manifest PM; hence, potential candidates for CRS+HIPEC. In the COLOPEC trial, patients were included based on the following high-risk factors such as T4 tumours and tumour perforation. Despite the fact that we do know that PM occurs in patients at high-risk, the pattern of recurrence (i.e. early or late) in the peritoneum is (still) speculative, and there is currently no consensus on how to determine which subgroups develop metastases early or late during follow-up. This is supported by findings from the COLOPEC trial in[143] which PM was detected during surgical re-exploration (prior to intentionally adjuvant HIPEC) and by the fact that 10% of patients with pT4 CRC had PM within 2 months after primary resection. Still, Klaver et al. found that some patients developed M-PM at a longer interval (>12 months) after the primary resection. These findings motivated the launch of the COLOPEC-II trial[238]. In this trial, second-look diagnostic laparoscopy at 6-9 months after primary CRC and third look diagnostic laparoscopy at 18 months after CRC are performed to detect PM at the subclinical stage, which may be considered an essential strategy in follow-up of these patients with a T4N0-2M0 CRC[238] (Clinicaltrials.gov: NCT03413254). Results from the COLOPEC-II trial are expected to describe the pattern of PM recurrence and to differentiate between those with early and late recurrence.

In conclusion, thorough knowledge of the metastatic pattern in CRC is warranted. Registries offer the possibility of monitoring prevalence, incidence, treatment methods, mortality rates and prognosis of a given disease; however, the feasibility of this approach hinges on the validity and completeness of the recorded data. To our knowledge, our algorithm introduced in Paper I is the first published algorithm to detect PM recurrence. However, results from Paper I show a low level of registration completeness of PM in the Danish medical registries. It is unknown whether this also applies to international registries, and any conclusions in this regard are speculative. Before implementation of the algorithm, the accuracy with which metastases are registered should be improved. Therefore, an important step in the improvement of research within the epidemiological field of PM and its treatment is to encourage clinicians to register the presence of (all) metastases.

No consensus exists regarding a uniform follow-up [146], and the assessment of follow-up balances between benefits and disadvantages. The existing evidence for an intense follow-up has demonstrated neither a reduction in overall survival nor a higher rate of recurrence[149,239] , and the effect of intense follow-up on HRQoL, anxiety and depression remain inconclusive. However, a

method to early detection of microscopic residual disease after curative CRC surgery is needed. This has led to a new randomised multicentre trial, IMPROVE-IT2, which investigates the potential of minimally invasive blood-based analysis of circulating tumour DNA (cDNA) to guide postoperative surveillance for UICC stage II –III cancers[240]. The study aims to increase the proportion of patients that potentially can receive curatively intended resection for limited recurrent CRC[240]. Results are awaited.

With the introduction of ctDNA[240] the potential exists for a follow-up that effectively identifies the presence of microscopic residual disease and facilitates early, targeted treatment of metastases. The patient's perspective on follow-up has been investigated sparsely[241]. It has been demonstrated that patient-led follow-up does not result in less use of healthcare resources or improved patient self-management or satisfaction. In an RCT investigating the effect of patient-led follow-up, a sub-study demonstrated that within the first 13 months of the trial, 113 out of the 262 patients invited declined to participate[242]. The main reason reported for declining to participate was lack of energy. As intensive follow-up does not improve survival or the proportion of diagnosed recurrence and as results from patient-led follow-up have proven less effective, the patient's perspective on follow-up should be taken into consideration.

7.5 Patient involvement

7.5.1 Patient-reported outcomes to achieve involvement

In the present dissertation, we consider PI as a strategy to achieve patient-centred care[243] and PROs as a tool to facilitate PI during follow-up[244] . The identification of physical, functional and mental symptoms has previously been demonstrated to be effective for monitoring cancer patients' individual needs and concerns as well as their symptoms and disease development; and for making them more active and committed to self-management[182,245-247]. In Paper IV, we confirmed that the identification of symptoms seemed to increase PI by widening the scope for dialogue and encouraging patients to ask questions and share their experiences and concerns during follow-up visits. Nevertheless, monitoring PRO does not in itself assure PI[246,248,249] , and it should be recognised that the impact PROs have may not lie in their mere use but in the role played by mediators, e.g. implementation of a PRO strategy[246,249], changes in patient-physician communication and increased patient-centredness[175,250] , and the impact their use has on the patient completing the ePRO. It has been demonstrated that patients who prepare themselves (i.e. complete the ePRO) before a medical consultation become more personally reflected and are better at linking

symptoms to the disease process [182,248]. In Paper III, we demonstrated that 21% of the ePRO consultations were not documented in the Ambuflex system or the medical record. Even so, in Paper IV our results do indicate that ePRO consultations seemed to increase PI. Hence, filling in the ePRO at home before the consultation has an impact in itself. However, to determine the magnitude of this impact, a sensitivity analysis should be performed, investigating the patient's assessment of PI in the 21% of ePROs that were not completed.

PROs were initially introduced as a tool to identify the patient's perspective on health, illness and effects of treatment. For example, the PRO measure of the EORTC was primarily developed to monitor HRQoL and effects of oncological treatment in clinical trials[213]. During the past few years, the use of PRO in other settings has rapidly increased[186,205] , e.g. PROs as mediators of PI[176]. The validity of PROs is evaluated in terms of their contents (i.e. the PRO includes all dimensions of a construct), criterion (i.e. predict directly observable phenomenon) and construct (i.e. the extent to which a survey measures the theoretical construct it is intended to measure). As no specific PROs were available for the population undergoing complex surgery[55], a valid construct was ensured by including validated PROs (EORTC QLQ C-30[213,251], O28[215] and CR29[214]) in the ePRO. Other studies have suggested that predetermined PROs (e.g. EORTC QLQ C-30), which are set up as original questionnaires or structured sequences of questions, may not encompass the most compelling topics for the patient to discuss[247,248]. As we considered patients to be individuals with different needs, we added three prioritised issues among patients' preferences. We performed no formal development and validation of the ePRO[193]; however, we performed structured interviews with both patients and clinicians to determine the appropriateness of the ePRO. The results demonstrated that patients found the ePRO sensitive to identifying their symptoms and sufficient with respect to covering the breadth of symptoms experienced. Hypothetically, a PI consultation could also have used other validated PROs or simple questions and it could have been facilitated by using tailored communication strategies or a combination of these measures. A disadvantage when applying validated PROs is that some patients might consider the PROs to be standardised and unsuited for assessing issues relevant to them[247]. On the other hand, an advantage of using the validated PROs is the ability this approach affords to screen broadly for physical and mental symptoms (including function) as well as sexual, social and economic issues. This forced patients to reflect on multiple symptoms and sequelae following complex surgery for their advanced cancer disease, and enabled the clinician to get a quick overview of which symptoms (among a broad

category of symptoms) particularly affected the patient. It could be argued that the involvement of patients in the research and in the selection process is highly relevant[252].

7.5.2 Patient-reported outcomes to measure involvement

Studies often focus on different aspects of PI, aiming to describe health care definitions, patients' and/or clinicians' preferences, experiences of PI or outcomes of person-centred care[184]. The scientific impact of PI is limited due to our current inability to define and measure PI in any uniform way[162] . In the present dissertation, we applied questions (indicator targets of PI developed by DEFACTUM[212]) aiming to detect the patient's experience of PI during follow-up. Furthermore, to analyse the effect of the intervention, we applied the PAM measurement, which is recognised as an outcome measurement in the evaluation of patient engagement [184,253]. It has been suggested that surveys alone do not provide the full picture of patient-centred care, and that surveys should be supplemented with interviews (with patients, relatives and clinicians) and observations of clinical encounters[184]. Retrospectively, to inform aspects of PI and PA in a population with advanced cancer subjected to a newly developed intervention, evaluating the clinician's perspective as well would have been beneficial[254,255].

7.5.3 Aspects of patient involvement in patients undergoing complex cancer surgery

Throughout the years, PI has become increasingly used both nationally and internationally, and PI has become a prioritised item on both politicians and healthcare professionals' agendas[176]. Despite this, the implementation of PI into a clinical setting is complicated. Some state that the involvement of patients and their perspectives is an established practice, whereas others consider PI to represent a paradigmatic shift away from the traditional paternalistic healthcare model [256]. It has been suggested that PI ranges along a continuum from a consultation to a partnership and shared decision-making[257]. Therefore, the discussion of PI in a clinical setting should not constitute an 'either or' but rather a 'how'. The results from Paper IV demonstrate that the implementation of ePRO in follow-up harbours a potential for improving PI in a population undergoing complex surgery for advanced cancer. As the treatment of metastatic cancer has improved, the population of patients surviving advanced cancer (i.e. metastatic cancer) is expected to increase. Therefore, further investigation into strategies to involve this population of patients is needed.

Several circumstances regarding this population should be considered prior to a potential PI intervention. The treatment of metastatic disease is often centralised, and the growing centralisation necessitates transitions between different healthcare departments, different healthcare systems and

different geographical locations[173]. One of the consequences of these transitions is that the patients may feel unimportant and left behind in the organisational system, and the task to navigate between hospitals and treatments is left to the patients, which compromises their everyday life by forcing them to be available to the healthcare system[173]. Furthermore, in the follow-up, HIPEC patients sought family, friends and complementary treatments (i.e. cannabis medication) to find relief of symptoms[173,258]. This shows that PI is of special importance in this population. In Paper IV, our results demonstrate that using PRO in a consultation might improve PI and they identify the unresolved potential for using PI.

Another consideration is the risk of recurrence. Patients are treated for advanced cancer (i.e. metastatic cancer), and approximately three quarters of them will experience recurrence [259]. As demonstrated in Paper III (Figure x), a consequence of this is that for patients the CT is an important issue because it may disclose potential recurrence. The CT scan strongly impacts the consultation and hypothetically impairs the possibility of introducing PI. For PI to be effective, the two parties involved must have equal power, which can never actually be guaranteed[260]. Patients are individuals with different needs and different needs at different times, affecting their behaviour. A model called The Preference Scale conceptualises patients' preference for involvement in decisions about their health. This scale may be used for different groups of patients. The active patient experiences a patient-controlled consultation. The collaborative patient experiences a consultation in which the doctor and the patient share treatment responsibility. The passive patient experiences a consultation controlled by the clinician[261]. This diversity in experience is supported by findings in paper III, where we demonstrated that 23% of the prioritised issues did not include a response, and that the remaining issues of prioritisation included a variety of symptoms. In a complex cancer setting, PI should be a dynamic process adapted to the patient's need for involvement in each consultation. *A priori* screening for patient symptoms and well-being guided the clinician in the process of 'cure sometimes, treat often, comfort always' and demonstrated that PI is possible in patients treated with complex surgery for advanced cancer.

8. Conclusions

Based on the four studies included in the present thesis, the following conclusions can be drawn:

- The Danish medical registries (DNPR/DNPatR) capture <50% of patients registered with S-PM, but completeness is higher for potential candidates for curative treatment
- Based on data from the Danish medical registries, the risk of M-PM is low in a low-risk population
- Advanced T and N category primarily drives the increased risk of M-PM
- Factors such as right-sided colonic cancers and tumours requiring emergency surgery independently increase the risk of M-PM, while extramural venous invasion and microscopic tumour-involved resection margins (R1 resections) are associated with an increased risk of M-PM
- Patients undergoing complex surgery for PM are willing to use ePRO in a follow-up
- In approximately one fifth of consultations, clinicians do not seem to apply the ePRO
- PRO-based follow-up does not improve the patient's knowledge, skills and confidence in self-management
- PRO-based follow-up seems to further dialogue and encourage patients to ask questions and share their experiences and concerns

9. Perspectives

In the present thesis, we demonstrated that improvements in the general management of CRC have not changed the incidence of PM in a low-risk population. We identified several risk factors of different magnitude associated with cancer recurrence in the peritoneum. Even so, uncertainty prevails as to how early recurrence is best detected, which treatment is most effective and what is the optimal design for patient follow-up.

None of the trials investigating the effect of second-look with HIPEC reported a beneficial reduction in the risk of M-PM. In the COLOPEC trial, 21% of the included patients (patients with T4 category tumours or perforated colorectal tumours) developed M-PM at various times during a relatively short follow-up (2-12 months)[238] after curative CRC surgery. This raises two important questions. What is the effect of HIPEC? How should we select high-risk patients? First, concerns regarding HIPEC as an adjuvant treatment have been focused on the applied drug, HIPEC perfusion time, hyperthermic temperature, and different time-points for HIPEC administration (simultaneously with primary surgery or as a staged postoperative procedure. This discussion has been fuelled by the results from the PRODIGE 7 trial. Second, the definition of high-risk patients is inconsistent leading to different inclusion criteria in the COLOPEC and the PROHYLOCHIP trial. There should be a distinguee between the high-risk patients with localized S-PM and/or synchronous ovarian metastases, and those with other high-risk factors such as advanced T and Ncategory. Those patients with localized S-PM and/or synchronous ovarian metastases should be considered as candidates for CRS+HIPEC, and if this is not an option, results from the PROPHYLOCHIP demonstrates that intensive surveillance within the first year after CRC resection is important. As the PROHYLOCHOP trial demonstrated that surveillance with CT is insufficient to detect recurrent PM, second-look should be considered in these patients within the first year after CRC.

According to our results from Paper II, the incidence of M-PM increases up to 5 years after CRC surgery, and alongside advanced T and N category constituting a risk for M-PM, factors such as right-colonic cancers, tumours requiring emergency surgery, extramural venous invasion and microscopic tumour-involved resection margins contributes to the risk of M-PM. Histopathological factors such as tumour histology, tumour deposit, mismatch repair has also been associated with a worse prognosis and a higher metastatic potential[262]. With the improvements within the diagnosis, treatment and staging of CRC, we are obliged to develop our selection criteria. Our results from paper II demonstrate that surveillance for at least 3 years is highly relevant, and that

histopathological factors (i.e. extramural venous invasion and microscopic tumour-involved resection margins) should be included in a more detailed staging of CRC patients, to inform efforts to distinguish between subgroups of patients in terms of their outcome risk. There is an untapped potential for knowledge and international agreement of the optimal selection and surveillance of high-risk CRC patients, which should be clarified before the initiation of more studies investigating the effect of adjuvant HIPEC. Surveillance with CT to detect PM is insufficient, and a diagnostic laparoscopy is preferred. This has been initiated with the COLOPEC II trial, which evaluates the effect of second- and third-look diagnostic laparoscopy to detect early PM. Unfortunately, inclusion criteria's are restricted to curative resection of pT4a,bN0-2M0 CRC without further pathological high-risk factors. A detailed staging of high-risk groups will require a multidisciplinary effort between researchers, surgical oncologists and experienced pathologists.

As some factors in the follow-up remain uncertain, research at a population-based level is needed to ensure evidence-based information regarding recurrence, survival and long-term sequelae as a foundation for future guidelines. As demonstrated in Paper I, the registration of peritoneal metastases following curatively intended colorectal surgery has a low level of completeness in the Danish medical registries, and improvements are warranted to monitor and ensure evidence of the metastatic pattern following CRC surgery. There is a good possibility for through registration of CRC patients and recurrence in Denmark, because multidisciplinary team meetings are mandatory to determine stage of disease and treatment, along with a mandatory registration of first time CRC in the DCCG database. The Danish follow-up is guided by national guidelines recommending a computed tomography of the thorax and abdomen at 12 and 36 months after surgery. With such a structured follow-up, should it be natural to register recurrence (yes/no), location of recurrence and potential long-term sequelae in a clinical database such as the DCCG. This would improve the knowledge of patterns of recurrence and long-term sequelae at a population-based level.

At an individual level, follow-up serves multiple purposes besides detection of recurrence. Our knowledge of patient-centred care and side effects following complex cancer treatment (i.e. CRS+HIPEC) stems from small cohort studies and systematic reviews (ref), and no guidelines exist for how to detect and report side-effects following CRS+HIPEC. When providing patient-centered care, identification of the individual problems and symptoms is a key element. In Paper III and IV, we demonstrated that patients undergoing complex surgery for PM were positive towards follow-up supplemented by PRO. Our results indicate that PRO-based follow-up seems to facilitate dialogue that encourages patients to share their concerns and ask relevant questions. This indicates a

potential for improvement of patient-centred care and the facilitating ability of using PROs to do so. In this context, it should be acknowledged that the use of PROs requires a coordinated effort. First, financial resources must be available to provide a digital solution for the PRO, including the daily administration of the tools used. Second, resources must be allocated to secure continuous application of PROs in patient encounters. Third, all clinicians should be trained in the use of PRO. In Paper III, we demonstrate that patients prioritise different issues prior to a clinical consultation; the majority (80%) of patients who did not have a prioritised issue underwent complex surgery > 6 months. This indicate that the essence of patient-centred care is to customise follow-up; still, this need for a customised follow-up with PROs may not be present throughout the whole follow-up period. One could argue that standardised questionnaires are inconsistent with customised follow-up. However, until PRO becomes an integrated part of a follow-up routine, standardisation is required to *a priori* screen for the patient's needs, symptoms and concerns.

10. English abstract

Registries contain comprehensive data that provide clinicians and researchers with the possibility to monitor prevalence, incidence, mortality and prognosis of a disease on the assumption of valid data. In general, the validity of metastases registered in medical registries is debated (Chawla, Warren, Ehrenstein). Little is known about the validity of registrations of peritoneal metastases. In the first paper, we aimed to investigate the completeness of registrations of synchronous peritoneal metastases at the time of colorectal cancer diagnosis. We found that the Danish medical registries capture <50% of patients registered with synchronous peritoneal metastases. The completeness is higher for potential candidates for curative treatment than for the total population of patients with synchronous peritoneal metastases.

With the introduction of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy, survival and prognosis for a selective group of patients with limited peritoneal disease following gastrointestinal cancer has improved. To detect PM at limited stage, investigations into early detection of peritoneal recurrence among patients with a high risk has been initiated. The inclusion of high-risk patients in these studies is based on previous register-based and prospective studies, including populations subjected to surgery prior to the general improvements observed in the current up-to-date management regime for patients with colorectal cancer. In Paper II, we aimed to identify if the outlined improvements had affected the incidence and risk factors of metachronous peritoneal metastases. We found an overall low risk of 2.2% for metachronous peritoneal metastases within 5 years after curative surgery for colorectal cancer. We found that advanced T- and N-category primarily drives the increased the risk of metachronous peritoneal metastases up to 3 years after surgery for colorectal cancer. Furthermore, factors such as right-sided colonic cancers and tumours requiring emergency surgery independently increase the risk of M-PM, while extra-mural venous invasion and microscopic tumour-involved resection margins (R1 resections) contributed to the risk of M-PM. This supports the need for surveillance for at least 3 years post-surgery and surveillance may also be beneficial when selecting patients who require extra attention during the surveillance period.

Survival and prognosis of patients undergoing cytoreductive surgery and hyperthermic intraperitoneal chemotherapy are described in detail; yet other aspects of treatment such as optimal patient-centred follow-up are sparsely described. To facilitate patient-centred care, patient involvement is a preferred strategy, and it has proven to have beneficial outcomes such as better health-related quality of life and emotional well-being and to facilitate discussion of symptoms.

However, patient involvement has rarely been investigated in populations with advanced cancer treated with complex surgery. In the present dissertation, to facilitate patient-centred care, we introduced a follow-up based on digitally captured patient-reported outcomes in patients undergoing complex surgery for peritoneal metastases (ePRO). The ePRO consisted of standardised questionnaires (European Organisation for Research and Treatment of Cancer and some items from the Hospital and Anxiety Depression Scale) and three prioritized issues among patients' preferences for items to be discussed. We interviewed five patients, who all found the ePRO to be appropriate. None of the clinicians had any suggestions for additions to the ePRO. Overall, we found that patients were positive towards a follow-up supplemented with PRO, and 73% of the participants responded to the ePRO. In approximately one fifth of follow-up consultations, clinicians did not seem to apply the ePRO.

We measured the effect of the ePRO-based consultation in terms of patient activation and patient involvement. We did not find PRO-based follow-up to improve patient activation, i.e. the patient's knowledge, skills and confidence for self-management. However, PRO-based follow-up seemed to facilitate patient-centred follow-up and involved patients by widening the scope for dialogue and encouraging them to ask questions and share their experiences and concerns.

De danske registre indeholder omfattende data om patienters kontakt til syghusvæsenet i form af diagnose- og procedurekoder. Såfremt disse data er valide, giver de klinikere og forskere mulighed for at overvåge en sygdoms forekomst, dødelighed og prognose. Generelt er registreringen af kræftdiagnoser valid i de danske registre, hvorimod registreringen af mulige metastaser har været dårlig. Der vides intet om validiteten af registrering af peritoneale metastaser fra kolorektal kræft. Formålet i studie I var at undersøge de danske registers komplethed i registrering af peritoneale metastaser på tidspunktet for en kolorektal kræftdiagnose. Vi fandt, at <50% af patienterne med synkrone peritoneale metastaser bliver registreret i de danske registre. Fuldstændigheden af registreringer er højere for de patienter, der er mulige kandidater til intenderet helbredende behandling, end i den samlede population af patienter med synkrone peritoneale metastaser som helhed.

Behandlingen af peritoneale metastaser med udgangspunkt fra tyk- og endetarm er blevet forbedret med introduktionen af cytoreduktiv kirurgi og hyperthermisk intraperitoneal kemoterapi, om end dette dog kun gælder for en selektiv gruppe af patienter med begrænset peritoneal sygdom. Derfor er undersøgelser af den tidlige påvisning af peritoneal tilbagefald iværksat samtidig med, at der implementeres profylaktiske strategier for patienter med en høj risiko for peritonealt tilbagefald (Klaver - COLOPEC, Elias). Disse højrisikopatienter er defineret forud for de generelle forbedringer, der er blev observeret i den nuværende diagnostik, behandling og opfølgning af patienter med kolorektal kræft. Formålet med studie II var derfor at undersøge, om forbedringerne inden for kolorektalkirurgien har påvirket forekomsten af og risikofaktorerne for metakrone peritoneale metastaser. Vi fandt en samlet lav risiko på 2,2% for metakrone peritoneale metastaser inden for 5 år efter helbredende kirurgi for tyk- og endetarmskræft. Vi fandt, at avanceret T- og N-kategori primært driver den øgede risiko for metakrone peritoneale metastaser op til 3 år efter operation for kolorektalkræft. Endvidere er højresidige kolontumorer og tumorer, som kræver akutkirurgi, selvstændige risikofaktorer for M-PM, mens ekstrainvasion og mikroskopiske tumorinvolverede resektionsmargener (R1-resektioner) er forbundet med en øget risiko for M-PM. Resultaterne fra studie II understøtter behovet for opfølgning af kolorektalkræftpatienter i mindst 3 år, og resultaterne identificerer hvilke patientkategorier, der bør følges med større overvågenhed.

Prognosen for patienter, der gennemgår cytoreduktiv kirurgi og hyperthermisk intraperitoneal kemoterapi, er beskrevet i detaljer, mens andre aspekter af behandlingen såsom optimal patientcentreret opfølgning kun er sparsomt belyst. Patientinvolvering en foretrukken strategi til

patientcentreret behandling, og brugen af patientinvolvering har vist gavnlige resultater såsom bedre livskvalitet og større mentalt velvære og har faciliteret en diskussion af symptomer. Imidlertid er patientinddragelse sjældent undersøgt i populationer med avanceret kræft, der kræver kompleks kirurgi, for eksempel peritoneale metastaser. For at fremme patientcentreret opfølgning efter kompleks kirurgi for peritoneale metastaser introducerede vi en opfølgning baseret på elektroniske patientrapporterede outcomes. Formålet med studie III var at beskrive udviklingen i og genførligheden af denne form for opfølgning. De elektroniske patientrapporterede outcomes bestod af standardiserede spørgeskemaer samt tre prioriterede spørgsmål i overensstemmelse med patientens præference. Anvendeligheden af de elektroniske patientrapporterede outcomes blev evalueret af fem patienter, som alle fandt fremgangsmåden passende. Generelt fandt vi, at patienterne var positive over for en opfølgning suppleret med elektroniske patientrapporterede outcomes, hvilket illustreres af en svarrate på 73% af studiepopulationen. De primære problemer, der blev prioriteret af patienter til opfølgningskonsultationen, var gastrointestinale symptomer, forklaring af CT-scanningen og bekymringer vedrørende prognose (dvs. risiko for tilbagefald) og opfølgning. I cirka en femtedel af opfølgningskonsultationerne blev der anvendt ePRO. Formålet med studie IV var at estimere effekten af konsultationerne støttet af elektroniske patient-rapporterede outcomes. Effektmålene var patientaktivering og patientinvolvering. Vi fandt, at en opfølgning støttet af elektroniske patientrapporterede outcomes ikke forbedrede patientaktiveringen, dvs. patientens viden, færdigheder og selvtillid til selvledelse. Til gengæld var der en tendens til, at patientcentreret opfølgning involverede patienterne ved at udvide muligheden for dialog og tilskyndede patienter til at stille spørgsmål og dele deres oplevelser og bekymringer.

12.0 References

1. Arnold M, Sierra MS, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global patterns and trends in colorectal cancer incidence and mortality. *Gut.* 2017;66(4):683-691.
2. Brenner H, Kloor M, Pox CP. Colorectal cancer. *Lancet.* 2014;383(9927):1490-1502.
3. Benitez Majano S, Di Girolamo C, Rachet B, et al. Surgical treatment and survival from colorectal cancer in Denmark, England, Norway, and Sweden: a population-based study. *Lancet Oncol.* 2019;20(1):74-87.
4. Arnold M, Rutherford MJ, Bardot A, et al. Progress in cancer survival, mortality, and incidence in seven high-income countries 1995-2014 (ICBP SURVMARK-2): a population-based study. *Lancet Oncol.* 2019.
5. Iversen LH. Aspects of survival from colorectal cancer in Denmark. *Dan Med J.* 2012;59(4):B4428.
6. Stelzner S, Radulova-Mauersberger O, Zschuppe E, et al. Prognosis in patients with synchronous colorectal cancer metastases after complete resection of the primary tumor and the metastases. *J Surg Oncol.* 2019;120(3):438-445.
7. Iversen LH, Green A, Ingeholm P, Osterlind K, Gogenur I. Improved survival of colorectal cancer in Denmark during 2001-2012 - The efforts of several national initiatives. *Acta Oncol.* 2016;55 Suppl 2:10-23.
8. Heald RJ, Ryall RD. Recurrence and survival after total mesorectal excision for rectal cancer. *Lancet.* 1986;1(8496):1479-1482.
9. Quirke P, Steele R, Monson J, et al. Effect of the plane of surgery achieved on local recurrence in patients with operable rectal cancer: a prospective study using data from the MRC CR07 and NCIC-CTG CO16 randomised clinical trial. *Lancet.* 2009;373(9666):821-828.
10. Enker WE. Total mesorectal excision--the new golden standard of surgery for rectal cancer. *Ann Med.* 1997;29(2):127-133.
11. Hohenberger W, Weber K, Matzel K, Papadopoulos T, Merkel S. Standardized surgery for colonic cancer: complete mesocolic excision and central ligation--technical notes and outcome. *Colorectal Dis.* 2009;11(4):354-364; discussion 364-355.
12. Sondenaa K, Quirke P, Hohenberger W, et al. The rationale behind complete mesocolic excision (CME) and a central vascular ligation for colon cancer in open and laparoscopic surgery : proceedings of a consensus conference. *Int J Colorectal Dis.* 2014;29(4):419-428.
13. Storli KE, Sondenaa K, Furnes B, et al. Short term results of complete (D3) vs. standard (D2) mesenteric excision in colon cancer shows improved outcome of complete mesenteric excision in patients with TNM stages I-II. *Tech Coloproctol.* 2014;18(6):557-564.
14. Golfinopoulos V, Salanti G, Pavlidis N, Ioannidis JP. Survival and disease-progression benefits with treatment regimens for advanced colorectal cancer: a meta-analysis. *Lancet Oncol.* 2007;8(10):898-911.
15. Nagtegaal ID, van de Velde CJ, van der Worp E, et al. Macroscopic evaluation of rectal cancer resection specimen: clinical significance of the pathologist in quality control. *J Clin Oncol.* 2002;20(7):1729-1734.
16. Quirke P, Morris E. Reporting colorectal cancer. *Histopathology.* 2007;50(1):103-112.
17. Archampong D, Borowski D, Wille-Jorgensen P, Iversen LH. Workload and surgeon's specialty for outcome after colorectal cancer surgery. *Cochrane Database Syst Rev.* 2012(3):CD005391.
18. Hsu RCJ, Salika T, Maw J, Lyratzopoulos G, Gnanapragasam VJ, Armitage JN. Influence of hospital volume on nephrectomy mortality and complications: a systematic review and meta-analysis stratified by surgical type. *BMJ Open.* 2017;7(9):e016833.

19. van Heek NT, Kuhlmann KF, Scholten RJ, et al. Hospital volume and mortality after pancreatic resection: a systematic review and an evaluation of intervention in the Netherlands. *Ann Surg.* 2005;242(6):781-788, discussion 788-790.
20. van Gestel YR, de Hingh IH, van Herk-Sukel MP, et al. Patterns of metachronous metastases after curative treatment of colorectal cancer. *Cancer Epidemiol.* 2014;38(4):448-454.
21. Ghiringhelli F, Hennequin A, Drouillard A, Lepage C, Faivre J, Bouvier AM. Epidemiology and prognosis of synchronous and metachronous colon cancer metastases: a French population-based study. *Dig Liver Dis.* 2014;46(9):854-858.
22. McArdle C. ABC of colorectal cancer: effectiveness of follow up. *BMJ.* 2000;321(7272):1332-1335.
23. 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.
24. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *Cell.* 2011;144(5):646-674.
25. van der Geest LG, Lam-Boer J, Koopman M, Verhoef C, Elferink MA, de Wilt JH. Nationwide trends in incidence, treatment and survival of colorectal cancer patients with synchronous metastases. *Clin Exp Metastasis.* 2015;32(5):457-465.
26. van der Pool AE, Damhuis RA, Ijzermans JN, et al. Trends in incidence, treatment and survival of patients with stage IV colorectal cancer: a population-based series. *Colorectal Dis.* 2012;14(1):56-61.
27. Cummings LC, Payes JD, Cooper GS. Survival after hepatic resection in metastatic colorectal cancer: a population-based study. *Cancer.* 2007;109(4):718-726.
28. Cunningham D, Atkin W, Lenz HJ, et al. Colorectal cancer. *Lancet.* 2010;375(9719):1030-1047.
29. Compton CC, Henson DE, Hutter RV, Sobin LH, Bowman HE. Updated protocol for the examination of specimens removed from patients with colorectal carcinoma. A basis for checklists. *Arch Pathol Lab Med.* 1997;121(12):1247-1254.
30. Sobin LH, Hermanek P, Hutter RV. TNM classification of malignant tumors. A comparison between the new (1987) and the old editions. *Cancer.* 1988;61(11):2310-2314.
31. Sobin LH. TNM, sixth edition: new developments in general concepts and rules. *Semin Surg Oncol.* 2003;21(1):19-22.
32. Sobin LH. TNM: principles, history, and relation to other prognostic factors. *Cancer.* 2001;91(8 Suppl):1589-1592.
33. Sugarbaker PH. Peritoneal Metastases from Gastrointestinal Cancer. *Curr Oncol Rep.* 2018;20(8):62.
34. Halkia E, Spiliotis J, Sugarbaker P. Diagnosis and management of peritoneal metastases from ovarian cancer. *Gastroenterol Res Pract.* 2012;2012:541842.
35. Bignell M, Carr NJ, Mohamed F. Pathophysiology and classification of pseudomyxoma peritonei. *Pleura Peritoneum.* 2016;1(1):3-13.
36. Carr NJ, Cecil TD, Mohamed F, et al. A Consensus for Classification and Pathologic Reporting of Pseudomyxoma Peritonei and Associated Appendiceal Neoplasia: The Results of the Peritoneal Surface Oncology Group International (PSOGI) Modified Delphi Process. *Am J Surg Pathol.* 2016;40(1):14-26.
37. Sugarbaker PH, Acherman YI, Gonzalez-Moreno S, et al. Diagnosis and treatment of peritoneal mesothelioma: The Washington Cancer Institute experience. *Semin Oncol.* 2002;29(1):51-61.

38.   Sugarbaker PH. Colorectal cancer metastases: a surgical perspective. *Surg Oncol Clin N Am.* 2013;22(2):289-298.
39.   Mikula-Pietrasik J, Uruski P, Tykarski A, Ksiazek K. The peritoneal "soil" for a cancerous "seed": a comprehensive review of the pathogenesis of intraperitoneal cancer metastases. *Cell Mol Life Sci.* 2018;75(3):509-525.
40.   Sugarbaker PH. Prevention and Treatment of Peritoneal Metastases: a Comprehensive Review. *Indian J Surg Oncol.* 2019;10(1):3-23.
41.   Ceelen WP, Bracke ME. Peritoneal minimal residual disease in colorectal cancer: mechanisms, prevention, and treatment. *Lancet Oncol.* 2009;10(1):72-79.
42.   Sugarbaker PH. Update on the prevention of local recurrence and peritoneal metastases in patients with colorectal cancer. *World J Gastroenterol.* 2014;20(28):9286-9291.
43.   Lemoine L, Sugarbaker P, Van der Speeten K. Pathophysiology of colorectal peritoneal carcinomatosis: Role of the peritoneum. *World J Gastroenterol.* 2016;22(34):7692-7707.
44.   Gerber SA, Rybalko VY, Bigelow CE, et al. Preferential attachment of peritoneal tumor metastases to omental immune aggregates and possible role of a unique vascular microenvironment in metastatic survival and growth. *Am J Pathol.* 2006;169(5):1739-1752.
45.   Clark R, Krishnan V, Schoof M, et al. Milky spots promote ovarian cancer metastatic colonization of peritoneal adipose in experimental models. *Am J Pathol.* 2013;183(2):576-591.
46.   Narasimhan V, Ooi G, Michael M, Ramsay R, Lynch C, Heriot A. Colorectal peritoneal metastases: pathogenesis, diagnosis and treatment options - an evidence-based update. *ANZ J Surg.* 2020.
47.   Xue L, Hyman NH, Turaga KK, Eng OS. Peritoneal Metastases in Colorectal Cancer: Biology and Barriers. *J Gastrointest Surg.* 2020;24(3):720-727.
48.   Gilly FN, Cotte E, Brigand C, et al. Quantitative prognostic indices in peritoneal carcinomatosis. *Eur J Surg Oncol.* 2006;32(6):597-601.
49.   Harmon RL, Sugarbaker PH. Prognostic indicators in peritoneal carcinomatosis from gastrointestinal cancer. *Int Semin Surg Oncol.* 2005;2(1):3.
50.   Jacquet P, Sugarbaker PH. Clinical research methodologies in diagnosis and staging of patients with peritoneal carcinomatosis. *Cancer Treat Res.* 1996;82:359-374.
51.   Verwaal VJ, van Tinteren H, van Ruth S, Zoetmulder FA. Predicting the survival of patients with peritoneal carcinomatosis of colorectal origin treated by aggressive cytoreduction and hyperthermic intraperitoneal chemotherapy. *Br J Surg.* 2004;91(6):739-746.
52.   Faron M, Macovei R, Goere D, Honore C, Benhaim L, Elias D. Linear Relationship of Peritoneal Cancer Index and Survival in Patients with Peritoneal Metastases from Colorectal Cancer. *Ann Surg Oncol.* 2016;23(1):114-119.
53.   Goere D, Souadka A, Faron M, et al. Extent of colorectal peritoneal carcinomatosis: attempt to define a threshold above which HIPEC does not offer survival benefit: a comparative study. *Ann Surg Oncol.* 2015;22(9):2958-2964.
54.   Laghi A, Bellini D, Rengo M, et al. Diagnostic performance of computed tomography and magnetic resonance imaging for detecting peritoneal metastases: systematic review and meta-analysis. *Radiol Med.* 2017;122(1):1-15.
55.   Koumpa FS, Xylas D, Konopka M, et al. Colorectal Peritoneal Metastases: A Systematic Review of Current and Emerging Trends in Clinical and Translational Research. *Gastroenterol Res Pract.* 2019;2019:5180895.
56.   Koh JL, Yan TD, Glenn D, Morris DL. Evaluation of preoperative computed tomography in estimating peritoneal cancer index in colorectal peritoneal carcinomatosis. *Ann Surg Oncol.* 2009;16(2):327-333.

57. Esquivel J, Chua TC, Stojadinovic A, et al. Accuracy and clinical relevance of computed tomography scan interpretation of peritoneal cancer index in colorectal cancer peritoneal carcinomatosis: a multi-institutional study. *J Surg Oncol.* 2010;102(6):565-570.

58. Chicago Consensus Working G. The Chicago Consensus on peritoneal surface malignancies: Management of colorectal metastases. *Cancer.* 2020;126(11):2534-2540.

59. Maciver AH, Lee N, Skitzki JJ, Boland PM, Francescutti V. Cytoreduction and hyperthermic intraperitoneal chemotherapy (CS/HIPEC) in colorectal cancer: Evidence-based review of patient selection and treatment algorithms. *Eur J Surg Oncol.* 2017;43(6):1028-1039.

60. Chicago Consensus Working G. The Chicago Consensus on Peritoneal Surface Malignancies: Standards. *Ann Surg Oncol.* 2020;27(6):1743-1752.

61. Fletcher RH, Fletcher SW, Fletcher GS. Chapter 2: Frequency. In: *Clinical Epidemiology: The essentials.* 5th ed. Philadelphia: Lippincott Williams & Wilkins; 2014.

62. Fletcher RH, Fletcher SW, Fletcher GS. Chapter 4: Risk - Basic Principles. In: *Clinical Epidemiology: The essentials.* 5th ed. Philadelphia: Lippincott Williams & Wilkins; 2014.

63. Fletcher RH, Fletcher SW, Fletcher GS. Chapther 5: Risk: Exposures to Disease. In: *Clinical Epidemiology: The essentials.* 5th ed. Philadelphia: Lippincott Williams & Wilkins; 2014.

64. Hentzen J, Rovers KP, Kuipers H, et al. Impact of Synchronous Versus Metachronous Onset of Colorectal Peritoneal Metastases on Survival Outcomes After Cytoreductive Surgery (CRS) with Hyperthermic Intraperitoneal Chemotherapy (HIPEC): A Multicenter, Retrospective, Observational Study. *Ann Surg Oncol.* 2019;26(7):2210-2221.

65. Mekenkamp LJ, Koopman M, Teerenstra S, et al. Clinicopathological features and outcome in advanced colorectal cancer patients with synchronous vs metachronous metastases. *Br J Cancer.* 2010;103(2):159-164.

66. Engstrand J, Stromberg C, Nilsson H, Freedman J, Jonas E. Synchronous and metachronous liver metastases in patients with colorectal cancer-towards a clinically relevant definition. *World J Surg Oncol.* 2019;17(1):228.

67. Segelman J, Granath F, Holm T, Machado M, Mahteme H, Martling A. Incidence, prevalence and risk factors for peritoneal carcinomatosis from colorectal cancer. *Br J Surg.* 2012;99(5):699-705.

68. Lemmens VE, Klaver YL, Verwaal VJ, Rutten HJ, Coebergh JW, de Hingh IH. Predictors and survival of synchronous peritoneal carcinomatosis of colorectal origin: a population-based study. *Int J Cancer.* 2011;128(11):2717-2725.

69. Jayne DG, Fook S, Loi C, Seow-Choen F. Peritoneal carcinomatosis from colorectal cancer. *Br J Surg.* 2002;89(12):1545-1550.

70. van Gestel YR, Thomassen I, Lemmens VE, et al. Metachronous peritoneal carcinomatosis after curative treatment of colorectal cancer. *Eur J Surg Oncol.* 2014;40(8):963-969.

71. Quere P, Facy O, Manfredi S, et al. Epidemiology, Management, and Survival of Peritoneal Carcinomatosis from Colorectal Cancer: A Population-Based Study. *Dis Colon Rectum.* 2015;58(8):743-752.

72. Koppe MJ, Boerman OC, Oyen WJ, Bleichrodt RP. Peritoneal carcinomatosis of colorectal origin: incidence and current treatment strategies. *Ann Surg.* 2006;243(2):212-222.

73. Baratti D, Kusamura S, Pietrantonio F, Guaglio M, Niger M, Deraco M. Progress in treatments for colorectal cancer peritoneal metastases during the years 2010-2015. A systematic review. *Crit Rev Oncol Hematol.* 2016;100:209-222.

74. Tong D, Russell AH, Dawson LE, Wisbeck W. Second laparotomy for proximal colon cancer. Sites of recurrence and implications for adjuvant therapy. *Am J Surg.* 1983;145(3):382-386.

75. Enblad M, Graf W, Birgisson H. Risk factors for appendiceal and colorectal peritoneal metastases. *Eur J Surg Oncol.* 2018;44(7):997-1005.

76. Kerscher AG, Chua TC, Gasser M, et al. Impact of peritoneal carcinomatosis in the disease history of colorectal cancer management: a longitudinal experience of 2406 patients over two decades. *Br J Cancer.* 2013;108(7):1432-1439.

77. Honore C, Goere D, Souadka A, Dumont F, Elias D. Definition of patients presenting a high risk of developing peritoneal carcinomatosis after curative surgery for colorectal cancer: a systematic review. *Ann Surg Oncol.* 2013;20(1):183-192.

78. Sammartino P, Sibio S, Accarpio F, Di Giorgio A. Prevention of peritoneal carcinomatosis from colorectal cancer: a critical issue. *Ann Surg.* 2014;259(3):e51.

79. Sugarbaker PH. Patient selection and treatment of peritoneal carcinomatosis from colorectal and appendiceal cancer. *World J Surg.* 1995;19(2):235-240.

80. Razenberg LG, van Gestel YR, Creemers GJ, Verwaal VJ, Lemmens VE, de Hingh IH. Trends in cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for the treatment of synchronous peritoneal carcinomatosis of colorectal origin in the Netherlands. *Eur J Surg Oncol.* 2015;41(4):466-471.

81. Razenberg LG, Lemmens VE, Verwaal VJ, et al. Challenging the dogma of colorectal peritoneal metastases as an untreatable condition: Results of a population-based study. *Eur J Cancer.* 2016;65:113-120.

82. Wisselink DD, Braakhuis LLF, Gallo G, et al. Systematic review of published literature on oxaliplatin and mitomycin C as chemotherapeutic agents for hyperthermic intraperitoneal chemotherapy in patients with peritoneal metastases from colorectal cancer. *Crit Rev Oncol Hematol.* 2019;142:119-129.

83. Sadeghi B, Arvieux C, Glehen O, et al. Peritoneal carcinomatosis from non-gynecologic malignancies: results of the EVOCAPE 1 multicentric prospective study. *Cancer.* 2000;88(2):358-363.

84. Franko J, Shi Q, Meyers JP, et al. Prognosis of patients with peritoneal metastatic colorectal cancer given systemic therapy: an analysis of individual patient data from prospective randomised trials from the Analysis and Research in Cancers of the Digestive System (ARCAD) database. *Lancet Oncol.* 2016;17(12):1709-1719.

85. Franko J, Shi Q, Goldman CD, et al. Treatment of colorectal peritoneal carcinomatosis with systemic chemotherapy: a pooled analysis of north central cancer treatment group phase III trials N9741 and N9841. *J Clin Oncol.* 2012;30(3):263-267.

86. Klaver YL, Simkens LH, Lemmens VE, et al. Outcomes of colorectal cancer patients with peritoneal carcinomatosis treated with chemotherapy with and without targeted therapy. *Eur J Surg Oncol.* 2012;38(7):617-623.

87. Scaringi S, Leo F, Canonico G, Batignani G, Ficari F, Tonelli F. The role of cytoreductive surgery alone for the treatment of peritoneal carcinomatosis of colorectal origin. A retrospective analysis with regard to multimodal treatments. *Hepatogastroenterology.* 2009;56(91-92):650-655.

88. Bloemendaal AL, Verwaal VJ, van Ruth S, Boot H, Zoetmulder FA. Conventional surgery and systemic chemotherapy for peritoneal carcinomatosis of colorectal origin: a prospective study. *Eur J Surg Oncol.* 2005;31(10):1145-1151.

89. Verwaal VJ, Bruin S, Boot H, van Slooten G, van Tinteren H. 8-year follow-up of randomized trial: cytoreduction and hyperthermic intraperitoneal chemotherapy versus

systemic chemotherapy in patients with peritoneal carcinomatosis of colorectal cancer. *Ann Surg Oncol.* 2008;15(9):2426-2432.

90. Klaver CE, Groenen H, Morton DG, et al. Recommendations and consensus on the treatment of peritoneal metastases of colorectal origin: a systematic review of national and international guidelines. *Colorectal Dis.* 2017;19(3):224-236.

91. Bushati M, Rovers KP, Sommariva A, et al. The current practice of cytoreductive surgery and HIPEC for colorectal peritoneal metastases: Results of a worldwide web-based survey of the Peritoneal Surface Oncology Group International (PSOGI). *Eur J Surg Oncol.* 2018;44(12):1942-1948.

92. Danish Colorectal Cancer Group. HIPEC behandling af peritoneal karcinose til patienter med kolorektalkræft (national guideline). 2019; Available at: https://dccg.dk/wp-content/uploads/2020/01/Peritoneal-karcinose-og-HIPEC_AdmGodk_100120.pdf. Accessed August, 2020.

93. van Oudheusden TR, Braam HJ, Nienhuijs SW, et al. Cytoreduction and hyperthermic intraperitoneal chemotherapy: a feasible and effective option for colorectal cancer patients after emergency surgery in the presence of peritoneal carcinomatosis. *Ann Surg Oncol.* 2014;21(8):2621-2626.

94. Sugarbaker PH. Peritonectomy procedures. *Ann Surg.* 1995;221(1):29-42.

95. Ceelen W, Braet H, van Ramshorst G, Willaert W, Remaut K. Intraperitoneal chemotherapy for peritoneal metastases: an expert opinion. *Expert Opin Drug Deliv.* 2020;17(4):511-522.

96. Rovers KP, Simkens GA, Punt CJ, van Dieren S, Tanis PJ, de Hingh IH. Perioperative systemic therapy for resectable colorectal peritoneal metastases: Sufficient evidence for its widespread use? A critical systematic review. *Crit Rev Oncol Hematol.* 2017;114:53-62.

97. Rovers KP, Bakkers C, Simkens G, et al. Perioperative systemic therapy and cytoreductive surgery with HIPEC versus upfront cytoreductive surgery with HIPEC alone for isolated resectable colorectal peritoneal metastases: protocol of a multicentre, open-label, parallel-group, phase II-III, randomised, superiority study (CAIRO6). *BMC Cancer.* 2019;19(1):390.

98. Lee ZJ, Chia SL, Tan G, Soo KC, Teo CCM. Cost Effectiveness of Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy for Management of Colorectal Peritoneal Carcinomatosis. *Ann Surg Oncol.* 2018;25(8):2340-2346.

99. Cashin PH, Mahteme H, Syk I, Frodin JE, Glimelius B, Graf W. Quality of life and cost effectiveness in a randomized trial of patients with colorectal cancer and peritoneal metastases. *Eur J Surg Oncol.* 2018;44(7):983-990.

100. Hamilton TD, MacNeill AJ, Lim H, Hunink MGM. Cost-Effectiveness Analysis of Cytoreductive Surgery and HIPEC Compared With Systemic Chemotherapy in Isolated Peritoneal Carcinomatosis From Metastatic Colorectal Cancer. *Ann Surg Oncol.* 2019;26(4):1110-1117.

101. Elekonawo FMK, van Eden WJ, van der Plas WY, et al. Effect of intraperitoneal chemotherapy concentration on morbidity and survival. *BJS Open.* 2020;4(2):293-300.

102. Smeenk RM, Verwaal VJ, Zoetmulder FA. Learning curve of combined modality treatment in peritoneal surface disease. *Br J Surg.* 2007;94(11):1408-1414.

103. Halkia E, Kopanakis N, Nikolaou G, Spiliotis J. Cytoreductive surgery and HIPEC for peritoneal carcinomatosis. A review on morbidity and mortality. *J BUON.* 2015;20 Suppl 1:S80-87.

104. Simkens GA, van Oudheusden TR, Luyer MD, et al. Predictors of Severe Morbidity After Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy for Patients With Colorectal Peritoneal Carcinomatosis. *Ann Surg Oncol.* 2016;23(3):833-841.

105. Mirnezami R, Mehta AM, Chandrakumaran K, et al. Cytoreductive surgery in combination with hyperthermic intraperitoneal chemotherapy improves survival in patients with colorectal peritoneal metastases compared with systemic chemotherapy alone. *Br J Cancer.* 2014;111(8):1500-1508.

106. Simkens GA, Verwaal VJ, Lemmens VE, Rutten HJ, de Hingh IH. Short-term outcome in patients treated with cytoreduction and HIPEC compared to conventional colon cancer surgery. *Medicine (Baltimore).* 2016;95(41):e5111.

107. Simkens GA, van Oudheusden TR, Braam HJ, et al. Treatment-Related Mortality After Cytoreductive Surgery and HIPEC in Patients with Colorectal Peritoneal Carcinomatosis is Underestimated by Conventional Parameters. *Ann Surg Oncol.* 2016;23(1):99-105.

108. Riss S, Mohamed F, Dayal S, et al. Peritoneal metastases from colorectal cancer: patient selection for cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. *Eur J Surg Oncol.* 2013;39(9):931-937.

109. Simkens GA, Rovers KP, Nienhuijs SW, de Hingh IH. Patient selection for cytoreductive surgery and HIPEC for the treatment of peritoneal metastases from colorectal cancer. *Cancer Manag Res.* 2017;9:259-266.

110. Klaver CE, Groenen H, Morton DG, et al. Recommendations and consensus on the treatment of peritoneal metastases of colorectal origin; a systematic review of national and international guidelines. *Colorectal Dis.* 2016.

111. Iversen LH, Rasmussen PC, Laurberg S. Value of laparoscopy before cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for peritoneal carcinomatosis. *Br J Surg.* 2013;100(2):285-292.

112. Hentzen J, Constansia RDN, Been LB, et al. Diagnostic Laparoscopy as a Selection Tool for Patients with Colorectal Peritoneal Metastases to Prevent a Non-therapeutic Laparotomy During Cytoreductive Surgery. *Ann Surg Oncol.* 2020;27(4):1084-1093.

113. von Breitenbuch P, Boerner T, Jeiter T, Piso P, Schlitt HJ. Laparoscopy as a useful selection tool for patients with prior surgery and peritoneal metastases suitable for multimodality treatment strategies. *Surg Endosc.* 2018;32(5):2288-2294.

114. Pomel C, Appleyard TL, Gouy S, Rouzier R, Elias D. The role of laparoscopy to evaluate candidates for complete cytoreduction of peritoneal carcinomatosis and hyperthermic intraperitoneal chemotherapy. *Eur J Surg Oncol.* 2005;31(5):540-543.

115. Nunez MF, Sardi A, Jimenez W, et al. Port-site metastases is an independent prognostic factor in patients with peritoneal carcinomatosis. *Ann Surg Oncol.* 2015;22(4):1267-1273.

116. Thomassen I, van Gestel Y, Aalbers AGJ, et al. Peritoneal carcinomatosis is less frequently diagnosed during laparoscopic surgery compared to open surgery in patients with colorectal cancer. *Eur J Surg Oncol.* 2014;40(5):511-514.

117. Pelz JO, Chua TC, Esquivel J, et al. Evaluation of best supportive care and systemic chemotherapy as treatment stratified according to the retrospective peritoneal surface disease severity score (PSDSS) for peritoneal carcinomatosis of colorectal origin. *BMC Cancer.* 2010;10:689.

118. Verwaal VJ, van Ruth S, de Bree E, et al. Randomized trial of cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy and palliative surgery in patients with peritoneal carcinomatosis of colorectal cancer. *J Clin Oncol.* 2003;21(20):3737-3743.

119. Elias D, Lefevre JH, Chevalier J, et al. Complete cytoreductive surgery plus intraperitoneal chemohyperthermia with oxaliplatin for peritoneal carcinomatosis of colorectal origin. *J Clin Oncol.* 2009;27(5):681-685.

120. Franko J, Ibrahim Z, Gusani NJ, Holtzman MP, Bartlett DL, Zeh HJ, 3rd. Cytoreductive surgery and hyperthermic intraperitoneal chemoperfusion versus systemic chemotherapy alone for colorectal peritoneal carcinomatosis. *Cancer.* 2010;116(16):3756-3762.

121. Vassos N, Piso P. Metastatic Colorectal Cancer to the Peritoneum: Current Treatment Options. *Curr Treat Options Oncol.* 2018;19(10):49.

122. Lemoine L, Sugarbaker P, Van der Speeten K. Drugs, doses, and durations of intraperitoneal chemotherapy: standardising HIPEC and EPIC for colorectal, appendiceal, gastric, ovarian peritoneal surface malignances and peritoneal mesothelioma. *Int J Hyperthermia.* 2017;33(5):582-592.

123. Quenet F, Elias D, Roca L, et al. A UNICANCER phase III trial of hyperthermic intra-peritoneal chemotherapy (HIPEC) for colorectal peritoneal carcinomatosis (PC): PRODIGE 7. 2018;36(18_suppl):LBA3503-LBA3503.

124. Konigsrainer A, Rau B. Cytoreductive Surgery (CRS) and Hyperthermic IntraPeritoneal Chemotherapy (HIPEC): don't throw the baby out with the bathwater. *Pleura Peritoneum.* 2018;3(4):20180131.

125. Grotz TE, Fournier KF, Boughey JC. Cytoreduction with or without HIPEC: Where do we go from here? 2019; Available at: https://bulletin.facs.org/2019/02/cytoreduction-with-or-without-hipec-where-do-we-go-from-here/. Accessed August, 2020.

126. Larentzakis A, O'Dwyer ST, Becker J, et al. Referral pathways and outcome of patients with colorectal peritoneal metastasis (CRPM). *Eur J Surg Oncol.* 2019;45(12):2310-2315.

127. Liberale G, Ameye L, Hendlisz A. PRODIGE 7 should be interpreted with caution. *Acta Chir Belg.* 2019;119(4):263-266.

128. Ceelen W. HIPEC with oxaliplatin for colorectal peritoneal metastasis: The end of the road? *Eur J Surg Oncol.* 2019;45(3):400-402.

129. Hallam S, Tyler R, Price M, Beggs A, Youssef H. Meta-analysis of prognostic factors for patients with colorectal peritoneal metastasis undergoing cytoreductive surgery and heated intraperitoneal chemotherapy. *BJS Open.* 2019;3(5):585-594.

130. Huang Y, Alzahrani NA, Chua TC, Liauw W, Morris DL. Impacts of peritoneal cancer index on the survival outcomes of patients with colorectal peritoneal carcinomatosis. *Int J Surg.* 2016;32:65-70.

131. Narasimhan V, Tan S, Kong J, et al. Prognostic factors influencing survival in patients undergoing cytoreductive surgery with hyperthermic intraperitoneal chemotherapy for isolated colorectal peritoneal metastases: a systematic review and meta-analysis. *Colorectal Dis.* 2020.

132. Sugarbaker PH. Successful management of microscopic residual disease in large bowel cancer. *Cancer Chemother Pharmacol.* 1999;43 Suppl:S15-25.

133. Glehen O, Osinsky D, Beaujard AC, Gilly FN. Natural history of peritoneal carcinomatosis from nongynecologic malignancies. *Surg Oncol Clin N Am.* 2003;12(3):729-739, xiii.

134. Cashin PH, Graf W, Nygren P, Mahteme H. Cytoreductive surgery and intraperitoneal chemotherapy for colorectal peritoneal carcinomatosis: prognosis and treatment of recurrences in a cohort study. *Eur J Surg Oncol.* 2012;38(6):509-515.

135. Benizri EI, Bernard JL, Rahili A, Benchimol D, Bereder JM. Small bowel involvement is a prognostic factor in colorectal carcinomatosis treated with complete cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy. *World J Surg Oncol.* 2012;10:56.

136. Elias D, Gilly F, Boutitie F, et al. Peritoneal colorectal carcinomatosis treated with surgery and perioperative intraperitoneal chemotherapy: retrospective analysis of 523 patients from a multicentric French study. *J Clin Oncol.* 2010;28(1):63-68.

137. Huang CQ, Yang XJ, Yu Y, et al. Cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy improves survival for patients with peritoneal carcinomatosis from colorectal cancer: a phase II study from a Chinese center. *PLoS One.* 2014;9(9):e108509.

138. Ihemelandu C, Sugarbaker PH. Management for Peritoneal Metastasis of Colonic Origin: Role of Cytoreductive Surgery and Perioperative Intraperitoneal Chemotherapy: A Single Institution's Experience During Two Decades. *Ann Surg Oncol.* 2017;24(4):898-905.

139. Lorimier G, Linot B, Paillocher N, et al. Curative cytoreductive surgery followed by hyperthermic intraperitoneal chemotherapy in patients with peritoneal carcinomatosis and synchronous resectable liver metastases arising from colorectal cancer. *Eur J Surg Oncol.* 2017;43(1):150-158.

140. Winer J, Zenati M, Ramalingam L, et al. Impact of aggressive histology and location of primary tumor on the efficacy of surgical therapy for peritoneal carcinomatosis of colorectal origin. *Ann Surg Oncol.* 2014;21(5):1456-1462.

141. Votanopoulos KI, Swett K, Blackham AU, et al. Cytoreductive surgery with hyperthermic intraperitoneal chemotherapy in peritoneal carcinomatosis from rectal cancer. *Ann Surg Oncol.* 2013;20(4):1088-1092.

142. Burnett A, Lecompte MA, Trabulsi N, et al. Peritoneal carcinomatosis index predicts survival in colorectal patients undergoing HIPEC using oxaliplatin: a retrospective single-arm cohort study. *World J Surg Oncol.* 2019;17(1):83.

143. Klaver CEL, Wisselink DD, Punt CJA, et al. Adjuvant hyperthermic intraperitoneal chemotherapy in patients with locally advanced colon cancer (COLOPEC): a multicentre, open-label, randomised trial. *Lancet Gastroenterol Hepatol.* 2019;4(10):761-770.

144. Goere D, Glehen O, Quenet F, et al. Second-look surgery plus hyperthermic intraperitoneal chemotherapy versus surveillance in patients at high risk of developing colorectal peritoneal metastases (PROPHYLOCHIP-PRODIGE 15): a randomised, phase 3 study. *Lancet Oncol.* 2020.

145. Steele SR, Chang GJ, Hendren S, et al. Practice Guideline for the Surveillance of Patients After Curative Treatment of Colon and Rectal Cancer. *Dis Colon Rectum.* 2015;58(8):713-725.

146. Bastiaenen VP, Hovdenak Jakobsen I, Labianca R, 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):392-416.

147. Rosen M, Chan L, Beart RW, Jr., Vukasin P, Anthone G. Follow-up of colorectal cancer: a meta-analysis. *Dis Colon Rectum.* 1998;41(9):1116-1126.

148. Pita-Fernandez S, Alhayek-Ai M, Gonzalez-Martin C, Lopez-Calvino B, Seoane-Pillado T, Pertega-Diaz S. Intensive follow-up strategies improve outcomes in nonmetastatic colorectal cancer patients after curative surgery: a systematic review and meta-analysis. *Ann Oncol.* 2015;26(4):644-656.

149. Wille-Jorgensen 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.

150. Sundhedsstyrelsen. Pakkeforløb og opfølgningsprogrammer. *Generel beskrivelse af ansvarsfordeling og organisering, forløbstider og monitorering i Sundhedsstyrelsens kræftpakker* 2018; Available at: https://www.sst.dk/-/media/Udgivelser/2019/Pakkeforloeb-kraeft-2015-2019/Pakkeforloeb-og-opfoelgningsprogrammer-Begreber-forloebstider-og-monitorering.ashx. Accessed August, 2020.

151. National Cancer Institute N. Follow-Up Medical Care. 2019; Available at: https://www.cancer.gov/about-cancer/coping/survivorship/follow-up-care. Accessed August, 2020.

152. Harrison JD, Young JM, Price MA, Butow PN, Solomon MJ. What are the unmet supportive care needs of people with cancer? A systematic review. *Support Care Cancer.* 2009;17(8):1117-1128.

153. Moghaddam N, Coxon H, Nabarro S, Hardy B, Cox K. Unmet care needs in people living with advanced cancer: a systematic review. *Support Care Cancer.* 2016;24(8):3609-3622.

154. Epstein RM. The science of patient-centered care. *J Fam Pract.* 2000;49(9):805-807.

155. Denlinger CS, Carlson RW, Are M, et al. Survivorship: introduction and definition. Clinical practice guidelines in oncology. *J Natl Compr Canc Netw.* 2014;12(1):34-45.

156. Seretis C, Youssef H. Quality of life after cytoreductive surgery and intraoperative hyperthermic intraperitoneal chemotherapy for peritoneal surface malignancies: a systematic review. *Eur J Surg Oncol.* 2014;40(12):1605-1613.

157. Shan LL, Saxena A, Shan BL, Morris DL. Quality of life after cytoreductive surgery and hyperthermic intra-peritoneal chemotherapy for peritoneal carcinomatosis: A systematic review and meta-analysis. *Surg Oncol.* 2014;23(4):199-210.

158. Duckworth KE, McQuellon RP, Russell GB, et al. Patient rated outcomes and survivorship following cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy (CS + HIPEC). *J Surg Oncol.* 2012;106(4):376-380.

159. McQuellon RP, Loggie BW, Fleming RA, Russell GB, Lehman AB, Rambo TD. Quality of life after intraperitoneal hyperthermic chemotherapy (IPHC) for peritoneal carcinomatosis. *Eur J Surg Oncol.* 2001;27(1):65-73.

160. Mead N, Bower P. Patient-centredness: a conceptual framework and review of the empirical literature. *Soc Sci Med.* 2000;51(7):1087-1110.

161. Reynolds A. Patient-centered Care. *Radiol Technol.* 2009;81(2):133-147.

162. Robinson JH, Callister LC, Berry JA, Dearing KA. Patient-centered care and adherence: definitions and applications to improve outcomes. *J Am Acad Nurse Pract.* 2008;20(12):600-607.

163. Langberg EM, Dyhr L, Davidsen AS. Development of the concept of patient-centredness - A systematic review. *Patient Educ Couns.* 2019;102(7):1228-1236.

164. Institute of Medicine I. *Crossing the quality chasm: A new health system for the twenty-first century.* Washington DC: National Academies Press; 2001.

165. Harkness J. Patient involvement: a vital principle for patient-centred health care. *World Hosp Health Serv.* 2005;41(2):12-16, 40-13.

166. Constand MK, MacDermid JC, Dal Bello-Haas V, Law M. Scoping review of patient-centered care approaches in healthcare. *BMC Health Serv Res.* 2014;14:271.

167. Greenfield S, Kaplan S, Ware JE, Jr. Expanding patient involvement in care. Effects on patient outcomes. *Ann Intern Med.* 1985;102(4):520-528.

168. Cooper LA, Roter DL, Carson KA, et al. A randomized trial to improve patient-centered care and hypertension control in underserved primary care patients. *J Gen Intern Med.* 2011;26(11):1297-1304.

169. Probst MA, Tschatscher CF, Lohse CM, Fernanda Bellolio M, Hess EP. Factors Associated With Patient Involvement in Emergency Care Decisions: A Secondary Analysis of the Chest Pain Choice Multicenter Randomized Trial. *Acad Emerg Med.* 2018;25(10):1107-1117.

170. Guo Y, Chen Y, Lane DA, Liu L, Wang Y, Lip GYH. Mobile Health Technology for Atrial Fibrillation Management Integrating Decision Support, Education, and Patient Involvement: mAF App Trial. *Am J Med.* 2017;130(12):1388-1396 e1386.

171. Holm KE, Casaburi R, Cerreta S, et al. Patient Involvement in the Design of a Patient-Centered Clinical Trial to Promote Adherence to Supplemental Oxygen Therapy in COPD. *Patient.* 2016;9(3):271-279.
172. van der Hout A, van Uden-Kraan CF, Holtmaat K, et al. Role of eHealth application Oncokompas in supporting self-management of symptoms and health-related quality of life in cancer survivors: a randomised, controlled trial. *Lancet Oncol.* 2020;21(1):80-94.
173. Thaysen HV, Lomborg K, Seibaek L. Patient involvement in comprehensive, complex cancer surgery: Perspectives of patients, relatives and health professionals. *Eur J Cancer Care (Engl).* 2019;28(4):e13071.
174. Europa Commission - Directorate-General for health and Consumers. *Patient Involvement - Eurobarometer qualitative study on patient involvement in healthcare.* Brussels2012.
175. Epstein RM, Duberstein PR, Fenton JJ, et al. Effect of a Patient-Centered Communication Intervention on Oncologist-Patient Communication, Quality of Life, and Health Care Utilization in Advanced Cancer: The VOICE Randomized Clinical Trial. *JAMA Oncol.* 2017;3(1):92-100.
176. Ahmad N, Ellins J, Krelle H, Lawrie M. *Person-centred care: from ideas to action.* London: The Health Foundation 2014.
177. Cribb A. *Involvement, Shared decision-making and Medicines.* Britain: Royal Pharmaceutical Society 2011.
178. Barry MJ, Edgman-Levitan S. Shared decision making--pinnacle of patient-centered care. *N Engl J Med.* 2012;366(9):780-781.
179. Breckenridge K, Bekker HL, Gibbons E, et al. How to routinely collect data on patient-reported outcome and experience measures in renal registries in Europe: an expert consensus meeting. *Nephrol Dial Transplant.* 2015;30(10):1605-1614.
180. Berry DL, Blumenstein BA, Halpenny B, et al. Enhancing patient-provider communication with the electronic self-report assessment for cancer: a randomized trial. *J Clin Oncol.* 2011;29(8):1029-1035.
181. Ruland CM, Holte HH, Roislien J, et al. Effects of a computer-supported interactive tailored patient assessment tool on patient care, symptom distress, and patients' need for symptom management support: a randomized clinical trial. *J Am Med Inform Assoc.* 2010;17(4):403-410.
182. Velikova G, Booth L, Smith AB, et al. Measuring quality of life in routine oncology practice improves communication and patient well-being: a randomized controlled trial. *J Clin Oncol.* 2004;22(4):714-724.
183. Boyes A, Newell S, Girgis A, McElduff P, Sanson-Fisher R. Does routine assessment and real-time feedback improve cancer patients' psychosocial well-being? *Eur J Cancer Care (Engl).* 2006;15(2):163-171.
184. Debra dS. *Helping measure person-centred care.* London: The Health Foundation; 2014.
185. Santana MJ, Manalili K, Jolley RJ, Zelinsky S, Quan H, Lu M. How to practice person-centred care: A conceptual framework. *Health Expect.* 2018;21(2):429-440.
186. Health USDo, Human Services FDACfDE, Research, et al. Guidance for industry: patient-reported outcome measures: use in medical product development to support labeling claims: draft guidance. *Health Qual Life Outcomes.* 2006;4:79.
187. Frost MH, Reeve BB, Liepa AM, Stauffer JW, Hays RD, Mayo FDAP-ROCMG. What is sufficient evidence for the reliability and validity of patient-reported outcome measures? *Value Health.* 2007;10 Suppl 2:S94-S105.

188.   Detmar SB, Muller MJ, Schornagel JH, Wever LD, Aaronson NK. Health-related quality-of-life assessments and patient-physician communication: a randomized controlled trial. *JAMA.* 2002;288(23):3027-3034.

189.   Greenhalgh J, Dalkin S, Gooding K, et al. In: *Functionality and feedback: a realist synthesis of the collation, interpretation and utilisation of patient-reported outcome measures data to improve patient care.* Southampton (UK)2017.

190.   Howell D, Molloy S, Wilkinson K, et al. Patient-reported outcomes in routine cancer clinical practice: a scoping review of use, impact on health outcomes, and implementation factors. *Ann Oncol.* 2015;26(9):1846-1858.

191.   Kotronoulas G, Kearney N, Maguire R, et al. What is the value of the routine use of patient-reported outcome measures toward improvement of patient outcomes, processes of care, and health service outcomes in cancer care? A systematic review of controlled trials. *J Clin Oncol.* 2014;32(14):1480-1501.

192.   Takeuchi EE, Keding A, Awad N, et al. Impact of patient-reported outcomes in oncology: a longitudinal analysis of patient-physician communication. *J Clin Oncol.* 2011;29(21):2910-2917.

193.   Fletcher RH, Fletcher SW, Fletcher GS. Chapter 3: Abnormality. In: *Clinical Epidemiology: The essentials.* 5 ed. Philadelphia: Lippincott Wiliams & Wilkins; 2014.

194.   Revicki DA, Cella D, Hays RD, Sloan JA, Lenderking WR, Aaronson NK. Responsiveness and minimal important differences for patient reported outcomes. *Health Qual Life Outcomes.* 2006;4:70.

195.   Elias D, Honore C, Dumont F, et al. Results of systematic second-look surgery plus HIPEC in asymptomatic patients presenting a high risk of developing colorectal peritoneal carcinomatosis. *Ann Surg.* 2011;254(2):289-293.

196.   Ehrenstein V, Hernandez RK, Maegbaek ML, et al. Validation of algorithms to detect distant metastases in men with prostate cancer using routine registry data in Denmark. *Clin Epidemiol.* 2015;7:259-265.

197.   Chawla N, Yabroff KR, Mariotto A, McNeel TS, Schrag D, Warren JL. Limited validity of diagnosis codes in Medicare claims for identifying cancer metastases and inferring stage. *Ann Epidemiol.* 2014;24(9):666-672, 672 e661-662.

198.   Warren JL, Mariotto A, Melbert D, et al. Sensitivity of Medicare Claims to Identify Cancer Recurrence in Elderly Colorectal and Breast Cancer Patients. *Med Care.* 2016;54(8):e47-54.

199.   Schmidt M, Schmidt SAJ, Adelborg K, et al. The Danish health care system and epidemiological research: from health care contacts to database records. *Clin Epidemiol.* 2019;11:563-591.

200.   Schmidt M, Pedersen L, Sorensen HT. The Danish Civil Registration System as a tool in epidemiology. *Eur J Epidemiol.* 2014;29(8):541-549.

201.   Ingeholm P, Gogenur I, Iversen LH. Danish Colorectal Cancer Group Database. *Clin Epidemiol.* 2016;8:465-468.

202.   Schmidt M, Schmidt SA, Sandegaard JL, Ehrenstein V, Pedersen L, Sorensen HT. The Danish National Patient Registry: a review of content, data quality, and research potential. *Clin Epidemiol.* 2015;7:449-490.

203.   Erichsen R, Lash TL, Hamilton-Dutoit SJ, Bjerregaard B, Vyberg M, Pedersen L. Existing data sources for clinical epidemiology: the Danish National Pathology Registry and Data Bank. *Clin Epidemiol.* 2010;2:51-56.

204.   Mikkelsen MS, Christiansen T, Petersen LK, Blaakaer J, Iversen LH. Morbidity after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy with carboplatin used for ovarian, tubal, and primary peritoneal cancer. *J Surg Oncol.* 2019;120(3):550-557.

205. Hjollund NH, Larsen LP, Biering K, Johnsen SP, Riiskjaer E, Schougaard LM. Use of Patient-Reported Outcome (PRO) Measures at Group and Patient Levels: Experiences From the Generic Integrated PRO System, WestChronic. *Interact J Med Res.* 2014;3(1):e5.

206. Hjollund NHI, Valderas JM, Kyte D, Calvert MJ. Health Data Processes: A Framework for Analyzing and Discussing Efficient Use and Reuse of Health Data With a Focus on Patient-Reported Outcome Measures. *J Med Internet Res.* 2019;21(5):e12412.

207. Sorensen HT, Sabroe S, Olsen J. A framework for evaluation of secondary data sources for epidemiological research. *Int J Epidemiol.* 1996;25(2):435-442.

208. Fletcher RH, Fletcher SW, Fletcher GS. Chapter 8: Diagnosis. In: *Clinical Epidemiology: The essentials.* 5 ed. Philadelphia: Lippincott Williams & Wilkins; 2014.

209. Whiting P, Rutjes AW, Reitsma JB, Glas AS, Bossuyt PM, Kleijnen J. Sources of variation and bias in studies of diagnostic accuracy: a systematic review. *Ann Intern Med.* 2004;140(3):189-202.

210. Ransohoff DF, Feinstein AR. Problems of spectrum and bias in evaluating the efficacy of diagnostic tests. *N Engl J Med.* 1978;299(17):926-930.

211. Hibbard JH, Mahoney ER, Stockard J, Tusler M. Development and testing of a short form of the patient activation measure. *Health Serv Res.* 2005;40(6 Pt 1):1918-1930.

212. Hørlück JT, Sevelsted J, Riiskjær E. Udvælgelse af indragelsesspørgsmål til patienter. 2017; Available at: http://www.defactum.dk/. Accessed August, 2020.

213. Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst.* 1993;85(5):365-376.

214. Thaysen HV, Jess P, Laurberg S, Groenvold M. Validation of the Danish version of the disease specific instrument EORTC QLQ-CR38 to assess health-related quality of life in patients with colorectal cancer. *Health Qual Life Outcomes.* 2012;10:150.

215. Greimel E, Bottomley A, Cull A, et al. An international field study of the reliability and validity of a disease-specific questionnaire module (the QLQ-OV28) in assessing the quality of life of patients with ovarian cancer. *Eur J Cancer.* 2003;39(10):1402-1408.

216. Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the Hospital Anxiety and Depression Scale. An updated literature review. *J Psychosom Res.* 2002;52(2):69-77.

217. Rothman KJ, Greenland S, Lash TL. Chapter 9: Validity in Epidemiologic Studies. In: *Modern Epidemiology.* 3 ed. Philadelphia: Lippincott Wiliams & Wilkins; 2008.

218. Jensen AO, Norgaard M, Yong M, Fryzek JP, Sorensen HT. Validity of the recorded International Classification of Diseases, 10th edition diagnoses codes of bone metastases and skeletal-related events in breast and prostate cancer patients in the Danish National Registry of Patients. *Clin Epidemiol.* 2009;1:101-108.

219. Lynge E. Occupational mortality. *Scand J Public Health.* 2011;39(7 Suppl):153-157.

220. Couture EM, Chouinard MC, Fortin M, Hudon C. The relationship between health literacy and patient activation among frequent users of healthcare services: a cross-sectional study. *BMC Fam Pract.* 2018;19(1):38.

221. Napoles TM, Burke NJ, Shim JK, Davis E, Moskowitz D, Yen IH. Assessing Patient Activation among High-Need, High-Cost Patients in Urban Safety Net Care Settings. *J Urban Health.* 2017;94(6):803-813.

222. Fletcher RH, Fletcher SW, Fletcher GS. Chapter 11: Chance. In: *Clinical epidemiology: The essentials.* 5 ed. Philadelphia: Lippincott Williams & Wilkins; 2014.

223. Thomassen I, van Gestel YR, Lemmens VE, de Hingh IH. Incidence, prognosis, and treatment options for patients with synchronous peritoneal carcinomatosis and liver metastases from colorectal origin. *Dis Colon Rectum.* 2013;56(12):1373-1380.

224. Simkens GA, Razenberg LG, Lemmens VE, Rutten HJ, Creemers GJ, de Hingh IH. Histological subtype and systemic metastases strongly influence treatment and survival in patients with synchronous colorectal peritoneal metastases. *Eur J Surg Oncol.* 2016;42(6):794-800.

225. Piso P, Stierstorfer K, Gerken M, Klinkhammer-Schalke M. Benefit of cytoreductive surgery combined with hyperthermic intraperitoneal chemotherapy in patients with isolated peritoneal metastases from colorectal cancer. *Int J Colorectal Dis.* 2018;33(11):1559-1567.

226. Klaver YL, Lemmens VE, de Hingh IH. Outcome of surgery for colorectal cancer in the presence of peritoneal carcinomatosis. *Eur J Surg Oncol.* 2013;39(7):734-741.

227. Shida D, Yoshida T, Tanabe T, Tsukamoto S, Ochiai H, Kanemitsu Y. Prognostic Impact of R0 Resection and Targeted Therapy for Colorectal Cancer with Synchronous Peritoneal Metastasis. *Ann Surg Oncol.* 2018.

228. Elias D, Mariani A, Cloutier AS, et al. Modified selection criteria for complete cytoreductive surgery plus HIPEC based on peritoneal cancer index and small bowel involvement for peritoneal carcinomatosis of colorectal origin. *Eur J Surg Oncol.* 2014;40(11):1467-1473.

229. Veld JV, Wisselink DD, Amelung FJ, et al. Synchronous and Metachronous Peritoneal Metastases in Patients with Left-Sided Obstructive Colon Cancer. *Ann Surg Oncol.* 2020;27(8):2762-2773.

230. Sugarbaker PH. Management of peritoneal metastases - Basic concepts. *J BUON.* 2015;20 Suppl 1:S2-11.

231. Pestieau SR, Sugarbaker PH. Treatment of primary colon cancer with peritoneal carcinomatosis: comparison of concomitant vs. delayed management. *Dis Colon Rectum.* 2000;43(10):1341-1346; discussion 1347-1348.

232. de Cuba EM, Kwakman R, Knol DL, Bonjer HJ, Meijer GA, Te Velde EA. Cytoreductive surgery and HIPEC for peritoneal metastases combined with curative treatment of colorectal liver metastases: Systematic review of all literature and meta-analysis of observational studies. *Cancer Treat Rev.* 2013;39(4):321-327.

233. Pinto A, Hobeika C, Philis A, Kirzin S, Carrere N, Ghouti L. Synchronous liver metastases and peritoneal carcinomatosis from colorectal cancer: different strategies for curative treatment? *Langenbecks Arch Surg.* 2019;404(4):477-488.

234. El-Nakeep S, Rashad N, Oweira H, et al. Intraperitoneal chemotherapy and cytoreductive surgery for peritoneal metastases coupled with curative treatment of colorectal liver metastases: an updated systematic review. *Expert Rev Gastroenterol Hepatol.* 2017;11(3):249-258.

235. Araghi M, Soerjomataram I, Jenkins M, et al. Global trends in colorectal cancer mortality: projections to the year 2035. *Int J Cancer.* 2019;144(12):2992-3000.

236. Dekker E, Rex DK. Advances in CRC Prevention: Screening and Surveillance. *Gastroenterology.* 2018;154(7):1970-1984.

237. Larsen MB, Mikkelsen EM, Rasmussen M, et al. Sociodemographic characteristics of nonparticipants in the Danish colorectal cancer screening program: a nationwide cross-sectional study. *Clin Epidemiol.* 2017;9:345-354.

238. Tanis PJ, Van der Bilt DW, Dijkgraaf MGW. COLOPEC II. 2020; Available at: https://dccg.nl/trial/colopec-ii. Accessed August, 2020.

239. Hoeg BL, Bidstrup PE, Karlsen RV, et al. Follow-up strategies following completion of primary cancer treatment in adult cancer survivors. *Cochrane Database Syst Rev.* 2019;2019(11).

240.   Nors J, Henriksen TV, Gotschalck KA, et al. 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.* 2020;59(3):336-341.

241.   Hovdenak Jakobsen I, Juul T, Bernstein I, et al. Follow-up after rectal cancer: developing and testing a novel patient-led follow-up program. Study protocol. *Acta Oncol.* 2017;56(2):307-313.

242.   Hovdenak Jakobsen I, Juul T, Thaysen HV, Johansen C, Laurberg S. Differences in baseline characteristics and 1-year psychological factors between participants and non-participants in the randomized, controlled trial regarding patient-led follow-up after rectal cancer (FURCA). *Acta Oncol.* 2019;58(5):627-633.

243.   Castro EM, Van Regenmortel T, Vanhaecht K, Sermeus W, Van Hecke A. Patient empowerment, patient participation and patient-centeredness in hospital care: A concept analysis based on a literature review. *Patient Educ Couns.* 2016;99(12):1923-1939.

244.   Handberg C, Beedholm K, Bregnballe V, Nellemann AN, Seibaek L. Reflections on patient involvement in research and clinical practice: A secondary analysis of women's perceptions and experiences of egg aspiration in fertility treatment. *Nurs Inq.* 2018;25(1).

245.   NCCN practice guidelines for the management of psychosocial distress. National Comprehensive Cancer Network. *Oncology (Williston Park).* 1999;13(5A):113-147.

246.   Cummings G. The road to improving patient-reported outcomes: measures or healthcare reform? *Healthc Pap.* 2011;11(4):24-28; discussion 55-28.

247.   Yang LY, Manhas DS, Howard AF, Olson RA. Patient-reported outcome use in oncology: a systematic review of the impact on patient-clinician communication. *Support Care Cancer.* 2018;26(1):41-60.

248.   Mejdahl CT, Schougaard LMV, Hjollund NH, Riiskjaer E, Thorne S, Lomborg K. PRO-based follow-up as a means of self-management support - an interpretive description of the patient perspective. *J Patient Rep Outcomes.* 2017;2:38.

249.   Greenhalgh J, Meadows K. The effectiveness of the use of patient-based measures of health in routine practice in improving the process and outcomes of patient care: a literature review. *J Eval Clin Pract.* 1999;5(4):401-416.

250.   Porter I, Goncalves-Bradley D, Ricci-Cabello I, et al. Framework and guidance for implementing patient-reported outcomes in clinical practice: evidence, challenges and opportunities. *J Comp Eff Res.* 2016;5(5):507-519.

251.   Groenvold M, Klee MC, Sprangers MA, Aaronson NK. Validation of the EORTC QLQ-C30 quality of life questionnaire through combined qualitative and quantitative assessment of patient-observer agreement. *J Clin Epidemiol.* 1997;50(4):441-450.

252.   Sacristan JA, Aguaron A, Avendano-Sola C, et al. Patient involvement in clinical research: why, when, and how. *Patient Prefer Adherence.* 2016;10:631-640.

253.   Hibbard JH, Stockard J, Mahoney ER, Tusler M. Development of the Patient Activation Measure (PAM): conceptualizing and measuring activation in patients and consumers. *Health Serv Res.* 2004;39(4 Pt 1):1005-1026.

254.   Ree E, Wiig S, Manser T, Storm M. How is patient involvement measured in patient centeredness scales for health professionals? A systematic review of their measurement properties and content. *BMC Health Serv Res.* 2019;19(1):12.

255.   Kreindler SA, Struthers A. Assessing the organizational impact of patient involvement: a first STEPP. *Int J Health Care Qual Assur.* 2016;29(4):441-453.

256.   Arnetz JE, Zhdanova L. Patient involvement climate: views and behaviours among registered nurses in myocardial infarction care. *J Clin Nurs.* 2015;24(3-4):475-485.

257. Ocloo J, Matthews R. From tokenism to empowerment: progressing patient and public involvement in healthcare improvement. *BMJ Qual Saf.* 2016;25(8):626-632.

258. Beck A, Thaysen HV, Soegaard CH, Blaakaer J, Seibaek L. Investigating the experiences, thoughts, and feelings underlying and influencing prehabilitation among cancer patients: a qualitative perspective on the what, when, where, who, and why. *Disabil Rehabil.* 2020:1-8.

259. Gelli M, Huguenin JFL, de Baere T, et al. Peritoneal and extraperitoneal relapse after previous curative treatment of peritoneal metastases from colorectal cancer: What survival can we expect? *Eur J Cancer.* 2018;100:94-103.

260. Hellstrom Muhli U, Trost J, Siouta E. Patient involvement in consultation for atrial fibrillation - the cardiologists' perspective. *Int J Health Care Qual Assur.* 2019;32(4):765-776.

261. Degner LF, Sloan JA, Venkatesh P. The Control Preferences Scale. *Can J Nurs Res.* 1997;29(3):21-43.

262. Nagtegaal ID, Knijn N, Hugen N, et al. Tumor Deposits in Colorectal Cancer: Improving the Value of Modern Staging-A Systematic Review and Meta-Analysis. *J Clin Oncol.* 2017;35(10):1119-1127.

13. Appendix

ORIGINAL RESEARCH

The Validity of Registered Synchronous Peritoneal Metastases from Colorectal Cancer in the Danish Medical Registries

Sissel Ravn [ID][1]
Christian F Christiansen [ID][2]
Rikke H Hagemann-Madsen[3]
Victor J Verwaal[1]
Lene H Iversen[1,4]

[1]Department of Surgery, Aarhus University Hospital, Aarhus, Denmark; [2]Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark; [3]Department of Pathology, Lillebaelt Hospital, Vejle, Denmark; [4]Danish Colorectal Cancer Group (DCCG), Copenhagen, Denmark

Introduction: Treatment options for peritoneal metastases (PM) from colorectal cancer (CRC) have increased, their efficiency should be monitored. For this purpose, register-based data on PM can be used, if valid.

Purpose: We aimed to evaluate the completeness and positive predictive value (PPV) of synchronous peritoneal metastases (S-PM) registered among CRC patients in the Danish National Patient Register (DNPR) and/or the Danish National Pathology Register (the DNPatR) using the Danish Colorectal Cancer Group database (DCCG) as a reference.

Patients and Methods: We identified Danish patients with newly diagnosed primary CRC in the DCCG during 2014–2015. S-PM were routinely registered in the DCCG. We excluded patients with non-CRC cancers and identified S-PM using all three registries. We estimated the completeness and the PPV of registered S-PM in the DNPR, the DNPatR and the DNPR and/or the DNPatR (DNPR/DNPatR) in combination using the DCCG as the reference. We stratified by age, gender, WHO performance status, tumour location and distant metastases to liver and/or lungs.

Results: We identified 9142 patients with CRC in DCCG. In DCCG, 366 patients were registered with S-PM, among whom 213 in DCCG only, whereas 153 in DCCG and in at least one of DNPR and/or DNPatR. In DNPR/DNPatR, S-PM was registered with a completeness of 42% [95% CI: 37–47] and a PPV of 60% [95% CI: 54–66]. In the DNPR only, the completeness was 32% [95% CI: 27–37] and the PPV 57% [95% CI: 50–64]. The completeness in the DNPatR was 19% [95% CI: 15–23] and the PPV was 76% [95% CI: 68–85]. In the DNPR/DNPatR patients aged <60 years (57% [95% CI: 46–69]), patients with WHO performance status 0 (46% [95% CI: 37–54]) and patients with no distant metastases (58% [95% CI: 50–65]) were registered with a higher completeness.

Conclusion: Our algorithm demonstrates that the DNPR/DNPatR captures less than half of CRC patients with S-PM. Potential candidates for curative treatment options are registered with a higher completeness. Clinicians should be encouraged to register the presence of S-PM to increase the validity of register-based S-PM data.

Keywords: validity, synchronous peritoneal metastases, registries, colorectal cancer, epidemiology, completeness

Introduction

Colorectal cancer (CRC) is the third most common cancer worldwide and in Denmark.[1] Approximately 18–19% of CRC patients present with metastatic disease.[2,3] Treatment of metastatic CRC in particular has improved considerably during the past decade, primarily due to a multidisciplinary approach offering metastasis-directed treatment. Such treatment options include, among others, surgical resection, ablative procedures

Correspondence: Sissel Ravn
Department of Surgery, Aarhus University Hospital, Aarhus N DK-8200, Denmark
Tel +45 51627366
Email sissel.ravn@rm.dk

(radiofrequency ablation (RFA) or microwave therapy), stereotactic radiotherapy, and cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC).[4,5] Treatment strategies for colorectal peritoneal metastases (PM) have changed from palliative treatment to intended curative treatment with CRS and HIPEC.[6,7] PM diagnosed concurrently with the primary CRC is referred to as synchronous peritoneal metastases (S-PM), while recurrence in the peritoneum is called metachronous peritoneal metastases. There is no well-defined distinction between synchronous and metachronous PM, however, an interval of 6 (or less) months after diagnosis of the primary CRC is often used to define synchronous PM (S-PM).[8,9]

The diagnosis of PM is challenging and not necessarily based on a histopathological verification. The sensitivity of a PM diagnosis is based on preoperative radiological assessment such as computer tomography (CT) scans, and has been reported with a great variance from 11% to 96%.[10] Currently, no radiological imaging is superior to an intra-operative assessment of the peritoneal cavity.[11]

Registries contain large comprehensive data, and the registration of S-PM enables clinicians and researchers to monitor prevalence and incidence along with treatment methods, mortality rates and the prognosis. However, this relies on the validity of S-PM data.[12] To our knowledge, the completeness of registered metastasis from CRC is poorly investigated. An algorithm to identify CRC recurrence in registries has been developed by Lash et al;[13] however, the algorithm is not specific for anatomic site of recurrence, especially not in the peritoneum. When investigating the validity of register-based data on metastasis, the value of medical charts as the golden standard has been questioned because metastasis not necessarily leads to medical attention, diagnostics and registration.[14,15] No algorithm to identify S-PM from CRC has been developed.

We aimed to evaluate the completeness and positive predictive value (PPV) of the registration of S-PM in the Danish medical registries.

Methods
Study Design and Setting
The study was designed as a nationwide population-based prevalence study using data from the Danish National Colorectal Cancer Group (DCCG) database, the Danish Civil Registration System (DCRS), the Danish National Patient Registry (DNPR) and The Danish National Pathology Registry (DNPatR). The study is reported according to the "Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)" guidelines.[16] We included all Danish patients registered in the DCCG database with primary CRC diagnosed in the period January 1st 2014 to December 31st 2015. The population of Denmark includes approximately 5.8 million inhabitants. All Danish citizens have access to a tax-supported primary and secondary health-care system.[17]

Study Population
The date of CRC diagnosis as registered in the DCCG database was defined as the index date. Patients with another primary, non-CRC diagnosis registered in the DNPR within a period of 5 years prior to and 180 days after index date were excluded to ensure that PM originated from CRC (Figure 1). However, patients remained in the study if S-PM was identified in the DCCG database or histopathological verified to originate from CRC.
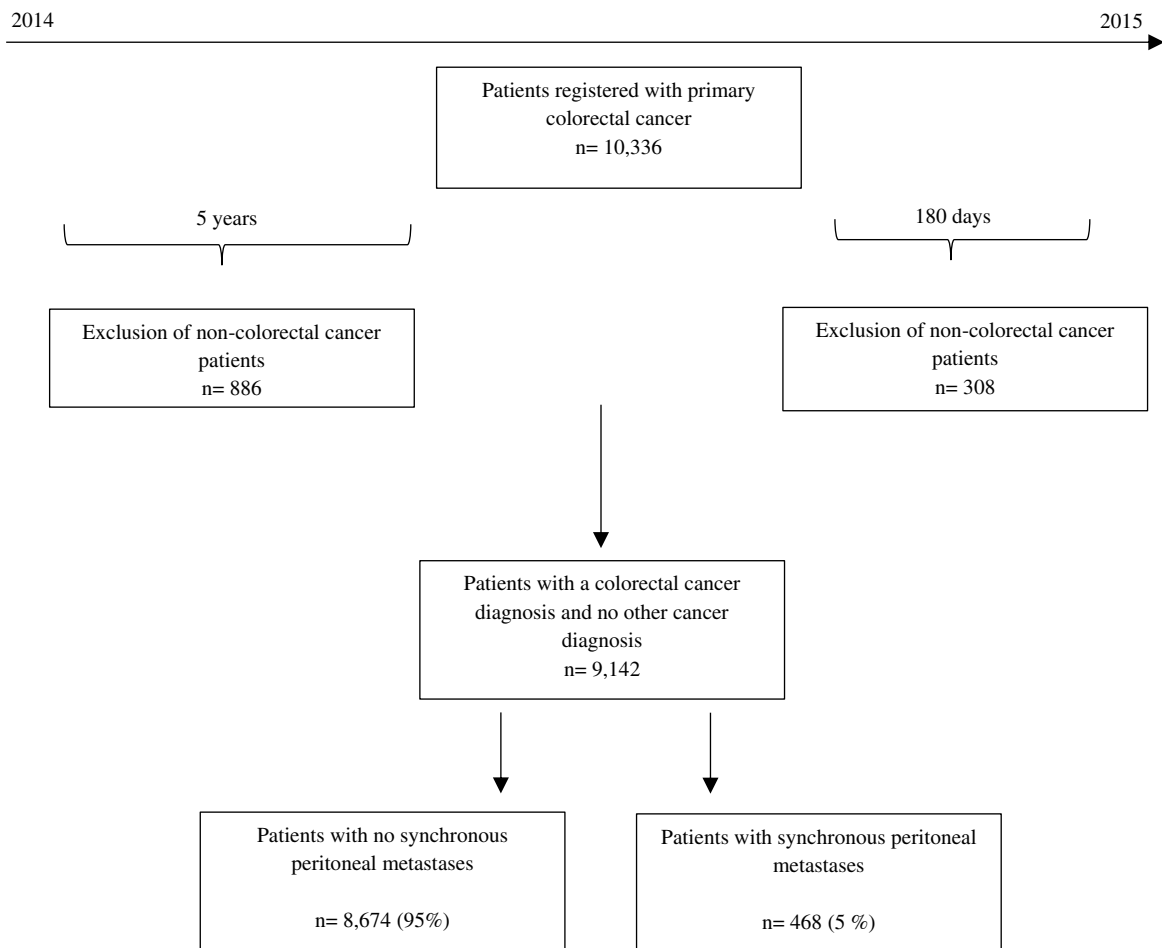
Data Sources
The Danish Colorectal Cancer Group
Since 2001, Danish patients with first-time, primary CRC managed at a surgical department have been registered in the DCCG database. The date of CRC is registered as the date of biopsy verification. If CRC is not histologically verified, the date of CRC diagnosis is registered as the date of surgery or the date when the patient is informed of the cancer. The completeness of CRC patients in the DCCG is >95%.[18] The DCCG database contains patient-related characteristics and information on diagnostic, surgical, pathological and few oncological procedures. All information is registered within 30 days from the CRC diagnosis. Recurrence of the CRC is not registered in the database. The DCCG database underwent a major revision in 2009 including more pathology and again in 2014, implicating an implementation of more detailed registration of several variables, including the registration of S-PM.

The Danish Civil Registration System
All Danish residents are registered in the DCRS, and assigned with a unique 10-digit civil person registration (CPR) number, entailing unambiguous individual-level record linkage to other Danish registers. The DCRS is updated with information on migration and vital status on a daily basis, allowing complete long-term follow-up.[19]

The Danish National Patient Registry
It is mandatory for all hospitals in Denmark to report information on all outpatient and inpatient hospital

2014   2015

Patients registered with primary
colorectal cancer
n= 10,336

5 years   180 days

Exclusion of non-colorectal cancer
patients
n= 886

Exclusion of non-colorectal cancer
patients
n= 308

Patients with a colorectal cancer
diagnosis and no other cancer
diagnosis
n= 9,142

Patients with no synchronous
peritoneal metastases

n= 8,674 (95%)

Patients with synchronous peritoneal
metastases

n= 468 (5 %)

Figure 1 Flowchart of Danish colorectal cancer patients diagnosed with synchronous peritoneal metastases (S-PM) between 2014 and 2015.

contacts to the DNPR. For each hospitalization, DNPR record dates of admission and discharge, one primary and potentially several secondary diagnoses using the Danish version of the International Classification 8th revision (ICD-8) from 1977 to 1993 and ICD-10 thereafter.[12]

The Danish National Pathology Registry

The DNPatR was established in 1997 and all pathological examinations performed in Denmark are registered according to national guidelines, including a topography- and morphology-code as a minimum. Each specimen is linked to the patient's CPR and the specific Danish Systematized Nomenclature of Medicine (SNOMED) codes.[20]

The Reference Database

We choose to use the DCCG database as the reference standard because we expected that these data would be of the highest completeness since the presence or absence of

PM is mandatorily registered by dedicated CRC-surgeons since 2014.

In general, the reference standard often used to validate register-based data is medical journals. However, the quality of medical journals as "golden standard" in the validation of registered metastases has been questioned, mainly because medical charts itself may be incomplete with respect to recording the presence and/or exact numbers and onset of metastases.[15] Further, some metastases may be asymptomatic and may not come to medical attention until routine checkups, and it is possible that recording of metastases in the medical charts is not prioritized for patients with a limited life expectancy.[15]

The registration of PM is even more difficult because the diagnosis of PM is challenging in its nature. For example, there is a large variability in the sensitivity of the radiological imaging ranging from CT scans, PET/CT and MRI and the variability is dependent on the anatomical site and size of the peritoneal metastases.[10]

Clinical Variables

All clinical- and patient-related variables were collected from the DCCG database. The Charlson Comorbidity Index (CCI) was categorized into three levels of comorbidity (0: no comorbidity, 1–2: mild to moderate comorbidity, and >2: severe comorbidity).[21]

Algorithm for Identification of Synchronous Peritoneal Metastases

The algorithm applied to identify S-PM patients included the identification of a PM diagnosis registered in at least one of the three registries (the DCCG database, the DNPR and the DNPatR) within 180 days after the date of CRC diagnosis.

For specific ICD-10 codes in the DNPR and specific SNOMED codes in the DNPatR please see the Appendix.

Statistical Analysis

To validate the registration of the ICD-10 codes in the DNRP and the SNOMED codes in the DNPatR we used registrations in the DCCG as reference.

The sensitivity formula was used as a measure of completeness, and estimated for each registry (DNPR and DNPatR) and for the registries in combination (DNPR/DNPatR).

The completeness was estimated by dividing the number of patients with a PM diagnosis in both the respective registry (DNPR, DNPatR or a combination (DNPR/DNPatR)) and the DCCG (numerator) by the number of all patients registered with PM in the DCCG (denominator).

The PPV was estimated for each registry (DNPR and DNPatR) and for the registries in combination (DNPR/DNPatR). The PPV was defined as the number of patients registered with a PM diagnosis in the respective registry (DNPR, DNPatR or a (DNPR/DNPatR)) and the DCCG (numerator), divided by the number of all patients with a PM diagnosis registered in the respective registry (DNPR, DNPatR or a combination).

We used 180 days after the index date to distinguish between synchronous and metachronous PM. The median days from CRC diagnosis until diagnosis of S-PM in one or more of the registries were presented with the interquartile range. The date of S-PM diagnosis in the DCCG was equal to the date of CRC cancer because this was registered concurrently. If patients were registered in both the DCCG and the DNPR/DNPatR, the date of S-PM in the DNPR/DNPatR was used, which ever came first.

To evaluate if the coding quality in the DNPR/DNPatR differed within clinical relevant subgroups, we stratified by age groups (≤60, 60–69, 70–74, 75–80 and ≥80 years), sex, WHO performance status, tumour location and distant metastases to the liver and/or the lungs (yes/no).

Patient characteristics are presented by patients registered in (1) Only the DCCG, (2) the DCCG and the DNPR/DNPatR, (3) only the DNPR/DNPatR and (4) the total number of patients registered with S-PM. Categorical variables are presented as numbers with percentages, whereas continuous variables are presented as the median with range. Statistical analyses are performed with STATA® software (version 15.1, STATA, College Station, TX, USA).

Ethics

The study was registered by the Danish Data Protection Agency through the Central Region of Denmark (record number 1-16-02-441-16). Ethical approval is not necessary for non-interventional register-based studies in Denmark.
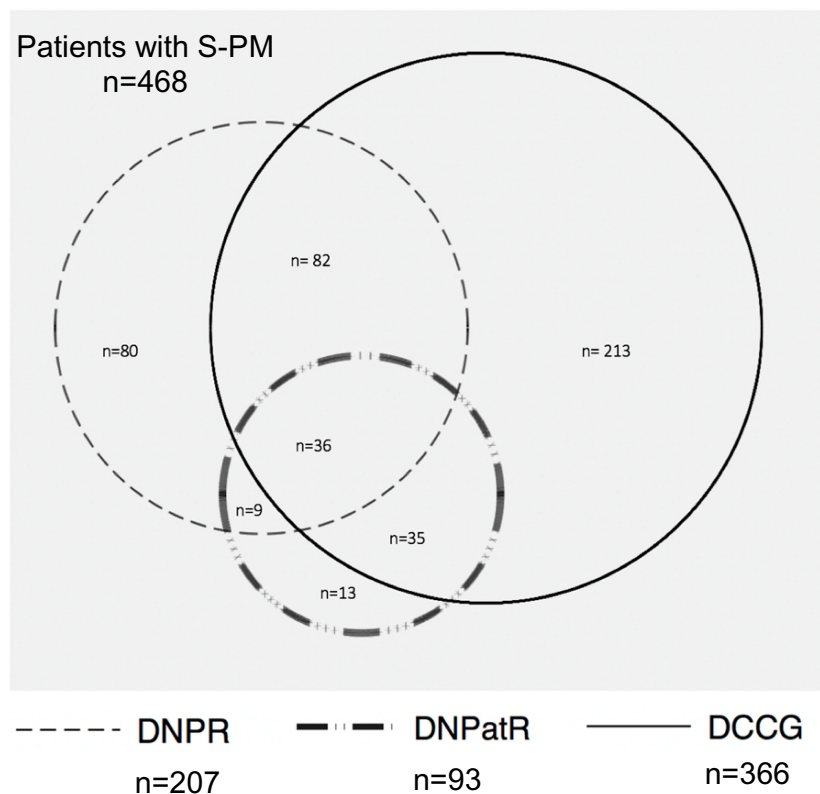
Results

During 2014–2015, 10,336 patients were diagnosed with primary CRC and identified in the DCCG database among whom 1194 patients were excluded due to a diagnosis of non-colorectal cancer within 5 years prior to or 180 days after the index date (Figure 1).

By the use of our algorithm, 366/9142 (4%) patients were registered with S-PM in the DCCG, among whom 153 patients were registered in all registries (DCCG, DNPR and DNPatR). Furthermore, we identified 102/9142 (1%) patients with a S-PM diagnosis registered in only the DNPR/DNPatR (Figure 2).

Patient Characteristics

We compared patients registered with S-PM in (1) only the DCCG, (2) the DCCG and the DNPR/DNPatR, and (3) only the DNPR/DNPatR (Table 1). Regarding the patients who were only registered in the DNPR/DNPatR: A marginal larger proportion was <60 years, while a larger proportion was males, presented with WHO performance status 0, had a rectal tumour and no distant metastases (apart from PM). Information on (y)pT-and (y)pN-categories were missing for 67% and 68% of all registered S-PM patients, presumably because few S-PM patients underwent initial surgery of the primary CRC tumour. However, this information was only missing for 43% and 44% of the patients

Patients with S-PM
n=468

n= 82

n=80

n= 213

n=36

n=9

n=35

n=13

- - - - - DNPR   — ·· — DNPatR   ——— DCCG

n=207   n=93   n=366

Figure 2 Number of patients diagnosed with synchronous peritoneal metastases (S-PM) in one or more of the 3 registries: The Danish Colorectal Cancer Group (DCCG) database, The Danish National Patient Registry (DNPR) and the Danish National Pathology Registry (DNPatR) during 2014–2015.

registered only in the DNPR/DNPatR. Among the patients only registered in the DNPR/DNPatR, 42% had a (y)pT4 tumour and 33% presented with a (y)pN2-category.

Registration of Synchronous Peritoneal Metastasis in the Different Registries

Of the 468 patients registered with S-PM, 78% were identified in the DCCG, whereas 45% were registered only in the DCCG, 33% were registered in both the DCCG and the DNPR/DNPatR, while 22% were registered only in the DNPR/DNPatR (Table 2 and Figure 2).

Completeness and Positive Predictive Value

Using a combination of both the DNPR/DNPatR, we found a completeness of 42% [95% CI: 37–47] and a PPV of 60% [95% CI: 54–66] (Table 3).

By the use of the DNPR only, the completeness was 32% [95% CI: 27–37] and the PPV 57% [95% CI: 50–64] (Table 3). When using only the DNPatR, the completeness

was 19% [95% CI: 15–23] and the PPV was 76% [95% CI: 68–85] (Table 3).

Stratified Analysis

According to our algorithm, the stratified analysis showed that some subgroups were registered with a higher completeness compared to the overall completeness (42% [95% CI: 37–47]). These groups were patients with age <60 years (57% [95% CI: 46–69]), WHO performance status 0 (46% [95% CI: 37–54]), and no distant metastases (58% [95% CI: 50–65]) (apart from PM) (Table 4). Contrary, some subgroups were registered with a lower completeness: patients aged >80 years (32% [95% CI: 22–42]), patients with a WHO performance status 2 (32% [95% CI: 20–44]), patients with rectal tumours (33% [95% CI: 19–48]), and patients with distant metastases (29% [95% CI: 22–35]) (apart from PM) Table 4).

Days from Colorectal Cancer to Synchronous Peritoneal Metastases

Median days from the diagnosis of CRC to the diagnosis of S-PM varied according to each register. When

Table 1 Baseline Characteristics

Patients Characteristics	Patients Registered Only in the DCCG	Patients Registered in the DCCG and DNPR and/or DNPatR	Patients Registered Only in the DNPR/ DNPatR	Total Number of Patients Registered with S-PM
	n = 213	n = 153	n = 102	n = 468
Median age (years, range)	72 (18–94)	69 (33–97)	72.5 (48–91)	71 (18–97)
Age Groups				
<60	29 (14)	39 (25)	21 (21)	89 (19)
60–69	58 (27)	39 (25)	21 (21)	118 (25)
70–74	37 (17)	27 (18)	17 (17)	81 (17)
75–80	36 (17)	23 (15)	26 (25)	85 (18)
>80	53 (25)	25 (16)	17 (17)	35 (20)
Sex				
Female	116 (54)	74 (48)	41 (40)	231 (49)
Male	97 (46)	79 (52)	61 (60)	237 (51)
Comorbidity, Charlson Score				
0	127 (60)	89 (58)	63 (62)	279 (60)
1–2	56 (26)	39 (25)	25 (24)	120 (26)
>2	30 (14)	25 (16)	14 (14)	69 (14)
WHO Performance Status				
Status 0	70 (33)	59 (39)	48 (47)	177 (38)
Status 1	61 (29)	50 (33)	26 (25)	137 (29)
Status 2	38 (18)	18 (12)	14 (14)	70 (15)
Status >2	22 (10)	13 (8)	6 (6)	41 (9)
Missing	22 (10)	13 (8)	8 (8)	43 (9)
Tumour Location				
Colon	185 (87)	139 (91)	85 (83)	409 (87)
Rectum	28 (13)	14 (9)	17 (17)	59 (13)
Pathological (y)pT[a]-Category				
T0 + T1	2 (1)	0(0)	1 (1)	3 (1)
T2	1 (0)	0 (0)	1 (1)	2 (0)
T3	10 (5)	4 (3)	12 (12)	26 (6)
T4	39 (18)	41 (27)	43 (42)	123 (26)
Tx	0 (0)	0 (0)	1 (1)	1 (0)
Missing	161 (76)	108 (71)	44 (43)	313 (67)
Pathological (y)pN[b]-Category				
N0	4 (2)	6 (4)	10 (10)	20 (4)
N1	21 (10)	14 (9)	15 (15)	50 (11)
N2	25 (12)	25 (16)	33 (33)	83 (18)
Nx	163 (77)	108 (71)	44 (44)	315 (68)
Distant Metastases to Either Lungs or Liver				
Yes	143 (67)	57 (38)	41 (40)	241 (52)
No	70 (33)	96 (63)	61 (60)	227 (48)

Notes: Patients registered with Synchronous peritoneal metastases (S-PM) from colorectal cancer. Data are presented as number of patients (%) with registration in 1) Only the Danish Colorectal Cancer Group (DCCG), 2) Both the DCCG and the Danish National Patient Registry (DNPR) and/or the Danish National Pathology Registry (DNPatR), 3) Only the DNPR and/or the DNPatR and 4) the total number of patients registered with synchronous peritoneal metastases. [a]Histopathologic Tumour-category. T indicates the size and extension of the tumour; p indicates that the category is given by a histopathologic examination and y indicates that the category is assessed after chemotherapy and/or radiation therapy. [b]Histopathologic Lymph node-category. N indicates the degree of spread to regional lymph nodes; p indicates that the category is given by a histopathologic examination and y indicates that the category is assessed after chemotherapy and/or radiation therapy.

Table 2 Number of Patients Diagnosed in One or More of the 3 Registries

Only DCCG	DCCG and DNPR and/or DNPatR	Only DNPR and/or DNPatR	Total	
n (%)	n (%)	n (%)	n (%)	
			DCCG	+ DNPR and/or DNPatR
213 (45)	153 (33)	102 (22)	366 (78)	102 (22)

Notes: The Danish Colorectal Cancer Group (DCCG) Database, The Danish National Patient Registry (DNPR) and the Danish National Pathology Registry (DNPatR) During 2015–2015.

Table 3 The Completeness and Positive Predictive Value

Registry	DCCG n = 366		Total	Completeness	PPV
	+	–			
DNPR and/or DNPatR	153	102	255	42 (37–47)	60 (54–66)
DNPR	118	89	207	32 (27–37)	57 (50–64)
DNPatR	71	22	93	19 (15–23)	76 (68–85)

Notes: The completeness: number of patients registered in the both the Danish Colorectal Cancer Group (DCCG) and each registry (the Danish National Patient Registry (DNPR) and the Danish National Pathology Registry (DNPatR)) (numerator), divided by the number (n=366) registered in the DCCG (denominator). The positive predictive value (PPV) was calculated as the number of patients with a registered diagnosis in both the DCCG and each registry, divided by the total number of patients registered with a diagnosis of peritoneal metastases in the respective registry.

registered in the DCCG, the diagnosis of S-PM was registered concurrently; therefore, the median day was 0 (IQR: 0–0). When the S-PM diagnosis was registered only in the DNPR/DNPatR, the median interval was 22 days (IQR: 7–116), while the median interval was 6 days (IQR: 0–19) when S-PM was registered in both the DCCG and the DNPR and/or the DNPatR (see Appendix for Illustration).

Discussion

In present study, we used the DCCG database as a reference to validate the registration of the ICD-10 codes and the SNOMED codes for PM in the DNPR/DNPatR. Using a combination of both the DNPR/DNPatR we found a completeness of 42% and a PPV of 60%. In the DNPR/DNPatR, some subgroups were found to be reported with a higher completeness; patients with age <60 years, WHO performance status 0 and no distant metastases. The DNPR and the DNPatR incompletely capture patients with S-PM.

Clinicians should be encouraged to register the presence of S-PM to increase the validity of register-based S-PM data.

We found that the completeness of S-PM registration is low in the DNPR and/or the DNPatR. However, advanced CRC and the registration of metastases at a specific anatomic location from any cancer disease are poorly investigated and even suggested to be underestimated in cancer registries.[22] It has been investigated in an epidemiological study from 2009, which assessed the validity of the specific ICD-10 code for bone metastases originating from breast and prostate cancer. They found a sensitivity of the DNRP-registered ICD-10 code for bone metastases from prostate cancer to be 44% and 32% from breast cancer, revealing that it fails to capture more than half of the patients with bone-specific metastases.[23] By the use of our algorithm, we found a similar tendency with a completeness of 32% when using only the DNPR, reaching only 42% when the DNPR was combined with the DNPatR.

Explanations for the underreporting of the registration of PM in the DNPR and the DNPatR might be several; when cancer patients present with metastases, these can be located at multiple sites, eg, liver and lungs and peritoneum, and thus with limited treatment options. In such cases, the clinicians' incentive to report all metastases is sparse, and often only those metastases that can be treated are reported to the national registries.[24] Further, recording of metastases may not be prioritized for patients with a limited life expectancy.[24] This is supported by the stratified analysis showing a higher completeness of S-PM registrations among potential candidates for curative treatment options as CRS and HIPEC; age <60 years, WHO performance status 0, and no distant metastases. Contrary, a lower completeness was found among patients aged >80 years, WHO performance status ≥ 2 and distant metastasis (liver and/or lung). This group of patients is according to national guidelines not eligible for CRS and HIPEC, which is a treatment offered to a selected group of patients with few, curable metastasis (≤3 curable liver metastasis, ≤2 curable lung metastasis), physiological age < 75 years and WHO performance status < 2.[25] However, the indications for CRS and HIPEC treatment are not fixed and keeps evolving.[26] Therefore, clinicians should be encouraged to register the presence of PM to ensure valid register-based data on PM from CRC in various patients.

The coding applied in the Danish registries is only used for evident medical disease. The diagnosis of PM is in its nature challenging to verify for clinicians; it does not

Table 4 Stratified Analysis

Variable	DCCG	DCCG and DNPR and/or DNPatR	DNPR and/or DNPatR	Total	Completeness in the DNPR and/or DNPatR
	n = 213	n = 153	n = 102	n = 468	% (95% Confidence Interval)
Age Groups					
<60	29 (14)	39 (25)	21 (21)	89 (19)	57 (46–69)
60–69	58 (27)	39 (25)	21 (21)	118 (25)	40 (30–50)
70–74	37 (17)	27 (18)	17 (17)	81 (17)	42 (30–54)
75–80	36 (17)	23 (15)	26 (25)	85 (18)	39 (27–51)
>80	53 (25)	25 (16)	17 (17)	95 (20)	32 (22–42)
Sex					
Female	116 (54)	74 (48)	41 (40)	231 (49)	39 (32–46)
Male	97 (46)	79 (52)	61 (60)	237 (51)	45 (38–52)
WHO Performance Status					
Status 0	70 (38)	59 (39)	48 (47)	177 (38)	46 (37–54)
Status 1	61 (29)	50 (33)	26 (25)	137 (29)	45 (36–54)
Status 2	38 (18)	18 (12)	14 (14)	70 (15)	32 (20–44)
Status >2	22 (10)	13 (8)	6 (6)	41 (9)	37 (21–53)
Missing	22 (10)	13 (8)	8 (8)	43 (9)	37 (21–53)
Tumour Location					
Colon	185 (87)	139 (91)	85 (83)	409 (87)	43 (38–48)
Rectum	28 (13)	14 (9)	17 (17)	59 (13)	33 (19–48)
Distant Metastases to Either Lungs or Liver					
Yes	143 (67)	57 (37)	41 (40)	241 (51)	29 (22–35)
No	70 (33)	96 (63)	61 (60)	227 (49)	58 (50–65)

Notes: Number of patients (%) registered in 1) Only the Danish Colorectal Cancer Group (DCCG), 2) Both the DCCG and the Danish National Patient Registry (DNPR) and/or Danish National Pathology Registry (DNPatR), 3) Only the DNPR and/or the DNPatR and 4) the total number of patients registered with synchronous peritoneal metastases. The Completeness of the registrations in the DNPR and/or the DNPatR: Number of patients registered in the both the DCCG and the DNPR and/or DNPatR (numerator), divided by the number registered in the DCCG (denominator).

necessarily rely on a histopathological verification, the sensitivity of a preoperative CT scan is low, and there is often a discrepancy between the radiological observed extent of peritoneal involvement and the findings during surgical exploration.[11,27] Clinicians are only allowed to register diagnoses with a high degree of certainty, so a diagnosis that is rarely histopathological verified, as PM, may be underreported. Our results show that the completeness in the DNPatR is 19% but the PPV is 76%. The low completeness in the DNPatR is potentially due to the fact that the majority of S-PM patients are not subjected to surgery, and therefore, a histopathological evaluation is lacking. Consequently, the majority of the registered S-PM diagnoses are most likely based on radiological findings or, in case of surgical exploration, the perioperative findings.

We developed a feasible algorithm to capture Danish patients with S-PM by combining the DCCG, the DNPR and the DNPatR. By combining the three registries, we found a 5% prevalence of S-PM among CRC patients (Figure 1). This prevalence is in accordance with international literature, and demonstrates a similar and thereby representativeness of our algorithm.[26] Yet, our results demonstrate that some subgroups are registered with a higher respective lower completeness in the DNPR/DNPatR. Further, patients who were only registered in the DNPR/DNPatR differed with respect to age, sex, tumour and presence of distant metastases other than PM. Explanations for this variation might be several: First, clinicians are not obligated to mandatorily register the presence of PM in the Danish registries. In the DCCG, the registration is performed by dedicated surgeons with the purpose to ensure the quality

of all types of treatment offered to Danish CRC patients.[18] Contrary, the diagnoses in the DNPR/DNPatR are registered by any clinician respective pathologist during in-hospital treatment of the patient. Even though the registration process should be simple, there might be a different acceptability among surgeons, clinicians and pathologists. Second, we choose to distinguish between synchronous and metachronous peritoneal metastases 180 days after CRC diagnosis. Our results demonstrate a difference in the median time interval (and Interquartile range (IQR)) from CRC diagnosis to S-PM diagnosis according to each register. When registered only in the DNPR/DNPatR, the median of 22 days with a wide IQR (7-116) compared to a median of 6 days with a narrow IQR (0-19) when registered in both the DCCG and the DNPR/DNPatR. Causes to this difference are unknown and explanations are speculative. A histopathological examination takes, as a minimum, 3 days to conduct, which might explain the delay in S-PM registration. On the other hand, a median of 22 days with a wide IQR may indicate that the PM barely has been evident at the time of CRC diagnosis. It is plausible that the diagnosis of PM has not been detected during resection of the primary tumour, but diagnosed as an incidental finding by histopathology of the resected tumour. In such case, with a histopathological identified PM diagnosis, a detailed examination of the possibilities for postoperative treatment might explain the delay in the diagnosis of S-PM. Hypothetically, a postoperative treatment could include CRS and HIPEC performed approximately 3 months, as a minimum, after the primary resection of the CRC cancer. This demonstrates a difference in the timeliness (ie, how quickly data flow from "real-time" to the register) according to each register, and should be taken into consideration in future register-based studies of S-PM patients.

Strengths and Limitations

The study is based on a national cohort of CRC patients from the DCCG database known with a high completeness of CRC patients, demonstrating a high acceptability for surveillance of CRC patients in the DCCG. To our knowledge, this is the first both national and international study describing the quality of S-PM registration among CRC patients.

We excluded patients with non-CRC, thereby ensuring that the ICD-10 codes represented PM originated from CRC. Our algorithm combines 3 variables from the DCCG, 2 ICD-10 codes and several SNOMED codes presented in the Appendix. The simplicity of the combination is high and should be reproducible for a potential external validation.

However, there is no perfect gold standard to identify S-PM, and consequently this limits the interpretation of the sensitivity of our algorithm applied. The value of medical charts as the golden standard has been questioned when searching for register-based metastases.[15]

We searched for patients with S-PM in a time period, where the awareness of PM and its treatment options have increased,[28] and the DCCG database has undergone revisions. Our algorithm combines the Danish medical registries and shows flexibility in accordance with the expansion in knowledge, subsequently the changes in each registry. However, changes may introduce misclassification of S-PM during the early phase of an implementation. Hypothetically, PM is registered with a lower completeness in the DNPR/DNPatR in periods where the focus on PM has been minimal. This potential source of bias should be taken into consideration in future analytical studies investigating an association between S-PM and a specific research question. Further, our results from the stratified analysis show that the registration of S-PM differs within subgroups (eg, a higher completeness of S-PM registrations among patients being potentially eligible for curative treatment options as CRS and HIPEC), thereby introducing potential differential misclassification. This may also have implications for future studies investigating the prognosis of S-PM. The effect of the differential misclassification, ie, under-/or overestimation of an association, depends on whether S-PM is used as an exposure or outcome. For example, if a study investigates survival after CRC surgery and register-based S-PM data are used as an exposure variable (or disease status), the association between S-PM and survival will be underestimated because patients with a good prognosis are registered with a higher completeness compared to patients with a poor prognosis.

Further, we interpreted ovarian metastases as PM, which is a debated subject internationally.[29] Finally, the current study only investigates the quality of peritoneal metastases registered synchronously with the CRC diagnosis; therefore, our results cannot be extrapolated to other populations, eg, register-based detection of recurrence in the peritoneum (metachronous peritoneal metastases).

Conclusion

The DNPR/DNPatR captures under half of patients with colorectal synchronous peritoneal metastases. Patients being potentially eligible for curative treatment options; patients with age <60 years, WHO performance status 0

and no distant metastasis (other than PM) are registered with a higher completeness.

Abbreviations

CRC, colorectal cancer; PM, peritoneal metastases; S-PM, synchronous peritoneal metastases; DNPR, The Danish National Patient Registry; DCCG, The Danish Colorectal Cancer Group; DNPatR, The Danish National Pathology Registry.

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Author Contributions

The corresponding author performed the data analysis. All authors contributed with a critical review of the data analysis and drafted/revised the article. All authors gave final approval of the version to be published and agreed to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest in this work.

References

1. Weitz J, Koch M, Debus J, Hohler T, Galle PR, Buchler MW. Colorectal cancer. *Lancet*. 2005;365(9454):153–165. doi:10.1016/S0140-6736(05)17706-X
2. Iversen LH. Aspects of survival from colorectal cancer in Denmark. *Dan Med J*. 2012;59(4):B4428.
3. Golfinopoulos V, Salanti G, Pavlidis N, Ioannidis JP. Survival and disease-progression benefits with treatment regimens for advanced colorectal cancer: a meta-analysis. *Lancet Oncol*. 2007;8 (10):898–911. doi:10.1016/S1470-2045(07)70281-4
4. Boysen AK, Spindler K-L, Hoyer M, et al. Metastasis directed therapy for liver and lung metastases from colorectal cancer - a population based study. *Int J Cancer*. 2018;143:3218–3226. doi:10.1002/ijc.31626
5. Iversen LH, Green A, Ingeholm P, Osterlind K, Gogenur I. Improved survival of colorectal cancer in Denmark during 2001–2012 - the efforts of several national initiatives. *Acta Oncol*. 2016;55(Suppl 2):10–23. doi:10.3109/0284186X.2015.1131331

6. Verwaal VJ, Bruin S, Boot H, van Slooten G, van Tinteren H. 8-year follow-up of randomized trial: cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy in patients with peritoneal carcinomatosis of colorectal cancer. *Ann Surg Oncol*. 2008;15(9):2426–2432. doi:10.1245/s10434-008-9966-2
7. Weber T, Roitman M, Link KH. Current status of cytoreductive surgery with hyperthermic intraperitoneal chemotherapy in patients with peritoneal carcinomatosis from colorectal cancer. *Clin Colorectal Cancer*. 2012;11(3):167–176. doi:10.1016/j.clcc.2012.01.001
8. Neo EL, Beeke C, Price T, et al. South Australian clinical registry for metastatic colorectal cancer. *ANZ J Surg*. 2011;81(5):352–357. doi:10.1111/ans.2011.81.issue-5
9. Wang X, Hershman DL, Abrams JA, et al. Predictors of survival after hepatic resection among patients with colorectal liver metastasis. *Br J Cancer*. 2007;97(12):1606–1612. doi:10.1038/sj.bjc.6604093
10. Koumpa FS, Xylas D, Konopka M, et al. Colorectal peritoneal metastases: a systematic review of current and emerging trends in clinical and translational research. *Gastroenterol Res Pract*. 2019;2019:5180895. doi:10.1155/2019/5180895
11. Dresen RC, De Vuysere S, De Keyzer F, et al. Whole-body diffusion-weighted MRI for operability assessment in patients with colorectal cancer and peritoneal metastases. *Cancer Imaging*. 2019;19(1):1. doi:10.1186/s40644-018-0187-z
12. Schmidt M, Schmidt SA, Sandegaard JL, Ehrenstein V, Pedersen L, Sorensen HT. The Danish National Patient Registry: a review of content, data quality, and research potential. *Clin Epidemiol*. 2015;7:449–490. doi:10.2147/CLEP.S91125
13. Lash TL, Riis AH, Ostenfeld EB, Erichsen R, Vyberg M, Thorlacius-ussing O. A validated algorithm to ascertain colorectal cancer recurrence using registry resources in Denmark. *Int J Cancer*. 2015;136 (9):2210–2215. doi:10.1002/ijc.v136.9
14. Ording AG, Heide-jorgensen U, Christiansen CF, Norgaard M, Acquavella J, Sorensen HT. Site of metastasis and breast cancer mortality: a Danish nationwide registry-based cohort study. *Clin Exp Metastasis*. 2017;34(1):93–101. doi:10.1007/s10585-016-9824-8
15. Ehrenstein V, Hernandez RK, Maegbaek ML, et al. Validation of algorithms to detect distant metastases in men with prostate cancer using routine registry data in Denmark. *Clin Epidemiol*. 2015;7:259–265. doi:10.2147/CLEP.S74991
16. Vandenbroucke JP, von Elm E, Altman DG, et al. Strengthening the reporting of observational studies in epidemiology (STROBE): explanation and elaboration. *Int J Surg*. 2014;12(12):1500–1524. doi:10.1016/j.ijsu.2014.07.014
17. Schmidt M, Schmidt SAJ, Adelborg K, et al. The Danish health care system and epidemiological research: from health care contacts to database records. *Clin Epidemiol*. 2019;11:563–591. doi:10.2147/CLEP.S179083
18. Ingeholm P, Gogenur I, Iversen LH. Danish colorectal cancer group Database. *Clin Epidemiol*. 2016;8:465–468. doi:10.2147/CLEP.S99481
19. Schmidt M, Pedersen L, Sorensen HT. The Danish civil registration system as a tool in epidemiology. *Eur J Epidemiol*. 2014;29 (8):541–549. doi:10.1007/s10654-014-9930-3
20. Erichsen R, Lash TL, Hamilton-dutoit SJ, Bjerregaard B, Vyberg M, Pedersen L. Existing data sources for clinical epidemiology: the Danish National Pathology Registry and Data Bank. *Clin Epidemiol*. 2010;2:51–56. doi:10.2147/clep.S9908
21. Thygesen SK, Christiansen CF, Christensen S, Lash TL, Sorensen HT. The predictive value of ICD-10 diagnostic coding used to assess Charlson comorbidity index conditions in the population-based Danish National Registry of Patients. *BMC Med Res Methodol*. 2011;11:83. doi:10.1186/1471-2288-11-83
22. Oppelt KA, Luttmann S, Kraywinkel K, Haug U. Incidence of advanced colorectal cancer in Germany: comparing claims data and cancer registry data. *BMC Med Res Methodol*. 2019;19(1):142. doi:10.1186/s12874-019-0784-y

23. Jensen AO, Norgaard M, Yong M, Fryzek JP, Sorensen HT. Validity of the recorded International Classification of Diseases, 10th edition diagnoses codes of bone metastases and skeletal-related events in breast and prostate cancer patients in the Danish National Registry of Patients. *Clin Epidemiol*. 2009;1:101–108. doi:10.2147/CLEP.S5446

24. Chawla N, Yabroff KR, Mariotto A, McNeel TS, Schrag D, Warren JL. Limited validity of diagnosis codes in Medicare claims for identifying cancer metastases and inferring stage. *Ann Epidemiol*. 2014;24(9):666–672, 672 e661–662. doi:10.1016/j.annepidem.2014.06.099

25. (Danish) DCCG. National guidelines. Available from: https://dccg.dk/wp-content/uploads/2018/12/2018-Peritoneal-karcinose-og-HIPEC-v-3_1.pdf. 2019 Accessed July 11, 2019.

26. Vassos N, Piso P. Metastatic colorectal cancer to the peritoneum: current treatment options. *Curr Treat Options Oncol*. 2018;19 (10):49. doi:10.1007/s11864-018-0563-8

27. Flicek K, Ashfaq A, Johnson CD, Menias C, Bagaria S, Wasif N. Correlation of radiologic with surgical peritoneal cancer index scores in patients with pseudomyxoma peritonei and peritoneal carcinomatosis: how well can we predict resectability?. *J Gastrointest Surg*. 2016;20(2):307–312. doi:10.1007/s11605-015-2880-6

28. Verwaal VJ, Rau B, Jamali F, et al. Registries on peritoneal surface malignancies throughout the world, their use and their options. *Int J Hyperthermia*. 2017;33(5):528–533. doi:10.1080/02656736.2017.1315178

29. Bignell MB, Mehta AM, Alves S, et al. Impact of ovarian metastases on survival in patients treated with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for peritoneal malignancy originating from appendiceal and colorectal cancer. *Colorectal Dis*. 2018;20(8):704–710. doi:10.1111/codi.2018.20.issue-8

Appendix II

Original article

Overall risk and risk factors for metachronous peritoneal metastasis after colorectal cancer surgery: a nationwide cohort study

S. Ravn[1] , **U. Heide-Jørgensen[2], C. F. Christiansen[2], V. J. Verwaal[1], R. H. Hagemann-Madsen[3] and L. H. Iversen[1,4]**

Departments of [1]Surgery and [2]Clinical Epidemiology, Aarhus University Hospital, Aarhus, [3]Department of Pathology, Lillebaelt Hospital, Vejle, and [4]Danish Colorectal Cancer Group, Copenhagen, Denmark
Correspondence to: Dr S. Ravn, Department of Surgery, Aarhus University Hospital, Palle Juul-Jensens Boulevard 99, DK-8200 Aarhus N, Denmark (e-mail: sissel.ravn@rm.dk)

Background: This study aimed to identify the cumulative incidence and risk factors of metachronous peritoneal metastasis (M-PM) from colorectal cancer in patients who had intended curative treatment.

Methods: Patients with colorectal cancer were identified using the Danish Colorectal Cancer Group database for 2006–2015. The Danish Pathology Registry and the Danish National Patient Registry were used to identify M-PM to 2017. Risk factors were estimated by multivariable absolute risk regression, treating death and other cancers as competing risks. Overall risk and risk differences (RDs) were estimated at 1, 3 and 5 years.

Results: In 22 586 patients with colorectal cancer, the overall risk of M-PM was reported to be 0·9 (95 per cent c.i. 0·8 to 1·0) per cent at 1 year, 1·9 (1·8 to 2·1) per cent at 3 years and 2·2 (2·0 to 2·4) per cent at 5 years. Advanced tumour category ((y)pT4 *versus* (y)pT1) increased the RD of both M-PM (2·9 (95 per cent c.i. 2·1 to 3·7) at 1 year and 6·0 (4·9 to 7·2) at 3 years) and lymph node involvement ((y)pN2 *versus* (y)pN0) (2·5 (1·8 to 3·2) at year and 4·3 (3·2 to 5·3) at 3 years). No further increase in risk was observed at 5 years. In a subanalysis, tumour-involved resection margin (R1 *versus* R0) was associated with M-PM with a RD of 3·9 (1·6 to 6·2) at 1 year and 5·9 (2·6 to 9·3) at 3 years.

Conclusion: The overall risk of M-PM in patients with colorectal cancer is low, but is increased in advanced T and N status. Follow-up of at least 3 years after colorectal cancer surgery may be necessary, given the potential curative treatment of early diagnosed M-PM.

Introduction

The long-term survival of patients with colorectal cancer has improved significantly over the past few years; in Denmark, the relative 5-year survival rate increased from 58–59 per cent in 2001–2004 to 63–65 per cent in 2009–2012[1]. The improvements made so far may be related to several factors, including multidisciplinary team management, the introduction of minimally invasive surgery, implementation of total mesorectal and complete mesocolic excision, specialization and centralization of treatments, pathological/molecular evaluations, and general improvements in radiological assessments, radiotherapy and medical oncology[1,2]. However, recurrence is still an issue.

Registry-based studies have reported the incidence of metachronous peritoneal metastasis (M-PM) to be 3·5 per cent at a median of 18 months after diagnosis[3], rising to 6 per cent within 5 years[4]. Risk factors identified for M-PM include advanced T and N categories[3,5–8], bowel perforation, emergency surgery[5,7,9] and non-radical resection[3,5].

Two different strategies for the prevention and early detection of M-PM have been proposed, including prophylactic adjuvant hyperthermic intraperitoneal

chemotherapy (HIPEC)[10] and early detection with second-look surgery plus HIPEC[11]. However, selection of appropriate patients for these treatment options was based on previously identified risk factors for M-PM[5,12], and needs further investigation.

This study aimed to describe the overall 5-year risk of developing M-PM in patients with colorectal cancer, and to identify risk factors for M-PM following intended curative surgery.

Methods

A nationwide registry-based cohort study was conducted in Denmark according to the STROBE criteria[13]. All 5·8 million Danish citizens have access to a public tax-supported healthcare system and are assigned a unique ten-digit personal registration number, enabling unambiguous individual-level record linkage between registers.

Patients diagnosed with colorectal cancer in the Danish Colorectal Cancer Group database between 2006 and 2015 were identified. In March 2014, the implementation of a national screening programme with faecal immunochemical testing[14] led to diagnoses of both symptomatic and asymptomatic patients with colorectal cancer. During the study period, national guidelines[15] recommended that follow-up of patients with colorectal cancer should include, as a minimum, CT of the thorax and abdomen at 12 and 36 months after surgery.

The Danish Data Protection Agency approved the study (number 1-16-02-441-16). Ethical approval is not required for registry-based studies.

Inclusion and exclusion criteria for the study population are summarized in *Fig. 1*. Patients were included if they had undergone a pathologically confirmed R0 or R1 bowel resection for colorectal cancer. Patients with metastasis to liver and/or lungs were included if the surgery was performed with curative intent. The date of colorectal cancer diagnosis plus 180 days was considered as the index date. To reduce immortal time bias, the index date was considered as the beginning of follow-up[16,17].

Patients were excluded if they had emigrated or had been diagnosed with other (non-colorectal cancer) malignancies within a period of 5 years plus 180 days before the index date. Finally, patients were excluded if diagnosed with synchronous peritoneal metastasis (S-PM) (identified before the index date) or if they had died between the diagnosis and index dates. Synchronous PMs were defined as PMs identified within 180 days of the diagnosis of colorectal cancer[18,19].

Registries

Data from the Danish Colorectal Cancer Group database were merged to identify M-PM and cross-check follow-up. In particular, the Danish National Patient Registry provided information about diagnostic coding of PM, the Danish National Pathology Registry was reviewed for histologically proven PM, and the Danish Civil Registration System for follow-up and vital status. The Danish Colorectal Cancer Group database contains information about all patients with first-time colorectal cancer since 2001, with data completeness of more than 95 per cent. The database also contains information on patient characteristics, radiological evaluation, surgical and oncological treatment, pathology reporting, and the postoperative course within 30 days of surgery[20].

The Danish National Patient Registry provides longitudinal data from 1977 regarding administrative and clinical data, and contains information about hospital admissions and outpatient contacts with the healthcare system. Diagnoses were recorded using ICD-10 codes from 1994, whereas treatment and procedures are registered by using a Danish version of the Nordic Medico-Statistical Committee (NOMESCO) Classification of Surgical Procedures.

The Danish National Pathology Registry was established in 1997, and all pathological examinations performed in Denmark are registered following a uniform guideline. Each specimen is linked to the personal registration number, the hospital department responsible for treatment, the date of request, the specific Danish Systematized Nomenclature of Medicine codes[21], and other sources of data.
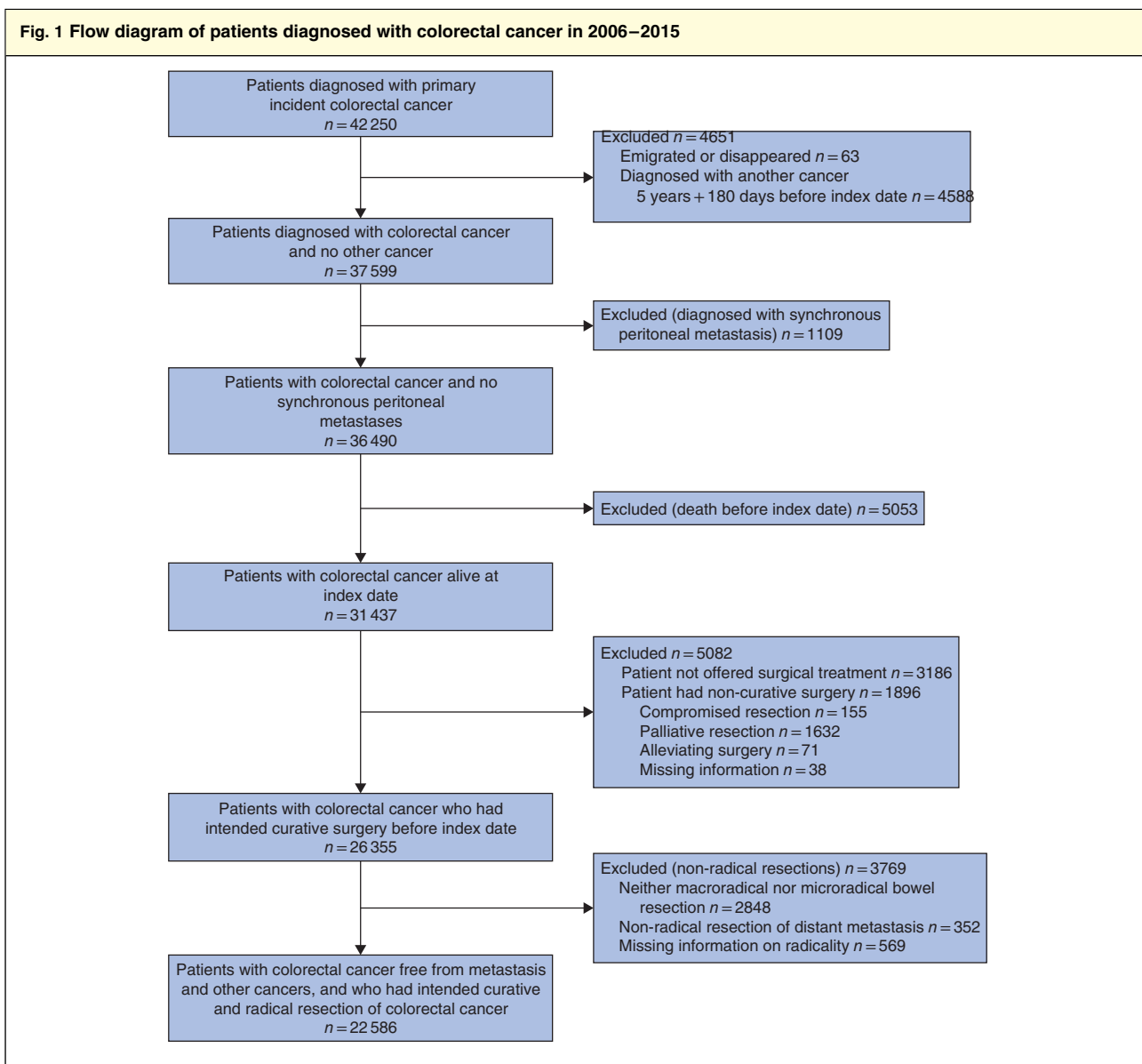
The Danish Civil Registration System is an administrative register established in 1968 to record information about residency and vital status of all Danish citizens. The register is updated daily and has a high accuracy, allowing for complete long-term follow-up[22].

Identification of metachronous peritoneal metastasis

In the Danish National Patient Registry, M-PM was identified by two ICD-10 codes: 'metastasis in the retroperitoneal space or in the peritoneum' (C786) and 'metastasis to the ovaries' (C796). In the Danish National Pathology Registry, M-PM was identified as a specimen/biopsy with a topography code as peritoneum, combined with a specific morphology code representing metastatic spread from the colon or rectum (*Appendix S1*, supporting information).

Potential risk factors

Variables included age (less than 60, 60–75 or more than 75 years), sex, tumour localization (right colon (caecum

Fig. 1 Flow diagram of patients diagnosed with colorectal cancer in 2006–2015

```
┌─────────────────────────────┐
│ Patients diagnosed with     │
│ primary incident colorectal │        ┌─────────────────────────────────────────┐
│ cancer                      │───────▶│ Excluded n = 4651                       │
│ n = 42 250                  │        │    Emigrated or disappeared n = 63      │
└─────────────────────────────┘        │    Diagnosed with another cancer        │
              │                        │       5 years + 180 days before index   │
              ▼                        │       date n = 4588                     │
┌─────────────────────────────┐        └─────────────────────────────────────────┘
│ Patients diagnosed with     │
│ colorectal cancer and no    │        ┌─────────────────────────────────────────┐
│ other cancer                │───────▶│ Excluded (diagnosed with synchronous    │
│ n = 37 599                  │        │ peritoneal metastasis) n = 1109         │
└─────────────────────────────┘        └─────────────────────────────────────────┘
              │
              ▼
┌─────────────────────────────┐
│ Patients with colorectal    │
│ cancer and no synchronous   │        ┌─────────────────────────────────────────┐
│ peritoneal metastases       │───────▶│ Excluded (death before index date)      │
│ n = 36 490                  │        │ n = 5053                                │
└─────────────────────────────┘        └─────────────────────────────────────────┘
              │
              ▼
┌─────────────────────────────┐        ┌─────────────────────────────────────────┐
│ Patients with colorectal    │        │ Excluded n = 5082                       │
│ cancer alive at index date  │        │    Patient not offered surgical         │
│ n = 31 437                  │───────▶│       treatment n = 3186                │
└─────────────────────────────┘        │    Patient had non-curative surgery     │
              │                        │       n = 1896                          │
              ▼                        │       Compromised resection n = 155     │
┌─────────────────────────────┐        │       Palliative resection n = 1632     │
│ Patients with colorectal    │        │       Alleviating surgery n = 71        │
│ cancer who had intended      │        │       Missing information n = 38        │
│ curative surgery before      │        └─────────────────────────────────────────┘
│ index date                  │
│ n = 26 355                  │        ┌─────────────────────────────────────────┐
└─────────────────────────────┘        │ Excluded (non-radical resections)       │
              │                        │ n = 3769                                │
              │───────────────────────▶│    Neither macroradical nor microradical│
              ▼                        │       bowel resection n = 2848          │
┌─────────────────────────────┐        │    Non-radical resection of distant     │
│ Patients with colorectal    │        │       metastasis n = 352                │
│ cancer free from metastasis │        │    Missing information on radicality     │
│ and other cancers, and who  │        │       n = 569                           │
│ had intended curative and   │        └─────────────────────────────────────────┘
│ radical resection of        │
│ colorectal cancer           │
│ n = 22 586                  │
└─────────────────────────────┘
```

The index date is 180 days after the date of colorectal cancer diagnosis.

and ascending colon), right colonic flexure, transverse colon, left colonic flexure, left colon (descending colon and sigmoid), rectum), surgery (elective or emergency), perforation of the tumour as assessed at operation by the surgeon (no; yes, encapsulated (perforation not free in the peritoneal cavity); or yes, free to the peritoneum), pathologically assessed T category ((y)pT0–1, (y)pT2, (y)pT3 or (y)pT4), pathologically assessed N category ((y)pN0, (y)pN1 or (y)pN2), tumour histology (adeno-carcinoma or other), extramural venous invasion (EMVI) (available from 2009), radicality of the resection (R0, no macroscopic or microscopic tumour residual left

in resection margins; R1, microscopic tumour residual left 1 mm or less from resection margins (included in 2014 owing to the implementation of new strict national guidelines); R2, macroscopic tumour tissue left during resection of the tumour), and systemic chemotherapy (yes or no).

Information on tumour histology was obtained from the Danish National Pathology Registry (*Appendix S1*, supporting information). Data on systemic chemotherapy before the index date were obtained from the Danish National Patient Registry using the specific NOMESCO codes for systemic chemotherapy (*Appendix S1*, supporting

information); however, no information about cycles, doses or frequency was available[23].

Statistical analysis

Patient characteristics and demographics are presented as categorical variables by counts and percentages.

Patients were followed up from the index date to the date of diagnosis of M-PM or non-colorectal cancer, death or to 25 January 2017. Cumulative incidence (risk) curves for M-PM were estimated; all-cause mortality (death) and diagnosis of non-colorectal cancer were considered to be competing risks[24,25].

Analysis of potential risk factors was done as a complete-case analysis: only patients with no missing values for potential risk factors were included. To assess 1-, 3- and 5-year risk differences (RDs) with 95 per cent c.i. for M-PM associated with each risk factor, a multivariable absolute risk regression model including all risk factors (except radicality and EMVI) was conducted, adjusting for year of colorectal cancer diagnosis and co-morbidity, as assessed by the Charlson Co-morbidity Index (CCI) (categorized as low (score 0), medium (score 1–2) or high (score greater than 2)). Death and non-colorectal cancer were considered as competing risks[26,27].

Details of radicality (R1) and EMVI were not available for the whole study period, and were therefore investigated in subgroups of the cohort restricted to relevant calendar periods, using models adjusted only for age, sex and co-morbidity (CCI) owing to the small number of patients with M-PM.

Statistical analysis was performed using STATA® software release IC15 (StataCorp, College Station, Texas, USA).

Results

Overall, 42 250 patients with colorectal cancer were identified in the DCCG database, 22 586 of whom met the study criteria (*Fig. 1*). These patients did not have a cancer diagnosis 5 years before the diagnosis of colorectal cancer, were assessed negative for synchronous PMs, and underwent intended curative resection (R0 or R1) of the tumour, including concomitant procedures if liver and/or lung metastases were present. Patient, tumour and treatment characteristics at the time of colorectal cancer diagnosis are shown in *Table 1*.

Overall risk of metachronous peritoneal metastases

Some 533 of the 22 586 patients (2·4 per cent) developed peritoneal metastases, among whom 84·4 per cent were

Table 1 Baseline characteristics of patients with colorectal cancer, diagnosed in 2006–2015, undergoing intended curative and macroscopically radical surgery for the primary colorectal tumour

	No. of patients (*n* = 22 586)
Age at diagnosis of colorectal cancer (years)	
< 60	4034 (17·9)
60–75	11 069 (49·0)
> 75	7483 (33·1)
Sex	
F	10 548 (46·7)
M	12 038 (53·3)
Charlson Co-morbidity Index score	
0	13 289 (58·8)
1–2	3991 (17·7)
> 2	5306 (23·5)
Tumour localization	
Right colon	4914 (21·8)
Right colonic flexure	968 (4·3)
Transverse colon	1110 (4·9)
Left colonic flexure	607 (2·7)
Left colon	7260 (32·1)
Rectum	7724 (34·2)
Colon unspecified	3 (0·0)
Metastasis to liver or lung at diagnosis of colorectal cancer	
Yes	91 (0·4)
No	22 495 (99·6)
Localization of metastasis	*n* = 91
Liver only	79 (87)
Lung only	7 (8)
Liver and lung	5 (5)
Priority of surgery	
Elective	21 261 (94·1)
Emergency*	1322 (5·9)
Missing	3 (0·0)
Intended operative approach	
Laparoscopy	12 528 (55·5)
Laparotomy	8569 (37·9)
Robot-assisted	660 (2·9)
Other minimally invasive†	84 (0·4)
Endoscopy	745 (3·3)
Tumour perforation	
No	21 951 (97·2)
Yes, encapsulated	381 (1·7)
Yes, free to peritoneum	254 (1·1)
(y)pT category‡	
T0–T1	2598 (11·5)
T2	3867 (17·1)
T3	13 376 (59·2)
T4	2576 (11·4)
Tx	153 (0·7)
Missing	16 (0·1)

Table 1 Continued	
	No. of patients (*n* = 22 586)
(y)pN category§	
N0	14 337 (63·5)
N1	4748 (21·0)
N2	2609 (11·6)
Nx	892 (3·9)
Microradical surgery	
Calendar years 2006–2013	*n* = 16 365
Yes, R0¶	16 365 (100)
Calendar years 2014–2016	*n* = 6221
Yes, R0¶	5801 (93·2)
No, R1#	420 (6·8)
Tumour histology	
Adenocarcinoma	21 200 (93·9)
Other**	1386 (6·1)
Extramural venous invasion††	
No	10 804 (47·8)
Yes	2862 (12·7)
Missing	1921 (8·5)
n.a.	6999 (31·0)
Postoperative oncological treatment within 180 days of diagnosis of colorectal cancer	
Yes	5924 (26·2)
No	16 662 (73·8)
Year of diagnosis of colorectal cancer	
2006–2007	4123 (18·3)
2008–2009	3945 (17·5)
2010–2011	3993 (17·7)
2012–2013	4304 (19·1)
2014–2015	6221 (27·5)

Values in parentheses are percentages. *Reason for emergency surgery: ileus (42·0 per cent), perforation (12·8 per cent), other (5·6 per cent), bleeding (0·6 per cent), missing (39·0 per cent). †Includes (amongst others) transanal total mesorectal excision. ‡ypT0–1, 298; ypT2, 386; ypT3, 825; ypT4, 149; ypTx, one. §ypN0, 1147; ypN1, 347; ypN2, 158; ypNx, seven. ¶R0, neither macroscopic nor microscopic tumour residual left in resection margins. #R1 included only from 2014 owing to implementation of new strict national guidelines recommending use and coding of the term 'not microscopically radical resection' included microscopic tumour residual left 1 mm or less from resection margins. **Includes: mucinous adenocarcinoma, low differentiated adenocarcinoma, signet ring cell carcinoma, medullary carcinoma, undifferentiated adenocarcinoma, serrated adenocarcinoma and carcinoma. ††Data available from 2009. n.a., Not applicable.

identified in the Danish National Patient Registry and 6·0 per cent in the Danish National Pathology Registry; an additional 9·6 per cent were identified in both registries. The overall risk of M-PM after intended curative surgery for colorectal cancer was 0·9 (95 per cent c.i. 0·8 to 1·0) per cent at 1 year, 1·9 (1·8 to 2·1) per cent at 3 years, and 2·2 (2·0 to 2·4) per cent at 5 years (*Fig. 2*). Death and non-colorectal cancer were assessed as the major competing risks (*Fig. 3*).

Fig. 2 Risk (cumulative incidence) of metachronous peritoneal metastases in Danish patients undergoing intended curative surgery for colorectal cancer in 2006–2015

No. at risk 22 586   19 856   15 579   12 244   9804   7645
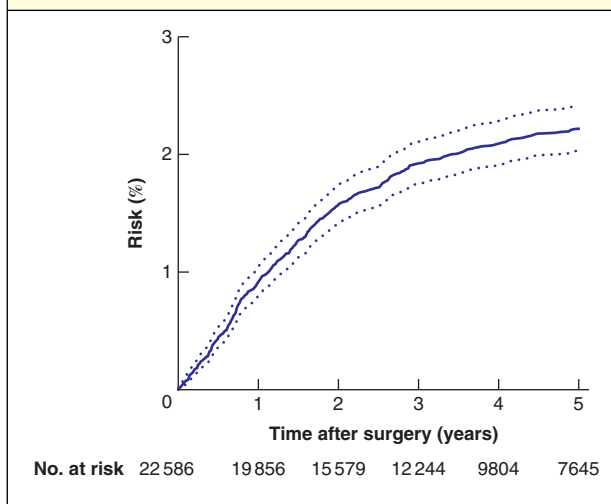
Dotted lines indicate 95 per cent confidence intervals of risk.

Fig. 3 Risk (cumulative incidence) of metachronous peritoneal metastasis, death (all-cause mortality) and non-colorectal cancer in Danish patients undergoing intended curative surgery for colorectal cancer in 2006–2015

No. at risk 22 586   19 856   15 579   12 244   9804   7645
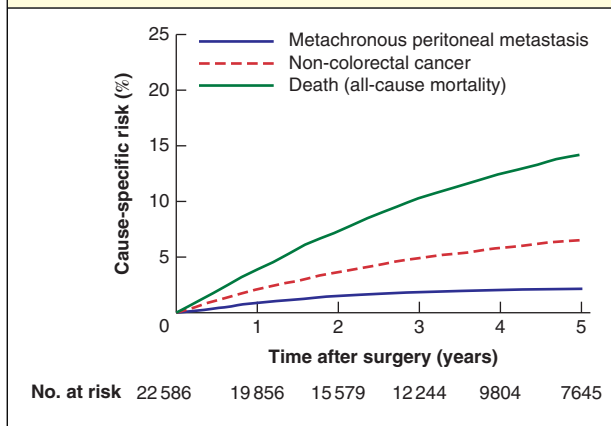
Risk factors for metachronous peritoneal metastases

Results of the absolute risk regression analyses are shown in *Table 2*. A total of 21 581 patients (95·6 per cent) had complete data for risk factors. The multivariable analysis showed that (y)pT4 status increased the absolute risk by 2·9 (95 per cent c.i. 2·1 to 3·7) per cent at 1 year and by 6·0 (4·9 to 7·2) per cent at 3 years. Compared with a (y)pN0 tumour, (y)pN2 status was associated with a 2·5 (1·8 to 3·2) per cent risk of M-PM at 1 year and a 4·3 (3·2 to 5·3) per cent

S. Ravn, U. Heide-Jørgensen, C. F. Christiansen, V. J. Verwaal, R. H. Hagemann-Madsen and L. H. Iversen

Table 2 Multivariable absolute risk differences for metachronous peritoneal metastases 1 and 3 years after intended curative colorectal cancer surgery

	Multivariable adjusted absolute risk difference (%)*	
	1 year†	3 years†
Age at diagnosis of colorectal cancer (years)		
< 60	0 (reference)	0 (reference)
60–75	−0.2 (−0.6, 0.2)	−0.5 (−1.1, 0.2)
> 75	−0.5 (−0.9, 0.0)	−1.0 (−1.7, −0.4)
Sex		
F	0 (reference)	0 (reference)
M	0.1 (−0.2, 0.4)	0.3 (−0.1, 0.7)
Tumour localization		
Left colon	0 (reference)	0 (reference)
Left colonic flexure	0.6 (−0.5, 1.6)	0.6 (−0.9, 2.2)
Transverse colon	0.2 (−0.5, 0.9)	0.2 (−0.9, 1.3)
Right colonic flexure	0.1 (−0.6, 0.7)	−0.2 (−1.2, 0.9)
Right colon	0.5 (0.1, 0.9)	0.6 (0.0, 1.3)
Rectum	−0.1 (−0.4, 0.2)	−0.3 (−0.8, 0.1)
Priority of surgery		
Elective	0 (reference)	0 (reference)
Emergency	0.9 (−0.1, 1.9)	1.9 (0.5, 3.4)
Tumour perforation		
No	0 (reference)	0 (reference)
Yes, encapsulated	−1.0 (−2.1, 0.1)	−0.3 (−2.5, 1.9)
Yes, free to peritoneum	−0.1 (−2.2, 2.0)	−0.2 (−3.4, 3.1)
(y)pT category		
T1	0 (reference)	0 (reference)
T2	−0.1 (−0.3, 0.2)	0.0 (−0.4, 0.4)
T3	0.1 (−0.2, 0.3)	0.6 (0.2, 1.0)
T4	2.9 (2.1, 3.7)	6.0 (4.9, 7.2)
(y)pN category		
N0	0 (reference)	0 (reference)
N1	0.5 (0.1, 0.9)	1.3 (0.7, 2.0)
N2	2.5 (1.8, 3.2)	4.3 (3.2, 5.3)
Tumour histology		
Adenocarcinoma	0 (reference)	0 (reference)
Other	0.2 (−0.6, 0.9)	0.4 (−0.8, 1.5)
Postoperative chemotherapy within 180 days of colorectal cancer diagnosis		
No	0 (reference)	0 (reference)
Yes	0.0 (−0.4, 0.4)	−0.2 (−0.8, 0.5)
Extramural venous invasion‡		
No	0 (reference)	0 (reference)
Yes	2.3 (1.7, 3.0)	3.4 (2.5, 4.4)
Radicality of surgery§		
R0	0 (reference)	0 (reference)
R1	3.9 (1.5, 6.2)	5.9 (2.6, 9.3)

Death and other cancer were treated as competing risks. Values in parentheses are 95 per cent confidence intervals. *A total of 21 581 complete cases were included in the multivariable analysis, adjusted for all risk factors in the table, including year of diagnosis and co-morbidity (Charlson Co-morbidity Index score). †The baseline risk of metachronous peritoneal metastases for a reference person was 0.2 (95 per cent c.i. 0 to 0.7) per cent at 1 year and 0.6 (0 to 1.5) per cent at 3 years. ‡Data available from 2009, adjusted only for age, sex and co-morbidity, for a restricted group of 13 222 patients (complete cases in the multivariable analysis and complete information for extravenous mural invasion). §Data available from 2014, adjusted only for age, sex and co-morbidity, for a restricted group of 5861 patients (complete cases in the multivariable analysis and complete information for R1 resection available from 2014 and 2015).

risk at 3 years. Estimates of the 5-year RD showed similar associations to the 3-year estimates (data not shown).

In addition, right-sided colonic cancers demonstrated an absolute risk of 0.5 (95 per cent c.i. 0.1 to 0.9) per cent at 1 year and 0.6 (0.0 to 1.3) per cent at 3 years, compared with left-sided colonic cancers. Emergency surgery increased the risk by 0.9 (−0.1 to 1.9) per cent at 1 year and 1.9 (0.5 to 3.4) per cent at 3 years. All estimates of the 5-year RD showed similar associations to the 3-year estimates (data not shown).

EMVI was associated with an absolute risk of 2.3 (95 per cent c.i. 1.7 to 3.0) and 3.4 (2.5 to 4.4) per cent at 1 and 3 years respectively, whereas the corresponding absolute RD for microscopic tumour-involved resection margins (R1) was 3.9 (1.5 to 6.2) and 5.9 (2.6 to 9.3) per cent.

In the multivariable absolute risk regression analysis, tumour perforation did not correlate with an increased risk of M-PM. Therefore, a *post hoc* analysis was conducted to compare mortality in patients with tumour perforation and in those without. This analysis showed that the risk of death was substantially higher in patients with tumour perforation (data not shown); thus the null result could be due to competing events.

The baseline risk of M-PM for a reference person (the risk in someone who presented with the reference value for all co-variables) was 0.6 (95 per cent c.i. 0.0 to 1.5) per cent at 3 years. *Table 2* shows the absolute RD for each factor; this should be added to the baseline risk to obtain the predictive risk of M-PM for a specific patient. According to this analysis, a patient with (y)pT3 N1 rectal cancer undergoing elective surgery would have an estimated total risk of M-PM of 2.2 per cent after 3 years: 0.6 per cent (overall risk) −0.3 per cent (rectal cancer) + 0.6 per cent ((y)pT3) + 1.3 per cent ((y)pN1) + 0 per cent (elective surgery).

In contrast, a patient with a right-sided (y)pT4 N2 colonic tumour undergoing emergency surgery would have an estimated risk of M-PM of 13.4 per cent (0.6 per cent (overall risk) + 0.6 per cent (right colonic cancer) + 6 per cent ((y)pT4) + 4.3 per cent ((y)pN2) + 1.9 per cent (emergency surgery)) at 3 years after intended curative surgery. As EMVI and radicality were not multivariably adjusted, the estimated RDs associated with these variables should be interpreted with caution.

Discussion

In this large population-based registry study, the risk of M-PM was nearly 1 per cent after 1 year, increasing to 2.2 per cent within 5 years. Overall, (y)pT4 and (y)pN2 categories were assessed as independent risk factors for M-PM,

driving the increased risk between 1 and 3 years. All estimates of the 5-year RD showed similar associations to the 3-year estimates. Additionally, right-sided colonic cancers and tumours that required emergency surgery independently increased the risk of M-PM. EMVI and microscopic tumour-involved margins (R1 resections) were also associated with an increased risk, although the estimated RDs for these may require further analysis.

In addition, the present study excluded patients who had non-colorectal cancer within 5 years before the colorectal cancer diagnosis, and non-colorectal cancer diagnosed during follow-up (*Fig. 3*) was considered as a competing risk to minimize the chances of including PMs that originated from other locations.

Previous studies[26,27] have reported different ranges for M-PM, a variation that may be explained by methodological issues and different time periods. In a prospective clinical study[6], 5·3 per cent (135 of 2542) of the patients were diagnosed with M-PM by CT. All patients included were diagnosed with colorectal cancer between 1989 and 1999, and the incidence of M-PM was not reported at specific time points[6]. In other clinical studies, rates of up to 19 per cent were reported, although these studies analysed M-PM before the further optimization of colorectal surgery[26]. In comparison, registry-based studies[3,5] have found the risk of M-PM to be in accordance with the results reported here.

In the present study, strict inclusion criteria were used, which could explain the lower incidence compared with that reported in other studies. Other reports included patients receiving a R2 resection, distinguished between synchronous and metachronous PMs as early as 30 days after colorectal cancer resection, included patients alive at 30 days after surgery, and did not report any information regarding the presence of other cancers. However, the low incidence observed in the present study may be related to the multidisciplinary improvement in surgical, radiological, oncological and pathological management of colorectal cancer.

The potential risk factors for M-PM were in accordance with those of previous studies[5,28], including T and N categories, surgical radicality and emergency surgery as independent risk factors for M-PM. Several other studies[3,8,12,29] have reported similar associations. Still, the identification of patients at high risk of developing M-PM with the aim of including them in preventive and prophylactic clinical trials is challenging[30]. The effects of early detection with second-look surgery including HIPEC were investigated in 41 patients with colorectal cancer 1 year after curative resection with no signs of clinical, biochemical or radiological signs of recurrence[11]. The study documented PMs in 23 of the 41 patients after the second-look procedure;

these metastases were treated with cytoreductive surgery and HIPEC, whereas other patients were treated using HIPEC alone. The results suggested a beneficial overall survival and low recurrence rate of PM at a median follow-up of 30 (9–109) months[11]. However, the patients selected for that study included those with S-PM, synchronous ovarian metastasis and tumour perforation. In this respect, the results of the present study suggest that patients with tumour perforation represent a very fragile subgroup with high short-term mortality. This should be taken into consideration when including these patients in future trials.

Of note, the impact of cytoreductive surgery and HIPEC in the present cohort was not investigated as it was considered beyond the scope of this analysis, which aimed to identify risk factors for M-PM. The recently published RCT[31] investigating adjuvant HIPEC in patients with T4 tumours or perforated colorectal cancer (COLOPEC trial), documented no benefit of adjuvant HIPEC in terms of peritoneal metastases-free survival at 18 months. However, during follow-up, PMs were reported in 21 per cent of the overall study population, indicating the magnitude of the risk in patients with high-risk colorectal cancer[31].

Given the potential for curative treatment of M-PM, the present results indicate that follow-up of at least 3 years after colorectal cancer surgery may be warranted to detect the majority of incident cases.

Although the registries provide complete information regarding follow-up, allowing assessment of the risk of M-PM at specific time points after colorectal cancer surgery, a general limitation of using these registry-based data is that the assessment of PM may not be uniform; the registration originates from diverse centres throughout Denmark and, according to the longitudinal design, treatments changed over the years[32]. This might introduce information bias, although data were adjusted for the year of colorectal cancer diagnosis in the multivariable absolute risk regression model.

In addition, M-PM was identified by the use of two nationwide registries: the Danish National Pathology Registry, where the diagnosis of M-PM is based on pathological examination of the tissue specimen, and/or the Danish National Patient Registry, where the diagnosis is based on the clinician's reporting of an ICD-10 diagnosis. Thus, the registration of PMs may be reported insufficiently.

Finally, the statistical model applied in the present study does not restrict probabilities to the interval of 0–1. The c.i. of some baseline risk estimates included negative numbers, in which case the lower limit was set to zero. Furthermore, the prediction model presented here has not been validated. The aim of the study was to determine individual

risk factors rather than to predict M-PM, and thus the model should not be used for prediction in future patients without external validation.

Acknowledgements

References

1 Iversen LH, Green A, Ingeholm P, Østerlind K, Gögenur I. Improved survival of colorectal cancer in Denmark during 2001–2012 – the efforts of several national initiatives. *Acta Oncol* 2016; **55**(Suppl 2): 10–23.

2 Iversen LH. Aspects of survival from colorectal cancer in Denmark. *Dan Med J* 2012; **59**: B4428.

3 van Gestel YR, Thomassen I, Lemmens VE, Pruijt JF, van Herk-Sukel MP, Rutten HJ *et al.* Metachronous peritoneal carcinomatosis after curative treatment of colorectal cancer. *Eur J Surg Oncol* 2014; **40**: 963–969.

4 Quere P, Facy O, Manfredi S, Jooste V, Faivre J, Lepage C *et al.* Epidemiology, management, and survival of peritoneal carcinomatosis from colorectal cancer: a population-based study. *Dis Colon Rectum* 2015; **58**: 743–752.

5 Segelman J, Granath F, Holm T, Machado M, Mahteme H, Martling A. Incidence, prevalence and risk factors for peritoneal carcinomatosis from colorectal cancer. *Br J Surg* 2012; **99**: 699–705.

6 Jayne DG, Fook S, Loi C, Seow-Choen F. Peritoneal carcinomatosis from colorectal cancer. *Br J Surg* 2002; **89**: 1545–1550.

7 Sugarbaker PH. Improving oncologic outcomes for colorectal cancer at high risk for local-regional recurrence with novel surgical techniques. *Expert Rev Gastroenterol Hepatol* 2016; **10**: 205–213.

8 Kerscher AG, Chua TC, Gasser M, Maeder U, Kunzmann V, Isbert C *et al.* Impact of peritoneal carcinomatosis in the disease history of colorectal cancer management: a longitudinal experience of 2406 patients over two decades. *Br J Cancer* 2013; **108**: 1432–1439.

9 Sugarbaker PH. Update on the prevention of local recurrence and peritoneal metastases in patients with colorectal cancer. *World J Gastroenterol* 2014; **20**: 9286–9291.

10 Klaver CEL, Stam R, Sloothaak DAM, Crezee J, Bemelman WA, Punt CJA *et al.* Colorectal cancer at high risk of peritoneal metastases: long term outcomes of a pilot study on adjuvant laparoscopic HIPEC and future perspectives. *Oncotarget* 2017; **8**: 51 200–51 209.

11 Elias D, Honoré C, Dumont F, Ducreux M, Boige V, Malka D *et al.* Results of systematic second-look surgery plus HIPEC in asymptomatic patients presenting a high risk of developing colorectal peritoneal carcinomatosis. *Ann Surg* 2011; **254**: 289–293.

12 Honoré C, Goéré D, Souadka A, Dumont F, Elias D. Definition of patients presenting a high risk of developing peritoneal carcinomatosis after curative surgery for colorectal cancer: a systematic review. *Ann Surg Oncol* 2013; **20**: 183–192.

13 Vandenbroucke JP, von Elm E, Altman DG, Gøtzsche PC, Mulrow CD, Pocock SJ *et al.*; STROBE Initiative. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. *Int J Surg* 2014; **12**: 1500–1524.

14 Larsen MB, Njor S, Ingeholm P, Andersen B. Effectiveness of colorectal cancer screening in detecting earlier-stage disease-a nationwide cohort study in Denmark. *Gastroenterology* 2018; **155**: 99–106.

15 Danish Colorectal Cancer Group. [*National Guidelines for Diagnosis and Treatment of Colorectal Cancer*]; 2015. https://dccg.dk/wp-content/uploads/2017/08/2015_Opfolgning.pdf [accessed 10 October 2019].

16 Suissa S. Immortal time bias in observational studies of drug effects. *Pharmacoepidemiol Drug Saf* 2007; **16**: 241–249.

17 Targownik LE, Suissa S. Understanding and avoiding immortal-time bias in gastrointestinal observational research. *Am J Gastroenterol* 2015; **110**: 1647–1650.

18 Neo EL, Beeke C, Price T, Maddern G, Karapetis C, Luke C *et al.* South Australian clinical registry for metastatic colorectal cancer. *ANZ J Surg* 2011; **81**: 352–357.

19 Wang X, Hershman DL, Abrams JA, Feingold D, Grann VR, Jacobson JS *et al.* Predictors of survival after hepatic resection among patients with colorectal liver metastasis. *Br J Cancer* 2007; **97**: 1606–1612.

20 Ingeholm P, Gögenur I, Iversen LH. Danish Colorectal Cancer Group database. *Clin Epidemiol* 2016; **8**: 465–468.

21 Erichsen R, Lash TL, Hamilton-Dutoit SJ, Bjerregaard B, Vyberg M, Pedersen L. Existing data sources for clinical epidemiology: the Danish National Pathology Registry and Data Bank. *Clin Epidemiol* 2010; **2**: 51–56.

22 Schmidt M, Pedersen L, Sørensen HT. The Danish Civil Registration System as a tool in epidemiology. *Eur J Epidemiol* 2014; **29**: 541–549.

23 Lund JL, Frøslev T, Deleuran T, Erichsen R, Nilsson T, Pedersen AN *et al.* Validity of the Danish National Registry of Patients for chemotherapy reporting among colorectal cancer patients is high. *Clin Epidemiol* 2013; **5**: 327–334.

24 Binder N, Gerds TA, Andersen PK. Pseudo-observations for competing risks with covariate dependent censoring. *Lifetime Data Anal* 2014; **20**: 303–315.

25 Overgaard M, Andersen PK, Parner ET. Regression analysis of censored data using pseudo-observations: an update. *Stata J* 2015; **15**: 809–821.

26 Koppe MJ, Boerman OC, Oyen WJ, Bleichrodt RP. Peritoneal carcinomatosis of colorectal origin: incidence and current treatment strategies. *Ann Surg* 2006; **243**: 212–222.

27 Klaver YL, Lemmens VE, Nienhuijs SW, Luyer MD, de Hingh IH. Peritoneal carcinomatosis of colorectal origin: incidence, prognosis and treatment options. *World J Gastroenterol* 2012; **18**: 5489–5494.

28 Segelman J, Akre O, Gustafsson UO, Bottai M, Martling A. Individualized prediction of risk of metachronous peritoneal carcinomatosis from colorectal cancer. *Colorectal Dis* 2014; **16**: 359–367.

29 Lemmens VE, Klaver YL, Verwaal VJ, Rutten HJ, Coebergh JW, de Hingh IH. Predictors and survival of synchronous peritoneal carcinomatosis of colorectal origin: a population-based study. *Int J Cancer* 2011; **128**: 2717–2725.

30 Goéré D, Sourrouille I, Gelli M, Benhaim L, Faron M, Honoré C. Peritoneal metastases from colorectal cancer: treatment principles and perspectives. *Surg Oncol Clin N Am* 2018; **27**: 563–583.

31 Klaver CEL, Wisselink DD, Punt CJA, Snaebjornsson P, Crezee J, Aalbers AGJ *et al.*; COLOPEC collaborators group. Adjuvant hyperthermic intraperitoneal chemotherapy in patients with locally advanced colon cancer (COLOPEC): a multicentre, open-label, randomised trial. *Lancet Gastroenterol Hepatol* 2019; **4**: 761–770.

32 Wille-Jørgensen P, Syk I, Smedh K, Laurberg S, Nielsen DT, Petersen SH *et al.*; COLOFOL Study Group. 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**: 2095–2103.

Supporting information

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

Appendix III:

Paper III

    1. <u>Interview. Following questions were applied in the patient interview.</u>

Kære x,

Tusinde tak, fordi du vil være med til at undersøge hvordan opfølgningen for HIPEC-patienter gøres bedre.

Nedenstående figur skal illustrere, hvordan opfølgningsforløbet for HIPEC-patienterne kommer til at se ud fra begyndelsen af 2018.

Nedenstående figur skal illustrere hvordan patientens besvarelser bliver præsenteret for lægen. Den enkelte farve repræsenterer sværhedsgraden af symptomet (grøn= ingen symptomer, orange= middel, rød = svære symptomer).

		Fr 07 nov 14		Ti 02 dec 14		Fr 09 jan 15	
Generelt	Vægt(kg)	Antal kg: 63		Antal kg: 62		Antal kg: 62	
	Højde(cm)	Antal cm: 172		Antal cm: 172		Antal cm: 172	
	Rygestatus		1		1		1
Helbred	Helbred		4		4		5
	Livskvalitet		4		4		6
Gener	Åndenød		3		2		3
	Hoste		1		1		2
	Hoste m. blod		1		1		1
	Appetit		2		2		2
	Kvalme		2		3		1
	Opkast		1		3		1
	Forstoppelse		1		1		1
	Diarre		1		1		1
	Synkebesvær		1		1		1
	Ømhed mund/tunge		1		1		1
	Stikken hænder/fødder		1		2		4
	Smerte		3		2		1
	Hukommelsesbesvær		1		1		1
Træthed	Søvn besvær		3		1		2
	Hvile		2		2		2
	Sove besvær		2		2		2
Funktion	Anstregende aktiviteter		3		2		4
	Gå lang tur		4		3		3
	Gå kort tur		1		1		2
	Sengeliggende		1		2		1
	Hjælp til selvpleje		1		1		1
Social	Begrænset i arbejde		2		2		4
	Begrænset i hobby		2		2		3
	Familieliv		2		2		1
Trivsel	Anspændt		3		2		1
	Bekymret		3		2		1
	Irritabel		1		1		1
	Deprimeret		2		2		1

Sammen med dette brev har jeg vedhæftet de spørgsmål (spørgeskemaer) som patienten skal udfylde inden konsultationen. Spørgsmålene er nummereret fra 1 til 80.

Når du udfylder spørgsmålene, vil jeg gerne have dig til at tænke over følgende:

- Dækker spørgsmålene det, der er betydningsfuldt for dig i konsultationen?
    - Er der noget der mangler?
    - Er der noget som er overflødigt?
- Er der nogen spørgsmål som overlapper?
    - Føler du, at du svarer på det samme?
- Kan spørgsmålene støtte dig i at få talt om, hvordan du har det?
- Er der spørgsmål, som absolut skal med for at belyse din tilstand?
- Hvor lang tid tog det at udfylde skemaerne (for lang tid/passende)
- Andet?

Jeg ringer dig op på x.

Tusinde tak. Jeg glæder mig til vi snakkes ved.

Mvh. Sissel Ravn

2. The manual used

Vi er interesserede i at vide noget om dig og dit helbred. Vær venlig at besvare alle spørgsmålene selv ved at markere det svar, som passer bedst på dig. Der er ingen "rigtige" eller "forkerte" svar. De oplysninger, som du giver os, vil forblive strengt fortrolige.

I løbet af den sidste uge:

	Slet ikke	Lidt	En del	Meget
Har du nogen vanskeligheder ved at udføre anstrengende aktiviteter, som f.eks. at bære en tung indkøbstaske eller kuffert?	☐	☐	☐	☐
Har du nogen vanskeligheder ved at gå en lang tur?	☐	☐	☐	☐
Har du nogen vanskeligheder ved at gå en kort tur udendørs?	☐	☐	☐	☐
Er du nødt til at ligge i sengen eller at sidde i en stol om dagen?	☐	☐	☐	☐
Har du brug for hjælp til at spise, tage tøj på, vaske dig eller gå på toilettet?	☐	☐	☐	☐
Var du begrænset i udførelsen af enten dit arbejde eller andre daglige aktiviteter?	☐	☐	☐	☐
Var du begrænset i at dyrke din hobby eller andre fritidsaktiviteter?	☐	☐	☐	☐
Havde du åndenød?	☐	☐	☐	☐
Har du haft smerter?	☐	☐	☐	☐
Vanskeliggjorde smerter dine daglige gøremål?	☐	☐	☐	☐
Var du træt?	☐	☐	☐	☐
Havde du brug for at hvile dig?	☐	☐	☐	☐
Har du haft søvnbesvær?	☐	☐	☐	☐
Har du følt dig svag?	☐	☐	☐	☐

I løbet af den sidste uge:

	Slet ikke	Lidt	En del	Meget
Har din mund været tør?	☐	☐	☐	☐
Har du tabt hår som følge af behandlingen?	☐	☐	☐	☐
Har du haft problemer med smagssansen?	☐	☐	☐	☐
Har du savnet appetit?	☐	☐	☐	☐
Har du haft kvalme?	☐	☐	☐	☐
Er du blevet for hurtig mæt, når du er begyndt at spise?	☐	☐	☐	☐
Har du kastet op?	☐	☐	☐	☐
Har du haft forstoppelse?	☐	☐	☐	☐
Har du haft diarré (tynd mave)?	☐	☐	☐	☐
Har du haft mavesmerter?	☐	☐	☐	☐
Har du haft smerter i bagdelen/endetarmsåbningen/endetarmen?	☐	☐	☐	☐
Har du følt dig oppustet i maven?	☐	☐	☐	☐
Har du haft blod i afføringen?	☐	☐	☐	☐
Har du haft slim i afføringen?	☐	☐	☐	☐
Har du haft hyppige vandladninger om dagen?	☐	☐	☐	☐
Har du haft hyppige vandladninger om natten?	☐	☐	☐	☐
Har du haft ufrivillig vandladning?	☐	☐	☐	☐
Har du haft smerter I forbindelse med vandladning?	☐	☐	☐	☐

VEJLEDNING: Læs hvert udsagn og marker det svar, som bedst beskriver, hvordan du følelsesmæssigt har haft det inden for <u>den sidste uge</u>.

I løbet af den sidste uge:

Jeg føler mig i godt humør:	☐ Aldrig	☐ Ikke særlig tit	☐ Lejlighedsvis	☐ Det meste af tiden
Jeg føler mig rastløs, som om jeg skal bevæge mig hele tiden:	☐ I udtalt grad	☐ En hel del	☐ Ikke så meget	☐ Slet ikke

I løbet af den sidste uge:

Har du haft svært ved at koncentrere dig om ting som f.eks. at læse avis eller se fjernsyn?	☐ Slet ikke	☐ Lidt	☐ En del	☐ Meget
Følte du dig anspændt?	☐ Slet ikke	☐ Lidt	☐ En del	☐ Meget
Var du bekymret?	☐ Slet ikke	☐ Lidt	☐ En del	☐ Meget
Følte du dig irritabel?	☐ Slet ikke	☐ Lidt	☐ En del	☐ Meget
Følte du dig deprimeret?	☐ Slet ikke	☐ Lidt	☐ En del	☐ Meget
Har du haft svært ved at huske?	☐ Slet ikke	☐ Lidt	☐ En del	☐ Meget
Har du været bekymret for dit fremtidige helbred?	☐ Slet ikke	☐ Lidt	☐ En del	☐ Meget
Har du været bekymret over din vægt?	☐ Slet ikke	☐ Lidt	☐ En del	☐ Meget
Har du følt dig fysisk mindre tiltrækkende på grund af sygdommen eller behandlingen?	☐ Slet ikke	☐ Lidt	☐ En del	☐ Meget
Har du følt dig mindre feminin/maskulin på grund af sygdommen eller behandlingen?	☐ Slet ikke	☐ Lidt	☐ En del	☐ Meget
Har du været utilfreds med din krop?	☐ Slet ikke	☐ Lidt	☐ En del	☐ Meget

Besvar <u>KUN</u> disse spørgsmål, HVIS DU <u>HAR EN STOMIPOSE</u>

	Ja	Nej
Bruger du stomipose (kolostomi/ileostomi)?	☐	☐

I løbet af den sidste uge:

	Slet ikke	Lidt	En del	Meget
Har du haft utilsigtet udslip af tarmluft fra din stomipose?	☐	☐	☐	☐
Har du haft lækage/udslip fra sin stomipose?	☐	☐	☐	☐
Har huden været øm omkring din stomi?	☐	☐	☐	☐
Måtte du skifte pose hyppigt om dagen?	☐	☐	☐	☐
Måtte du skifte pose hyppigt om natten?	☐	☐	☐	☐
Har du været flov over din stomi?	☐	☐	☐	☐
Har du haft problemer med at passe din stomi?	☐	☐	☐	☐
Er der sivet afføring ud fra endetarmsåbningen?	☐	☐	☐	☐

Besvar KUN disse spørgsmål, HVIS DU IKKE HAR EN STOMIPOSE:

I løbet af den sidste uge:

	Slet ikke	Lidt	En del	Meget
Har du haft utilsigtet udslip af tarmluft fra endetarmsåbningen?	☐	☐	☐	☐
Er der sivet afføring ud fra endetarmsåbningen?	☐	☐	☐	☐
Har huden været øm omkring endetarmsåbningen?	☐	☐	☐	☐
Har du haft hyppig afføring om dagen?	☐	☐	☐	☐
Har du haft hyppig afføring om natten?	☐	☐	☐	☐

I løbet af de sidste 4 uger:

Kun for mænd

	Slet ikke	Lidt	En del	Meget
I hvor høj grad var du interesseret i sex?	☐	☐	☐	☐
Har du haft svært ved at opnå eller holde rejsning?	☐	☐	☐	☐

Kun for kvinder:

	Slet ikke	Lidt	En del	Meget
I hvor høj grad var du interesseret i sex?	☐	☐	☐	☐
Havde du smerter eller ubehag under samleje?	☐	☐	☐	☐

I løbet af den sidste uge:

Har din fysiske tilstand eller medicinske behandling vanskeliggjort dit <u>familieliv</u>?	☐ Slet ikke	☐ Lidt	☐ En del	☐ Meget
Har din fysiske tilstand eller medicinske behandling vanskeliggjort din <u>omgang med andre mennesker</u>?	☐ Slet ikke	☐ Lidt	☐ En del	☐ Meget
Har din fysiske tilstand eller medicinske behandling medført økonomiske vanskeligheder for dig?	☐ Slet ikke	☐ Lidt	☐ En del	☐ Meget

Ved de næste 2 spørgsmål bedes du markere det tal mellem 1 og 7, som passer bedst på dig

		1	2	3	4	5	6	7	
Hvordan vil du vurdere dit samlede <u>helbred</u> i den forløbne uge?	Meget dårligt	☐	☐	☐	☐	☐	☐	☐	Særdeles godt
Hvordan vil du vurdere din samlede <u>livskvalitet</u> i den forløbne uge?	Meget dårlig	☐	☐	☐	☐	☐	☐	☐	Særdeles god

Hvad er vigtigst for dig at få talt om i den forestående konsultation? Angiv 3 emner/anliggender:

Emne 1: ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐

Vi er interesserede i at vide noget om dig og dit helbred. Vær venlig at besvare alle spørgsmål ved at markere det udsagn, som passer bedst til dig. Der er ingen "rigtige" eller "forkerte" svar.

I den forløbne uge:

	Slet ikke	Lidt	En del	Meget
Har du nogen vanskeligheder ved at udføre anstrengende aktiviteter, som f.eks. at bære en tung indkøbstaske eller kuffert?	☐	☐	☐	☐
Har du nogen vanskeligheder ved at gå en lang tur?	☐	☐	☐	☐
Har du nogen vanskeligheder ved at gå en kort tur udendørs?	☐	☐	☐	☐
Er du nødt til at ligge i sengen eller at sidde i en stol om dagen?	☐	☐	☐	☐
Har du brug for hjælp til at spise, tage tøj på, vaske dig eller gå på toilettet?	☐	☐	☐	☐
Var du begrænset i udførelsen af enten dit arbejde eller andre daglige aktiviteter?	☐	☐	☐	☐
Var du begrænset i at dyrke din hobby eller andre fritidsaktiviteter?	☐	☐	☐	☐
Havde du åndenød?	☐	☐	☐	☐
Har du haft smerter?	☐	☐	☐	☐
Vanskeliggjorde smerter dine daglige gøremål?	☐	☐	☐	☐
Var du træt?	☐	☐	☐	☐
Havde du brug for at hvile dig?	☐	☐	☐	☐
Har du haft søvnbesvær?	☐	☐	☐	☐
Har du følt dig svag?	☐	☐	☐	☐
Har du savnet appetit?	☐	☐	☐	☐
Har du haft kvalme?	☐	☐	☐	☐
Er du blevet for hurtig mæt, når du er begyndt at spise?	☐	☐	☐	☐

I den forløbne uge:

	Slet ikke	Lidt	En del	Meget
Har du kastet op?	☐	☐	☐	☐
Har du haft forstoppelse?	☐	☐	☐	☐
Har du haft diarré (tynd mave)?	☐	☐	☐	☐
Har du haft smerter i maven?	☐	☐	☐	☐
Har du haft en oppustet fornemmelse i maven?	☐	☐	☐	☐
Har du haft problemer med, at dit tøj føltes for stramt?	☐	☐	☐	☐
Har du oplevet ændring i dit afføringsmønster som følge af din sygdom eller behandling?	☐	☐	☐	☐
Har du været generet af afgang af tarmluft?	☐	☐	☐	☐
Har du haft fordøjelsesbesvær eller halsbrand?	☐	☐	☐	☐
Har du haft hyppig vandladning?	☐	☐	☐	☐
Har du haft hårtab?	☐	☐	☐	☐
Skal <u>kun</u> udfyldes hvis du har haft hårtab:Var du ked af hårtabet?	☐	☐	☐	☐
Smagte mad og drikke anderledes end normalt?	☐	☐	☐	☐
Har du haft stikken og prikken i hænder eller fødder?	☐	☐	☐	☐
Har du været følelsesløs i fingre eller tæer?	☐	☐	☐	☐
Har du følt dig kraftesløs i arme eller ben?	☐	☐	☐	☐
Har du haft ømhed eller smerter i muskler eller led?	☐	☐	☐	☐
Har du haft problemer med hørelsen?	☐	☐	☐	☐
Har du haft hudproblemer (f.eks. kløe, tørhed)?	☐	☐	☐	☐

I den forløbne uge:

	Slet ikke	Lidt	En del	Meget
Har du haft hedeture?	☐	☐	☐	☐
Har du haft natlige svedudbrud?	☐	☐	☐	☐

	Aldrig	Ikke særlig tit	Lejlighedsvis	Det meste af tiden
Jeg føler mig i godt humør:	☐	☐	☐	☐

	I udtalt grad	En hel del	Ikke så meget	Slet ikke
Jeg føler mig rastløs, som om jeg skal bevæge mig hele tiden:	☐	☐	☐	☐

	Slet ikke	Lidt	En del	Meget
Har du haft svært ved at koncentrere dig om ting som f.eks. at læse avis eller se fjernsyn?	☐	☐	☐	☐
Følte du dig anspændt?	☐	☐	☐	☐
Var du bekymret?	☐	☐	☐	☐
Følte du dig irritabel?	☐	☐	☐	☐
Følte du dig deprimeret?	☐	☐	☐	☐
Har du haft svært ved at huske?	☐	☐	☐	☐
Har du været bekymret for dit fremtidige helbred?	☐	☐	☐	☐
Har du følt dig mindre fysisk tiltrækkende på grund af din sygdom eller behandling?	☐	☐	☐	☐
Har du været utilfreds med din krop?	☐	☐	☐	☐

I de sidste fire uger:

	Slet ikke	Lidt	En del	Meget
I hvilket omfang har du været interesseret i sex?	☐	☐	☐	☐
I hvilket omfang har du været seksuelt aktiv?	☐	☐	☐	☐

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Besvar kun følgende to spørgsmål, hvis du har været seksuelt aktiv:

	Slet ikke	Lidt	En del	Meget
I hvilket omfang nød du det seksuelle samvær?	☐	☐	☐	☐
Har du haft tørhed i skeden ved seksuelt samvær?	☐	☐	☐	☐

I den forløbne uge:

	Slet ikke	Lidt	En del	Meget
Hvor meget har din sygdom belastet dig?	☐	☐	☐	☐
Hvor meget har din behandling belastet dig?	☐	☐	☐	☐
Har din fysiske tilstand eller medicinske behandling vanskeliggjort dit familieliv?	☐	☐	☐	☐
Har din fysiske tilstand eller medicinske behandling vanskeliggjort din omgang med andre mennesker?	☐	☐	☐	☐
Har din fysiske tilstand eller medicinske behandling medført økonomiske vanskeligheder for dig?	☐	☐	☐	☐

Ved de næste 2 spørgsmål bedes du markere det tal mellem 1 og 7, som passer bedst på dig

		1	2	3	4	5	6	7	
Hvordan vil du vurdere dit samlede helbred i den forløbne uge?	Meget dårligt	☐	☐	☐	☐	☐	☐	☐	Særdeles godt
Hvordan vil du vurdere din samlede livskvalitet i den forløbne uge?	Meget dårlig	☐	☐	☐	☐	☐	☐	☐	Særdeles god

Hvad er vigtigst for dig at få talt om i den forestående konsultation? Angiv 3 emner/anliggender:

Manual:

Consultation with feedback based on patient reported outcome (PRO)

The intervention is implemented at three different departments at Aarhus University Hospital, Denmark. To be able to compare the studies it is important that you follow the guide below
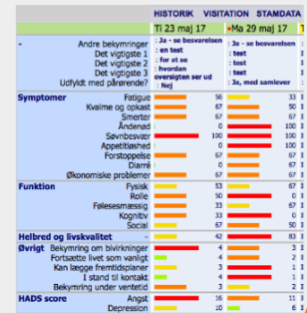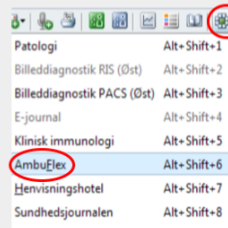
New:

- The patient is prepared for the consultation

- The consultation departs from patient reported outcome

- The answers is presented visually with color codes showing what is most important for the patient

BEFORE THE CONSULTATION

PREPARATION
- Minimize interruptions from phones or colleagues
- Examine PRO data before the patient enters the consultation

DURING THE CONSULTATION

INITIATION
- Turn the computer towards the patient so you can see PRO data together.
- Use the PRO data to guide the dialogue

" Thank you for your answers, they give me a good insight into how you are doing it"

" Let's discuss your answers"

" Looking at your PROs, I see... Is that correct?

- Ask for elaboration and clarification
- Any changes over time that necessitate new plans or initiatives?

CLOSING
- Encourage the patient to prepare for the next consultation by answering the questionnaire beforehand

AFTER THE CONSULTATION

DOCUMENTATION
- Document the use of PRO data in the consultation by approval of the PRO data within the patient' electronic medical record
- A new request to respond to PRO measures is then automatically triggered for the patient before the next visit
- Document any new PRO-mediated plan in the patient' electronic medical record

- **You have now complied with the manual. Thank you!**

Contact:
- Name
- Telephone number
- E-mail

Cancer follow-up supported by electronic Patient-Reported Outcomes: Development and implementation

Ravn S[1], Thaysen HV[1], HIPEC ePRO collaborative, Seibaek L[2], Verwaal VJ[1], Iversen LH[1]

[1] *Department of Surgery, Aarhus University Hospital, Aarhus, Denmark*

[2] *Department of Gynaecology and Obstetrics, Aarhus University Hospital, Aarhus, Denmark*

Author of correspondence:

Sissel Ravn

Department of Surgery, Aarhus University Hospital

Palle Juul-Jensens Boulevard 99, DK-8200 Aarhus N, Denmark.

Email: sissel.ravn@rm.dk

Telephone: +45 51627366

Abstract

Background and aim

Cancer survivors experience unmet needs during follow-up. Besides recurrence, a follow-up includes detection of late side effects, and provision of rehabilitation, palliation and individualized care. We aimed to describe the development and implementation of a follow-up supported by electronic patient-reported outcomes (ePRO).

Method

The study was carried out as an explorative interventional study at a Surgical and a Gynecological Department offering complex surgery and follow-up for advanced cancer. The ePRO aimed to facilitate dialogue, by screening for a priori defined clinical important symptoms and needs. We included following questionnaires in the ePRO; the general European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 and the EORTC validated for colorectal and ovarian cancer patients. In addition, we included three prioritized issues of the patient's preference in each ePRO. The response-algorithm was aggregated based on the severity of the patient's response. To ensure the sensitivity of the ePRO, we performed semi-structured interviews with five patients. All clinicians (surgeons and gynecologists) performing the consultations reviewed the ePRO.

Results

In total, 187 patients were included in the study, of which 73% (n=136/187) patients participated in the ePRO-based follow-up. The ePRO was documented as applied in 79% of the follow-up visits. In total, 23% of the prioritized issues did not include a response. Stratified by time since surgery, a significantly larger proportion of patients who did not fill out a prioritized issue had a follow-up >6 months since surgery. A range from 19.3–56.3% of patients assessed the follow-up visit to provide support within physical (42% of patients), mental (56%), sexual (19%) or dietary (27%) issues. Further, a range from 34–60% of the patients reported that they did not need support regarding physical (43% of patients), mental (34%), sexual (63%) or dietary (57%) issues.

Conclusion

We implemented a follow-up based on ePRO that was applied in nearly 80% of the consultations, and supported most patients following complex surgery for advanced cancer. Before implementation in routine clinic, the effect on patient-centered care of a PRO-based follow-up must be evaluated.

Keywords: Electronic, Patient Reported Outcomes (PRO), individual, follow-up, cytoreductive surgery, advanced cancer, peritoneal metastases

Introduction

During the past decades, the population of cancer survivors has increased in high-income countries, which requires development and adjustments in the cancer follow-up (1). Currently, the primary focus of a cancer follow-up is to detect and initiate early potential curative treatment for recurrent disease (2-5). However, it has been demonstrated repeatedly that some cancer survivors experience unmet needs during the follow-up period (6, 7). In Denmark in 2015, the National Board of Health therefore decided that the national follow-up for cancer patients should include detection of late side effects, rehabilitation, palliation, and patient involvement (2). There is no precise definition of patient involvement, but it is considered as a key element of patient-centered care (8, 9). The latter is defined as care based on the individual patient's preferences, needs and values (10), and is characterized by two fundamental characteristics (a) patient involvement and (b) individualization (9). Therefore, while the healthcare system is obliged to streamline cancer follow-up it is on the other hand committed to adapt to patients' individual needs.

To meet these requirements Patient-Reported Outcomes (PRO) has been introduced as a tool with several purposes, among others to achieve individualized patient care, guide the clinical consultation and facilitate dialogue between patient and clinician (11, 12). PRO is defined as 'any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else' (13). The systematic collection of PRO enables a comprehensive insight of the patient's symptoms, needs and preferences (14-16). The PRO data can be used during the consultation to screen for a priori defined symptoms suspected of recurrence, and to prioritize issues based on the patient's preferences (17). Some innovative electronic solutions have provided the opportunity to integrate PRO in an clinical follow-up (18-20), yet electronic PRO's do not ensure individualized follow-up in itself, but must be assisted by training an flexibility of the users (clinicians and patients) to achieve successful implementation (21-23).

The use of PRO to promote patient-centered care among cancer patients has been investigated in few randomized clinical trials (RCT) (24). However, target populations include patients with various cancer diagnoses, health care professionals, and different health care settings as such (24). Further, PRO's are heterogeneous as well as the applied outcome measurements, and results from these RCT's are ambiguous (12).

With the introduction of centralized and highly specialized complex cancer surgery offering treatment with curative intent, survival has improved (25). Still, long-term symptoms and patient's

needs after complex cancer surgery remain undescribed (10). No guidelines for optimal follow-up exist (26).

The aim of this paper was to describe the development and evaluate the implementation of follow-up after complex cancer surgery supported by electronic patient-reported outcomes (ePRO).

Method:

Setting

The study was conducted in Denmark, a country where all, approximately 5.9 million (27), citizens have access to tax-supported public health-care. The study was carried out as an explorative interventional study at two departments, Department of Surgery (Dep A) and Department of Gynecology (Dep B), at Aarhus University Hospital. Both departments offered complex cancer surgery in terms of Cytoreductive Surgery (CRS) and Hyperthermic Intraperitoneal Chemotherapy (HIPEC), of which Dep A was a national treatment centers receiving patients from all parts of Denmark.

The CRS+HIPEC procedure was offered with curative intent for patients suffering from peritoneal metastases of gastrointestinal and ovarian origin. At Dep A, CRS+HIPEC has been a well-established treatment modality and performed as a standard of care since 2006 (25). At Dep B, the treatment has been performed as a part of a clinical trial from January 2016 to the end of 2018 with a catchment area including 1.3 million inhabitants (28). Highly specialized consultant surgeons and gynecologists performed both the CRS+HIPEC procedure as well as the postoperative follow-up at both departments. The consultant surgeons and gynecologists are referred to as 'clinicians' in the manuscript.

Development of the ePRO

We aimed to develop and implement a follow-up supported by ePRO. The purpose of the ePRO was to facilitate the dialogue between the clinician and the patient, by screening for a priori defined clinical important patient symptoms and needs. The ePRO was developed in collaboration with AmbuFlex/WestChronic (17). The AmbuFlex system is an electronic solution consisting of following elements; PRO data collection, PRO-based graphical colored overview to support clinical decision and PRO-based automated decision algorithm (29). The development process of the ePRO is presented in Figure 1.

## Selection of electronic patient-reported outcomes

Initially, we performed a systematic search for existing and validated questionnaires specific for patients undergoing CRS+HIPEC (30). We identified no questionnaires specific for patients undergoing CRS+HIPEC, however the previous literature demonstrated heterogeneity in the use of the different questionnaires; Functional Assessment of Cancer Therapy (FACT), the 36-item Short Form Health Survey, the European Organization for Research and Treatment of Cancer (EORTC) QlQ-C30 EORTC CR-29/38 and EORTC OV28 (31-34). The most frequently used questionnaires were the generic EORTC QLQ-C30 and the EORTC validated for colorectal and ovarian cancer patients (EORTC CR-29/38 and EORTC OV28), hence these were included in the ePRO (35). We added the Hospital Anxiety and Depression Scale (HADS) (36), since a large proportion of patients with advanced cancer experience anxiety and depression (37-40). Furthermore, to ensure a patient-centered approach we included a section of three prioritized issues of the patient's own preference. These prioritized issues provided the patient with the possibility to write a short free text, indicating topics they wished to address at the follow-up.

Development of electronic patient-reported outcome response algorithm

After the selection of questionnaires, AmbuFlex/WestChronic developed the technical configuration of the questionnaires (ePRO).

In collaboration with AmbuFlex, a response-algorithm was developed from the data aggregation of The EORTC QLQ-C30, CR29 and OV28 based on; green = "Not at All" (1), yellow = "A Little" (2), orange = "Quite a Bit" (3) and red = "Very Much" (4). A similar response-algorithm of The HADS was performed; green = "None" (0), yellow = "Mild" (1), orange = "Intermediate" (2) and red = "Severe" (3) (Figure 1).

Figure 1. The development process of the ePRO.
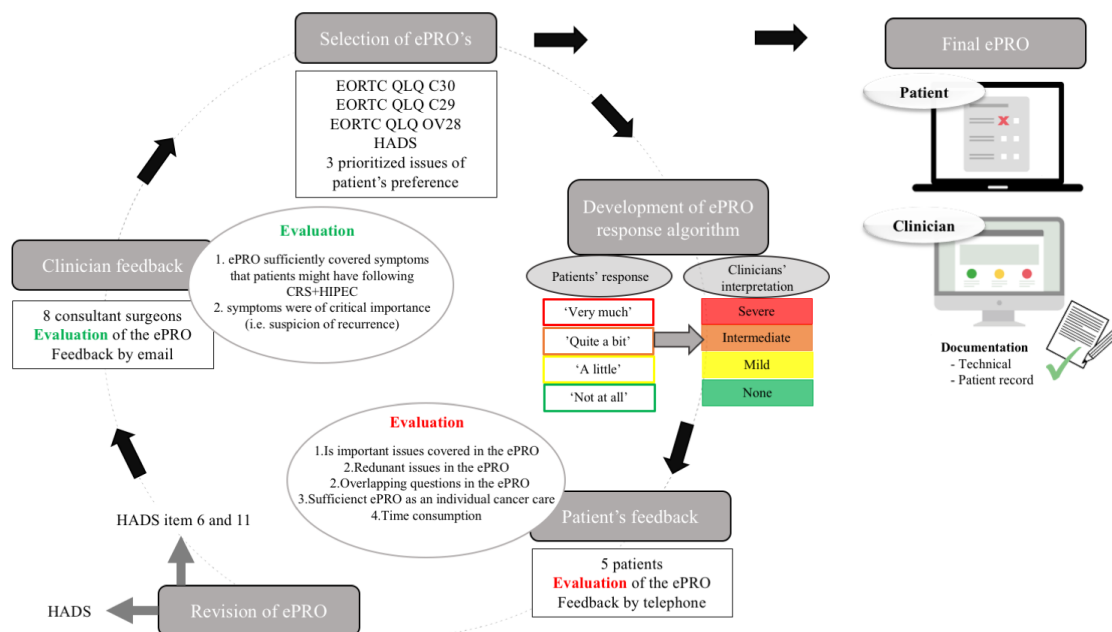
Patient's feedback through semi-structured interviews

After selection of questionnaires entailed in the ePRO, development of the response algorithm and technical aggregation of the ePRO, patient evaluation was performed as individual semi-structured interviews. We selected five patients on the basis of different sex, age and follow-up time. All patients were asked to review and comment on the ePRO regarding the following; 1) If the ePRO captured important issues for patients with peritoneal metastases (PM), 2) Overlapping questions, 3) The sufficiency of the ePRO in relation to the needs of patients with PM and 4) The time consumption of the ePRO (Figure 1). The interviews were performed by telephone by the first author, transcribed, and analysed ad modum Kvale (41).

Clinician's feedback

All clinicians who performed individual follow-up consultations after CRS+HIPEC were asked to review and comment on the ePRO by e-mail. First, they were asked to evaluate if the ePRO sufficiently covered symptoms that patients might have following CRS+HIPEC. Second, they were asked to assess if any reported symptoms were of clinical importance (i.e. suspicion of recurrence) and should be interpreted as severe in the response-algorithm.

To prepare the clinicians for the follow-up based on ePRO, they were introduced to a one-page manual (42). The manual provided clinicians with a brief overview of how to prepare for, undergo

and document an ePRO-based consultation (42). The manual was supplied by a brief one-hour training session, which included evidence-based knowledge about the rationale, benefits and challenges of using ePROs, and experimental training and instructions for the use in clinical practice(42). In the clinic ad hoc training and feedback was preformed ongoing.

Routine Follow-up

At Dep A, patients were routinely followed in the out-patient clinic at 3, 6, 12, 18, 24, 36, 48 and 60 months postoperatively. Each consultation was preceded by a Computed Tomography (CT) scan of the thorax, abdomen and pelvis. All consultations were performed by four experienced clinicians all performing CRS+HIPEC. The consultation included a clinical examination and a description of the performed CT scan.

At Dep B, patients were followed with a consultation at 1, 6, and 12 months postoperatively. Each consultation included a blood test of cancer antigen 125 (CA 125) and a clinical examination. If any of the above-mentioned parameters were abnormal, a CT scan was performed to investigate a potential recurrence.

The Intervention: PRO-based follow-up

The interventional follow-up is depicted in Figure 2.

Figure 2. The intervention: Follow-up based on electronic patient-reported outcomes
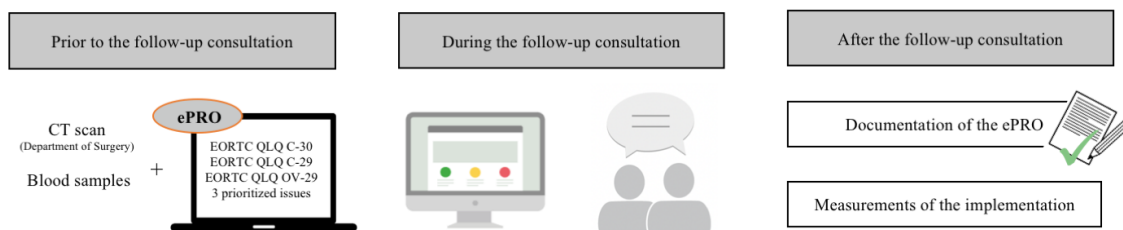
The intervention aimed to provide a follow-up supported by electronically collected ePRO along with the results of the CT scan. The ePRO should the dialogue between the clinician and the patient, by screening for a priori defined clinical important patient symptoms and needs.

The first author set up each patient with follow-up dates in the Ambuflex system. The ePRO was sent electronically to the patient seven days prior to the follow-up, with one reminder after three days in case of a non-response. Still, weekly review of the calendar in the outpatient clinic and the Ambuflex system was necessary, because follow-up dates frequently changes due to unexpected events in this cohort of patients. In the AmbuFlex system, the ePRO was integrated and assessed in

the Electronic Medical Record. A graphic presentation of the ePRO was available for the clinician to facilitate flagging of important symptoms. Clinicians were required to document the use of the ePRO, either technically in the AmbuFlex system or with a comment in the Electronic Medical Record (Figure 1).

Evaluation of the implementation
Handling of the ePRO

- Patients' response rate of ePRO

- Proportion of ePRO administered and documented by the clinician

- The primary author performed a thematic categorization of the prioritized issues, where each free form sentence/word was converted to a spreadsheet. The thematic categorization was based on 1) subscales from the EORTC QLQ-C30 (gastrointestinal, mental, somatic, pain cognitive, mental), 2) issues related to the CRS+HIPEC course (disease and treatment related, general sequelae, status of the CT scan, future follow-up, future prognosis, elaborative conversation, treatment of recurrence), 3) concerns regarding body image, 4) practical concerns and 5) other issues. Subsequently, the author group discussed the categorization in plenum.

- Patients' prioritized issues prior to the consultation (refined to 'yes' / 'no'), stratified by time since surgery (<6 (+1 month) months/ >6 (+ 1 month) months) and gender (male/female)).

Patients' evaluation

After each follow-up visit, patients received an electronically questionnaire, which evaluated the follow-up visit along with a measurement of outcomes related to ePRO-based follow-up.

After the consultation, patients were asked to evaluate following:

- The need and purpose of the follow-up visit (question: '*Please evaluate the necessity of the follow-up visit*') (possible answers: 'It was necessary so I could get explanations to my CT scan AND nothing else', 'It was necessary so I could get explanations to my CT scan AND talk about my other problems', 'It seemed unnecessary, but it was nice to get explanations to my CT scan' or 'It seemed unnecessary, I could have done without it')

- The time allocated for the follow-up visit. (possible answers*: sparse, appropriate, too long*)

- Assessment of the support provided during the follow-up visit (question: '*If you have experienced the following (physical, mental, sexual or dietary issues), to what extent has the follow-up visit supported you to deal with these*?) (possible answers: *Very much, some, less, not at all, I have not needed help*). For feasible presentation and interpretation, we categorized the answering categories into the following: Support (very much, some, less,) / no support (not at all) / no support needed. We performed a sensitivity analysis stratifying time since surgery (<6 months and > 6 months) and gender.

Inclusion of patients

The inclusion was performed continuously during February 2017 - December 2018, prior to a consultation in the outpatient clinic; i.e. patients could be included at any time during their follow-up period (3, 6, 12, 18, 24, 36, 48 and 60 months postoperatively). Patients who underwent CRS+HIPEC were considered eligible for study inclusion, with the exception of following conditions. Patients: 1) who were unable to speak and read Danish, 2) whose forthcoming consultation was the last 48 months, 3) with no digital e-mail solution reached by public authorities and/or e-mail, 4) informed of recurrence at the consultation subjected to inclusion and 5) in a diagnostic process of recurrence.

The inclusion was performed in the outpatient clinic or by telephone. Informed written consent was signed on-site or sent by e-mail and returned either personally or by mail.

Ethical approval and consent to participate

The collection and storage of data was approved by the Danish Data Protection Agency (Project ID: 1-16-02-572-16). All study participants delivered an informed written consent in accordance with the ethical standards of the Helsinki Declaration. The Danish ethical committee has assessed notification of the study was not required.

Results:

Development of the final ePRO

Patients feedback through semi-structured interviews

The characteristics of the five patients who were invited for individual semi-structured interviews were as followed: 3 females, 2 males, a median age of 57 (range: 41-64) with a median of 19.5 months (range: 3.1-80.7) since CRS+HIPEC.

All interviewed patients stated that the ePRO adequately covered issues and symptoms experienced after CRS+HIPEC, but the order of questions should be gathered according to physical function, somatic symptoms and cognitive symptoms. All interviewed patients found that the ePRO was appropriate time-consuming, varying from 5-7 minutes.

The two males stated that the majority of questions in the HADS (screening for anxiety and depression) were redundant, and sufficiently covered by the EORTC QLQ-C30 (q20-q25), while the women found the HADS questions appropriate to expand the issue of anxiety and depression. As a consequence, in collaboration with Ambuflex we decided that the ePRO should include only two items form the HADS (item 6 and item 11) (Figure1). The final version of the ePRO differed according to the Department of follow-up. At Dep. A, the ePRO included 67 items + 3 prioritized issues of patient's own preference (stoma / no stoma), whereas the ePRO consisted of 52 items + 3 prioritized issues of patient's own preference at Dep. B.

Clinicians feedback

None of the clinicians found that significant items were missing in the ePRO, and all found the response-algorithm relevant.

Patient inclusion and baseline characteristics

In total, 218 patients were eligible for inclusion. As demonstrated in Figure 3, 187/218 (85%) were included in the study. The majority of not included patients (45% (14/31)) declined due to a lack of interest (Figure 3).

Figure 3 – Inclusion and response rates

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Patients followed in the outpatient clinic after
Cytoreductive Surgery and Hyperthermic
Intraperitoneal Chemotherapy
n =255
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```
Not eligible for inclusion
(n = 37)

Last follow-up (n = 16)
Recurrence (n = 10)
No electronic mail (n = 6)
Linguistic (n = 5)
```

```
Patients eligible for the study inclusion
n =218
```

```
Not included
(n = 31)

Not interested  (n = 14)
No explanation (n = 12)
Medical disease at inclusion (n = 5)
```

```
Patients included in the study
n =187
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```
Non-responders to the e-PRO
(n = 51)

1 Recurrence (n = 21)
2 No regular FU (n = 19)
3 Sent e-PRO (n =5)
4 FU at local department (n = 4)
5 NA (n = 2)
```

```
Responders to the e-PRO

n =136

1 response (n =80)
2 responses (n = 45)
3 responses (n =11)
```

```
Responders to the e-PRO
and the evaluation

n = 118

1 response (n = 69)
2 responses (n = 40)
3 responses (n = 9)
```

Patient characteristics are shown in Table 1.

Figure 1. Baseline characteristics

Variable	Responders to the ePRO n=136
Sex (number, %)	
Female	75 (55)
Male	61 (45)
Age at the time of surgery (median, range)	60 (26 – 78)
Age at the time of surgery (number, %)	
<60	66 (49)
60-65	21 (15)
65-70	33 (24)
>70	16 (12)
Disease (number, %)	
Pseudomyxoma Peritonei	37 (27)
Colorectal Cancer	63 (46)
Appendix incl. Goblet Cell	19 (14)
Malignant mesothelioma	5 (4)
Ovarian	12 (9)
Civil status (number, %)	

13

Married / relationship	102 (75)
Divorced / Single	19 (14)
Other	1 (1)
Missing	14 (10)
Time from surgery to first ePRO response	
Median months (IQR)	9 (3.9 - 20.4)
Time since surgery (number, %)	
< 6 months	54 (40)
>6 months	77 (57)
Missing	5 (3)

Evaluation of the implementation

Patient response rate

As demonstrated in Figure 3, 136/187 (73%) patients responded to the ePRO and were subjected to an ePRO-based follow-up consultation. In total, we performed 203 ePRO-based consultations. The reasons to non-response are shown in Figure 3.

EPRO administered and documented by clinicians

In total, 57/203 (28%) of the ePRO consultations were not technically documented as administered in the Ambuflex system. A review of the patient's electronic medical record demonstrated that 9/57 of the ePROs were used in the consultation and documented in the medical record but not in the Ambuflex- system. Further, in 6/57 consultations the ePRO was neither applied nor documented due to organizational challenges (technical problems with the ePRO, recurrence of disease found at the CT scan, or the patient did not show up). Therefore, a total of 42/203 (21%) were not documented in the Ambuflex system or the medical record. We interpreted these as not used in the individualized cancer follow-up. These 42 ePRO's and follow-up visits were equally distributed throughout the study period (data not shown).

Prioritized issues

In total, 203 ePROs were completed, in which ePRO response included three prioritized issues available for the patient to fill out. This resulted in a maximum of 609 (3 x 203) possible issues of prioritization. In total, 139/609 (23%) of the prioritized issues did not include a response from the patient. Stratified by time since CRS+HIPEC, a significantly larger proportion of patients who did not fill out a prioritized issue, had a follow-up > 6 months after CRS+HIPEC (figure 4). Stratified by gender, there was no difference (data not shown).

Figure 4. In total, 139/609 of the prioritized issues did not include a response. Displayed is the proportional (%) distribution (with 95% confidence intervals) of the number of 'No prioritized issues' stated prior to the consultation stratified by time since Cytoreductive surgery and Hyperthermic Intraperitoneal Chemotherapy
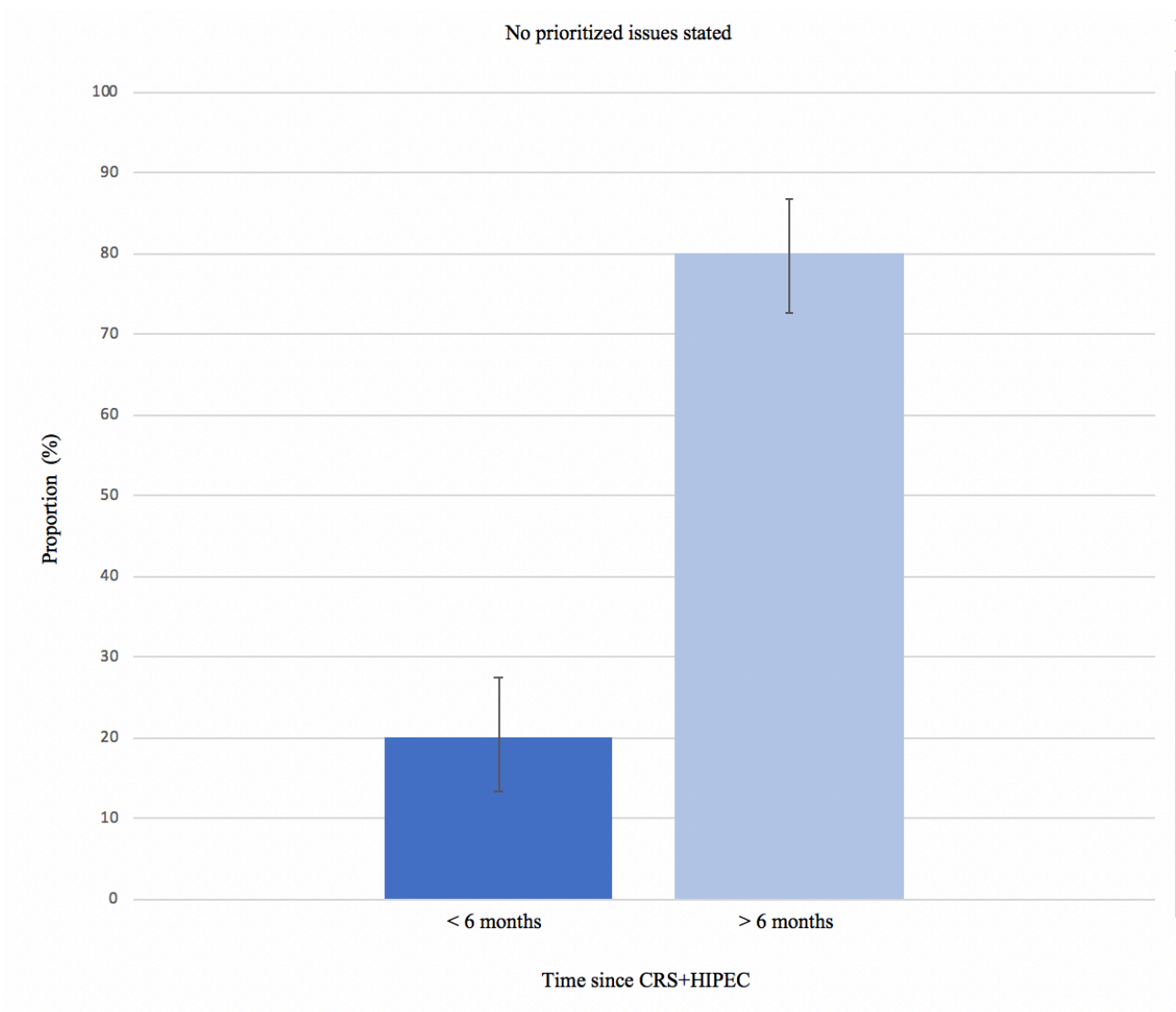
Among the 470 issues with a prioritized topic, the distribution of the prioritized topics is demonstrated in Figure 5.

Figure 5. The percentage with 95% confidence intervals of each categorized topic among patients' prioritized issues.
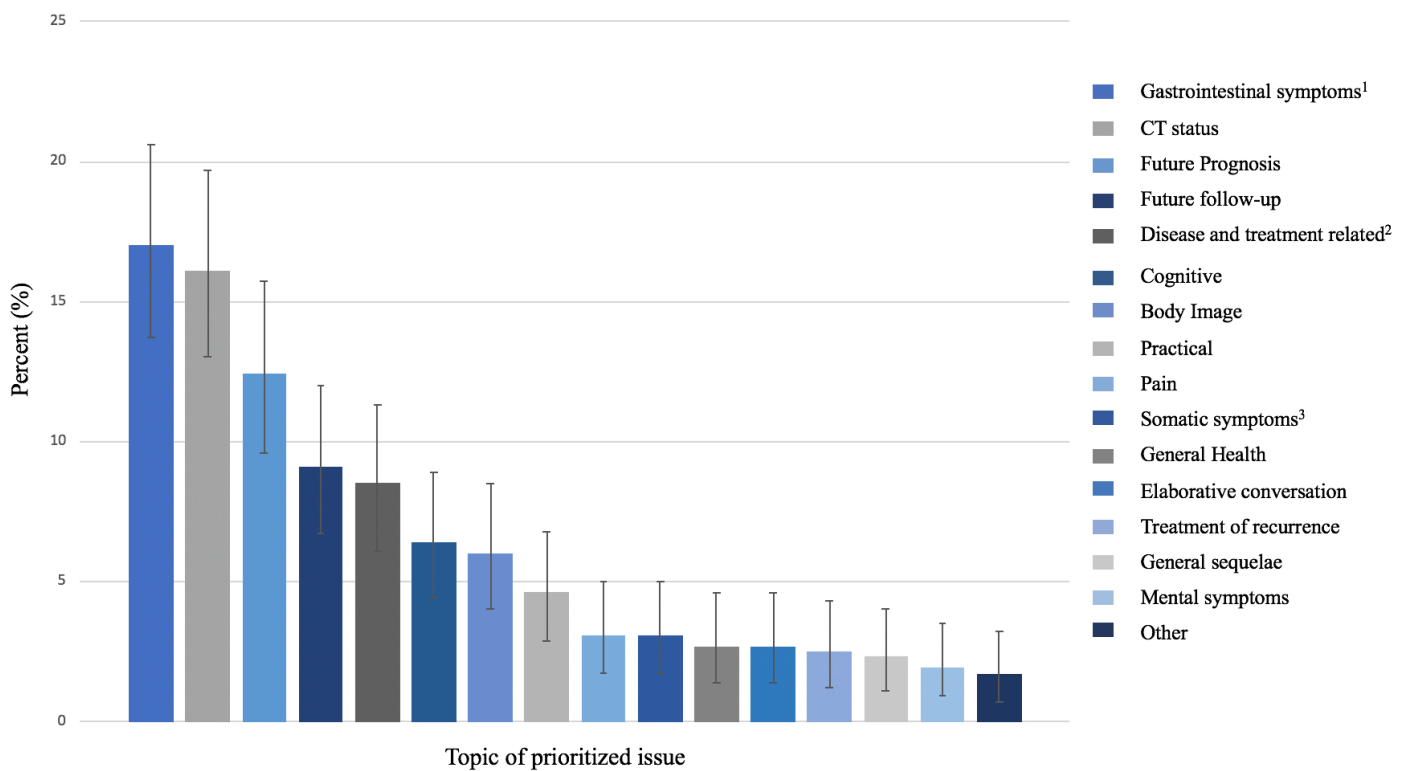
Y-axis: Percent (%)
X-axis: Topic of prioritized issue

Legend:
- Gastrointestinal symptoms[1]
- CT status
- Future Prognosis
- Future follow-up
- Disease and treatment related[2]
- Cognitive
- Body Image
- Practical
- Pain
- Somatic symptoms[3]
- General Health
- Elaborative conversation
- Treatment of recurrence
- General sequelae
- Mental symptoms
- Other

[1]Included problems related to ostomies and hernias

[2]Including treatment related side-effects

[3]Included symptoms related to sexual dysfunction

Evaluation of the follow-up visit

In total, 118 patients filled out an ePRO and then evaluation of the follow-up consultation (Figure 3), thus a number of 176 evaluations are applied in the analyses below.

The necessity of the follow-up visit

Among the 176 evaluations, 127 (72 %) patients evaluated the follow-up to be necessary in order to discuss the outcome of the CT scan, symptoms, and/or prioritized issues (answer: "*It was necessary so I could get explanations to my CT scan AND talk about my other problems*"). Patients found the follow-up necessary to discuss only the result of the CT scan in 33/176 (19%) (answer: "*It was necessary so I could get explanations to my CT scan AND nothing else*") of the evaluations. Further, 4.5% of the consultations were assessed as not necessary ("*It seemed unnecessary, but it was nice to get explanations to my CT scan*" (3.4%) or "*It seemed unnecessary, I could have done without it*" (1.1%)). In total, 4.5% did not respond to the evaluation questions. Concerning the

timeframe of the follow-up consultation, 88% of the patients found the timeframe appropriate, while 8% thought it was too sparse. Further, 4% did not respond.

Assessment of follow-up support
The majority of follow-up visits (range: 19.3 – 56.3%) were evaluated to be supportive in terms of physical (42%), mental (56.3%), sexual (19.3%) or dietary (26.7%) issues raised (Figure 5). Further, a range from 34 – 62.5% of the patients reported that they did not need support related to these issues. Still, a range from 7.4 - 15.9% of the follow-up were not assessed to provide sufficient support regarding physical (12.5%), mental (7.4%), sexual (15.9%) or dietary (14.2%) issues (Figure 6). Sub-analyses stratified by time since surgery (<6 months and > 6 months) and gender, revealed no clear difference in the assessments of the support provided at the follow-up visit (data not shown).

Figure 6. Patients' assessment (percentage with 95% confidence interval) of follow-up support.
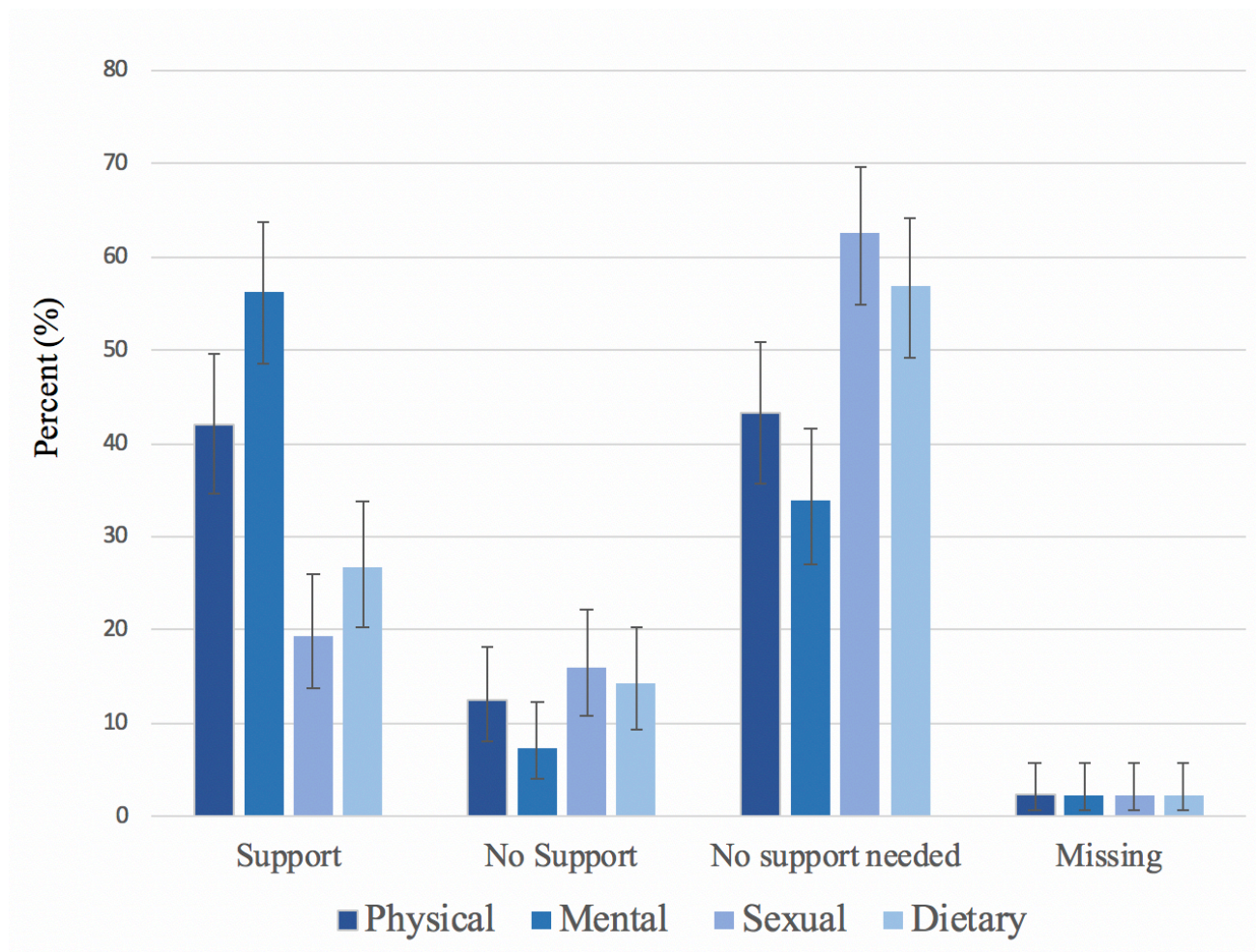
Discussion

In current study, we have developed and implemented a cancer follow-up based on ePRO. In total, 73% of the included patients responded to the ePRO and were subjected to an ePRO-based follow-up consultation. We demonstrated that the clinician applied the ePRO in 79% of the consultations. The majority of patients assessed the follow-up visit to provide support with respect to physical, mental, sexual or dietary issues. Patients with a consultation more than 6 months following CRS+HIPEC responded significantly less prioritized issues for the consultation.

Development

PRO's were originally developed to measure treatment effects (13) but is now widely applied in clinical settings to monitor, improve, and evaluate patient care (43-45). To our knowledge, no specific PRO's exist for patients undergoing CRS+HIPEC, and yet, no patients undergoing CRS+HIPEC have been involved in the development of specific PRO's (31-34, 46-48). A general challenge is to select sensitive and valid PRO's (49). Therefore, we involved patients in the development process to create an ePRO relevant and sensitive for patients undergoing CRS+HIPEC.

Previously, a number of categories have been identified where patients could be involved in the development of PRO, although only few studies have involved the patients in the development and selection of PRO's in cancer follow-up (50). Following categories could potentially involve patients; the determination of health outcomes, development of items, and testing for comprehensibility. (50) We involved patients in two of the categories: the selection of items and tested the ePRO's comprehensibility. All patients commented on the order of the items (e.g. grouping of symptoms) and the comprehensibility in terms of the linguistic phrasing and were thus involved in the development process. However, the structured interviews indicated some gender differences with respect to the content of the ePRO. Females and males requested issues such as distress and mood (i.e. the HADS) differently. This difference has been described in other settings. For example, it has been investigated that patient-reported stress and anxiety is higher among female patients treated for painful conditions in the emergency department. (51) However, this gender difference with respect to the requirements for the ePRO should be interpreted with caution due to the small number of patients interviewed. Still, the use of ePRO might hold a gender-specific aspect concerning the psychosocial aspects of follow-up which should be taken into consideration.

Evaluation of the implementation

A follow-up based on ePRO can be considered as a complex intervention to implement, because it includes several components that can act both independently or interdependently, include different organizational levels and must be tailored to a specific setting that changes depending on the status of the disease (52). Several outcomes may be used in the evaluation of a complex intervention (52), where descriptions of applied tools, planned strategies, facilitators and barriers and their effectiveness in everyday practice are essential (52, 53).

We evaluated the proportion of consultations completed with the ePRO, which in current study was performed in 79% of the patient consultations. Still, in 20% of the consultations the ePRO was not applied. In our setting, the clinician was responsible for the use and administration of the ePRO. It has previously been described that implementation of new, complex initiatives in an institutional and organizational process will possibly encounter resistance (53). Previously, barriers to the use of ePRO in a clinical outpatient setting have been investigated. (54-57) Some of the organizational barriers described included increased workload, lack of time, interference with existing workflow, and lack of financial resources. Additionally, it has been suggested that the clinician's attitude and management of the PRO's was an important barrier for a feasible implementation (55). In addition, previous research has found that clinicians were ambivalent towards individualized follow-up based on PRO; some were positive and thought the PRO's were beneficial, while others considered the PRO as a deterioration of the patient care and expressed suspicion regarding the value (55, 56). It has also been suggested that clinicians could find it difficult to respond and take action on the symptoms reported by the patient (58). Based on these investigations, to enable clinicians to manage PRO, training and preparation of the clinical staff members is recommended.

In current study, patients were asked to report prioritized issues prior to the consultation. However, prioritized issues were not reported in 23% of the responses. Our sub-analyses revealed that the majority of patients who did not report a prioritized issue had a follow-up >6 months since CRS+HIPEC. It has previously been described that patients valued PRO as a tool to raise issues, but thought is required to which patients may actually benefit from PRO (16). This generates the hypothesis that patient's needs during a follow-up period might vary and could be affected by multiple factors, e.g. the time since treatment (i.e. surgery), potential recurrence, personal preferences, social network, and personal coping strategies. This is supported by the fact that nearly 20% of the patients found the follow-up visit to be a necessity exclusively for getting the results of the CT scan. A substantial part (a range from 34 – 62.5% of the patients) reported that they did not

need support related to following issues physical (43.2%), mental (34%), dietary (56.8%) or sexual (62.5%) in the follow-up consultation.. However, it is outside the scope of this study to thoroughly clarify if ePRO's in a follow-up visit are beneficial for all patients at all times postoperatively, and requires further investigations.

Strengths and limitations

When developing and implementing a complex intervention in clinical practice, there is little control of contextual variables, setting and the heterogeneity among clinicians and patients. (53) However, a strength of this study is the well-established treatment center as a setting, where the clinical management (including follow-up) of patients was handled by the same clinicians. The ePRO was based on validated questionnaires, previously applied for this cohort with the purpose to observe the development of Health-related Quality of Life (35, 59). Patient's response (i.e. prioritized issues) is a direct line to target the patient's thoughts, feelings, and experiences. 'When converting free form text responses from a survey (qualitative data) into pre-defined categories (quantitative), one may risk losing some important information. It could have been an advantage for the study, if the categorization of the prioritized issues had been extern validated.
We involved both patients and clinicians in the development of the ePRO. Though, in current study we did not include clinicians in the evaluation of the feasibility of ePRO's in a clinical follow-up, which limits the analysis of potential barriers to use of ePRO in a clinical outpatient setting. Further, only few patients were included in the development of the ePRO, which might limit the patient's input. (60)

Conclusion

In advanced cancer patients undergoing highly specialized surgical treatment, a follow-up based on ePRO can be implemented and applied in nearly 80% of follow-up visits. The majority of patients assessed the follow-up visit to provide support with respect to physical, mental, sexual or dietary issues, still, patients with a consultation more than 6 months following CRS+HIPEC stated significantly less prioritized issues for the consultation A follow-up based on ePRO requires a surplus of financial, staff and organizational resources. Before implementation in routine clinic, the effect on patient-centered care of a PRO-based follow-up must be evaluated.

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References

1.	Arnold M, Rutherford MJ, Bardot A, Ferlay J, Andersson TM, Myklebust TA, et al. Progress in cancer survival, mortality, and incidence in seven high-income countries 1995-2014 (ICBP SURVMARK-2): a population-based study. Lancet Oncol. 2019.

2.	(DCCG) TDCCG. National guidelines. https://dccg.dk/wp-content/uploads/2017/08/2015_Opfolgning.pdf. 2015.

3.	(DGCG) TDGCG. 2019.

4.	Tjandra JJ, Chan MK. Follow-up after curative resection of colorectal cancer: a meta-analysis. Dis Colon Rectum. 2007;50(11):1783-99.

5.	Wille-Jorgensen P, Syk I, Smedh K, Laurberg S, Nielsen DT, Petersen SH, 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):2095-103.

6.	Armes J, Crowe M, Colbourne L, Morgan H, Murrells T, Oakley C, et al. Patients' supportive care needs beyond the end of cancer treatment: a prospective, longitudinal survey. J Clin Oncol. 2009;27(36):6172-9.

7.	Berian JR, Cuddy A, Francescatti AB, O'Dwyer L, Nancy You Y, Volk RJ, et al. A systematic review of patient perspectives on surveillance after colorectal cancer treatment. J Cancer Surviv. 2017;11(5):542-52.

8.	Thomsen TG, Soelver L, Hølge-Hazelton B. The influence of contextual factors on patient involvement during follow-up consultations after colorectal cancer surgery: a case study. J Clin Nurs. 2017;26(21-22):3688-98.

9.	Robinson JH, Callister LC, Berry JA, Dearing KA. Patient-centered care and adherence: definitions and applications to improve outcomes. J Am Acad Nurse Pract. 2008;20(12):600-7.

10.	Thaysen HV, Lomborg K, Seibaek L. Patient involvement in comprehensive, complex cancer surgery: Perspectives of patients, relatives and health professionals. Eur J Cancer Care (Engl). 2019;28(4):e13071.

11.	Hjollund NH, Larsen LP, Biering K, Johnsen SP, Riiskjaer E, Schougaard LM. Use of Patient-Reported Outcome (PRO) Measures at Group and Patient Levels: Experiences From the Generic Integrated PRO System, WestChronic. Interact J Med Res. 2014;3(1):e5.

12.	Johansen MA, Berntsen GK, Schuster T, Henriksen E, Horsch A. Electronic symptom reporting between patient and provider for improved health care service quality: a systematic review of randomized controlled trials. part 2: methodological quality and effects. J Med Internet Res. 2012;14(5):e126.

13.	Health USDo, Human Services FDACfDE, Research, Health USDo, Human Services FDACfBE, Research, et al. Guidance for industry: patient-reported outcome measures: use in medical product development to support labeling claims: draft guidance. Health Qual Life Outcomes. 2006;4:79.

14.	Kargo AS, Coulter A, Jensen PT, Steffensen KD. Proactive use of PROMs in ovarian cancer survivors: a systematic review. J Ovarian Res. 2019;12(1):63.

15.	Chen J, Ou L, Hollis SJ. A systematic review of the impact of routine collection of patient reported outcome measures on patients, providers and health organisations in an oncologic setting. BMC Health Serv Res. 2013;13:211.

16.	Greenhalgh J, Gooding K, Gibbons E, Dalkin S, Wright J, Valderas J, et al. How do patient reported outcome measures (PROMs) support clinician-patient communication and patient care? A realist synthesis. J Patient Rep Outcomes. 2018;2:42.

17.	Hjollund NHI, Valderas JM, Kyte D, Calvert MJ. Health Data Processes: A Framework for Analyzing and Discussing Efficient Use and Reuse of Health Data With a Focus on Patient-Reported Outcome Measures. J Med Internet Res. 2019;21(5):e12412.

18.	Girgis A, Durcinoska I, Levesque JV, Gerges M, Sandell T, Arnold A, et al. eHealth System for Collecting and Utilizing Patient Reported Outcome Measures for Personalized Treatment and Care (PROMPT-Care) Among Cancer Patients: Mixed Methods Approach to Evaluate Feasibility and Acceptability. J Med Internet Res. 2017;19(10):e330.

19.	Ashley L, Jones H, Thomas J, Newsham A, Downing A, Morris E, et al. Integrating patient reported outcomes with clinical cancer registry data: a feasibility study of the electronic Patient-Reported Outcomes From Cancer Survivors (ePOCS) system. J Med Internet Res. 2013;15(10):e230.

20.	Hjollund NHI. Fifteen Years' Use of Patient-Reported Outcome Measures at the Group and Patient Levels: Trend Analysis. J Med Internet Res. 2019;21(9):e15856.

21.	Donaldson MS. Taking PROs and patient-centered care seriously: incremental and disruptive ideas for incorporating PROs in oncology practice. Qual Life Res. 2008;17(10):1323-30.

22.	Snyder CF, Aaronson NK, Choucair AK, Elliott TE, Greenhalgh J, Halyard MY, et al. Implementing patient-reported outcomes assessment in clinical practice: a review of the options and considerations. Qual Life Res. 2012;21(8):1305-14.

23.	Absolom K, Gibson A, Velikova G. Engaging Patients and Clinicians in Online Reporting of Adverse Effects During Chemotherapy for Cancer: The eRAPID System (Electronic Patient Self-Reporting of Adverse Events: Patient Information and aDvice). Med Care. 2019;57 Suppl 5 Suppl 1:S59-S65.

24.	Johansen MA, Henriksen E, Horsch A, Schuster T, Berntsen GK. Electronic symptom reporting between patient and provider for improved health care service quality: a systematic review of randomized controlled trials. part 1: state of the art. J Med Internet Res. 2012;14(5):e118.

25.	Iversen LH, Rasmussen PC, Hagemann-Madsen R, Laurberg S. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for peritoneal carcinomatosis: the Danish experience. Colorectal Dis. 2013;15(7):e365-72.

26.	Gamboa AC, Zaidi MY, Lee RM, Speegle S, Switchenko JM, Lipscomb J, et al. Optimal Surveillance Frequency After CRS/HIPEC for Appendiceal and Colorectal Neoplasms: A Multi-institutional Analysis of the US HIPEC Collaborative. Ann Surg Oncol. 2019.

27.	Statistics D. Population in Denmark. Retrived August 2020.

28.	Mikkelsen MS, Christiansen T, Petersen LK, Blaakaer J, Iversen LH. Morbidity after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy with carboplatin used for ovarian, tubal, and primary peritoneal cancer. J Surg Oncol. 2019;120(3):550-7.

29.	Schougaard LM, Larsen LP, Jessen A, Sidenius P, Dorflinger L, de Thurah A, et al. AmbuFlex: tele-patient-reported outcomes (telePRO) as the basis for follow-up in chronic and malignant diseases. Qual Life Res. 2016;25(3):525-34.

30.	Bayat Z, Taylor EL, Bischof DA, McCart JA, Govindarajan A. Impairments in Bowel Function, Social Function and Quality of Life After Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy. Ann Surg Oncol. 2019.

31.	Hamilton TD, Taylor EL, Cannell AJ, McCart JA, Govindarajan A. Impact of Major Complications on Patients' Quality of Life After Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy. Ann Surg Oncol. 2016;23(9):2946-52.

32.	Dodson RM, McQuellon RP, Mogal HD, Duckworth KE, Russell GB, Votanopoulos KI, et al. Quality-of-Life Evaluation After Cytoreductive Surgery with Hyperthermic Intraperitoneal Chemotherapy. Ann Surg Oncol. 2016;23(Suppl 5):772-83.

33.	Shan LL, Saxena A, Shan BL, Morris DL. Quality of life after cytoreductive surgery and hyperthermic intra-peritoneal chemotherapy for peritoneal carcinomatosis: A systematic review and meta-analysis. Surg Oncol. 2014;23(4):199-210.

34.	Seretis C, Youssef H. Quality of life after cytoreductive surgery and intraoperative hyperthermic intraperitoneal chemotherapy for peritoneal surface malignancies: a systematic review. Eur J Surg Oncol. 2014;40(12):1605-13.

35.	Thaysen HV, Jess P, Laurberg S, Groenvold M. Validation of the Danish version of the disease specific instrument EORTC QLQ-CR38 to assess health-related quality of life in patients with colorectal cancer. Health Qual Life Outcomes. 2012;10:150.

36.	Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the Hospital Anxiety and Depression Scale. An updated literature review. J Psychosom Res. 2002;52(2):69-77.

37.	Tang ST, Chen JS, Chou WC, Chang WC, Wu CE, Hsieh CH, et al. Longitudinal Analysis of Severe Anxiety Symptoms in the Last Year of Life Among Patients With Advanced Cancer: Relationships With Proximity to Death, Burden, and Social Support. J Natl Compr Canc Netw. 2016;14(6):727-34.

38.	Simon AE, Thompson MR, Flashman K, Wardle J. Disease stage and psychosocial outcomes in colorectal cancer. Colorectal Dis. 2009;11(1):19-25.

39.	Miovic M, Block S. Psychiatric disorders in advanced cancer. Cancer. 2007;110(8):1665-76.

40.	Mitchell AJ, Chan M, Bhatti H, Halton M, Grassi L, Johansen C, et al. Prevalence of depression, anxiety, and adjustment disorder in oncological, haematological, and palliative-care settings: a meta-analysis of 94 interview-based studies. Lancet Oncol. 2011;12(2):160-74.

41.	Kvale S BS. Interviews. In Learning the craft of qualitative research interviewing. SAGE Publications, London. 2009.

42.	Skovlund PC, Ravn S, Seibaek L, Thaysen HV, Lomborg K, Nielsen BK. The development of PROmunication: a training-tool for clinicians using patient-reported outcomes to promote patient-centred communication in clinical cancer settings. J Patient Rep Outcomes. 2020;4(1):10.

43.	Howell D, Molloy S, Wilkinson K, Green E, Orchard K, Wang K, et al. Patient-reported outcomes in routine cancer clinical practice: a scoping review of use, impact on health outcomes, and implementation factors. Ann Oncol. 2015;26(9):1846-58.

44.	Mercieca-Bebber R, King MT, Calvert MJ, Stockler MR, Friedlander M. The importance of patient-reported outcomes in clinical trials and strategies for future optimization. Patient Relat Outcome Meas. 2018;9:353-67.

45.	Black N. Patient reported outcome measures could help transform healthcare. BMJ. 2013;346:f167.

46.	Passot G, Bakrin N, Roux AS, Vaudoyer D, Gilly FN, Glehen O, et al. Quality of life after cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy: a prospective study of 216 patients. Eur J Surg Oncol. 2014;40(5):529-35.

47.		Piso P, Glockzin G, von Breitenbuch P, Popp FC, Dahlke MH, Schlitt HJ, et al. Quality of life after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for peritoneal surface malignancies. J Surg Oncol. 2009;100(4):317-20.

48.		Duckworth KE, McQuellon RP, Russell GB, Cashwell CS, Shen P, Stewart JH, et al. Patient rated outcomes and survivorship following cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy (CS + HIPEC). J Surg Oncol. 2012;106(4):376-80.

49.		Deshpande PR, Rajan S, Sudeepthi BL, Abdul Nazir CP. Patient-reported outcomes: A new era in clinical research. Perspect Clin Res. 2011;2(4):137-44.

50.		Wiering B, de Boer D, Delnoij D. Patient involvement in the development of patient-reported outcome measures: a scoping review. Health Expect. 2017;20(1):11-23.

51.		Patel R, Biros MH, Moore J, Miner JR. Gender differences in patient-described pain, stress, and anxiety among patients undergoing treatment for painful conditions in the emergency department. Acad Emerg Med. 2014;21(12):1478-84.

52.		Mohler R, Kopke S, Meyer G. Criteria for Reporting the Development and Evaluation of Complex Interventions in healthcare: revised guideline (CReDECI 2). Trials. 2015;16:204.

53.		Craig P, Dieppe P, Macintyre S, Michie S, Nazareth I, Petticrew M. Developing and evaluating complex interventions: the new Medical Research Council guidance. Int J Nurs Stud. 2013;50(5):587-92.

54.		Schepers SA, Haverman L, Zadeh S, Grootenhuis MA, Wiener L. Healthcare Professionals' Preferences and Perceived Barriers for Routine Assessment of Patient-Reported Outcomes in Pediatric Oncology Practice: Moving Toward International Processes of Change. Pediatr Blood Cancer. 2016;63(12):2181-8.

55.		Mejdahl CT, Schougaard LMV, Hjollund NH, Riiskjaer E, Lomborg K. Exploring organisational mechanisms in PRO-based follow-up in routine outpatient care - an interpretive description of the clinician perspective. BMC Health Serv Res. 2018;18(1):546.

56.		Boyce MB, Browne JP, Greenhalgh J. The experiences of professionals with using information from patient-reported outcome measures to improve the quality of healthcare: a systematic review of qualitative research. BMJ Qual Saf. 2014;23(6):508-18.

57.		Greenhalgh J, Dalkin S, Gooding K, Gibbons E, Wright J, Meads D, et al. Functionality and feedback: a realist synthesis of the collation, interpretation and utilisation of patient-reported outcome measures data to improve patient care. Health Services and Delivery Research. Southampton (UK)2017.

58.		Greenhalgh J, Abhyankar P, McCluskey S, Takeuchi E, Velikova G. How do doctors refer to patient-reported outcome measures (PROMS) in oncology consultations? Qual Life Res. 2013;22(5):939-50.

59.		Ravn S, Thaysen HV, Harslof S, Sorensen MM, Iversen LH. Incisional hernia and its impact on health-related quality of life after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy: a national prospective cohort study. World J Surg Oncol. 2018;16(1):85.

60.		Kallio H, Pietila AM, Johnson M, Kangasniemi M. Systematic methodological review: developing a framework for a qualitative semi-structured interview guide. J Adv Nurs. 2016;72(12):2954-65.

Abbreviations:
ePRO: Electronic Patient-reported Outcomes

CRS: Cytoreductive Surgery

HIPEC: Hyperthermic Intraperitoneal Chemotherapy

Appendix IV

Cancer follow-up supported by Patient-reported outcomes in patients undergoing intended curative complex surgery for advanced cancer

Ravn S[1], Thaysen HV[1], Verwaal VJ[1], HIPEC ePRO collaborative, Seibaek L[2], Iversen LH[1]

[1] *Department of Surgery, Aarhus University Hospital, Aarhus, Denmark*

[2] *Department of Gynaecology and Obstetrics, Aarhus University Hospital, Aarhus, Denmark*

Author of correspondence:

Sissel Ravn

Department of Surgery, Aarhus University Hospital

Palle Juul-Jensens Boulevard 99, DK-8200 Aarhus N, Denmark.

Email: sissel.ravn@rm.dk

Telephone: +45 51627366

Abstract (a maximum of 250 words. Wordcount: 238)

Background and aim

Patient activation (PA) and Patient Involvement (PI) are considered elements in good survivorship. We aimed to evaluate the effect of a follow-up based on electronic patient-reported outcomes (ePRO) on PA and PI.

Method

From February 2017 to January 2019, we conducted an interventional feasibility study. We included 187 patients followed after intended curative complex surgery for advanced cancer at two different Departments at a University Hospital. Prior to each follow-up consultation, patients used the ePRO to screen themselves for clinical important symptoms, function and needs. The ePRO was graphically presented to the clinician during the follow-up, aiming to facilitate the patient activation and involvement in each follow-up.

According to the time-period and type of follow-up, patients were divided into groups; '-ePRO' (routine follow-up), '+ePRO' (ePRO based follow-up) and '-/+ePRO' group (routine *and* ePRO based follow-up). PA was measured by the Patient Activation Measurement (PAM), while PI was measured by five indicator questions.

Results

The mean PAM score was similar between all groups. Based on the five PI-indicator questions, a larger proportion of patients with a +ePRO consultation evaluated themselves as "much" involved in consultation; the ePRO provided a wider scope of dialogue, encouraged patients to ask questions and share their experiences and concerns.

Conclusion

Follow-up consultations based on ePRO seem to increase PI by offering a wider scope of dialogue, and encourage patients to ask questions and share their experiences and concerns during follow-up visits.

Declarations

Funding

Conflict of interst

Availability of data and material

Code availability

Authors contributions

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Introduction

Patients with metastases to the peritoneal surface (i.e. advanced cancer) have historically been treated with palliative intent receiving either systemic chemotherapy with or without symptom-directed surgery, or no treatment at all, depending on their overall health performance [1-3]. With the introduction of intended curative complex cancer surgery (i.e. Cytoreductive Surgery (CRS) and Hyperthermic Intraperitoneal Chemotherapy (HIPEC), the prognosis for these patients has improved significantly [4-6]. Along with improved survival, survivorship issues have therefore become increasingly important [7]

Survivorship is defined as the "health and well-being of a person with cancer from the time of diagnosis until the end of life" according to the National Cancer Institute National Comprehensive Cancer Network [8]. A key element in survivorship is good Health-related Quality of Life (HRQoL) and decreased symptom distress [7]. Patient-centred care has been suggested as a strategy to ensure this [9, 10], e.g. involving patients' preferences, needs and values, and engaging them in their own care and follow-up. In continuation hereof, patient involvement (PI) can be seen as a strategy to achieve patient-centeredness, as it includes the patients' rights and opportunity to influence their healthcare. In a clinical setting, PI therefore comprises initiatives to support active patient participation, thus contributing in their care pathway [11, 12].

Patient activation (PA) can be defined as the patients' individual level of knowledge, confidence and skills to manage their own health [13]. A number of studies have indicated that active patients are able to participate in follow-up, raise questions, make requests, state preferences and introduce topics [14, 15]. It has been demonstrated that an increase in patients' activation is associated with a positive change in general health and lower health care costs [16, 17]. PA can be influenced by self-management strategies, and the use of patient-reported outcomes (PRO) in the consultations has been suggested as a tool to support PA and self-management, thus facilitating patient involvement [18, 19].

In the management of patients with metastases to the peritoneal surface, the primary focus has up till now been on the surgical treatment, morbidity, recurrence and survival [3, 20] and to a lesser extent the survivorship. Therefore, we conducted an interventional study to evaluate if patient-centered follow-up based on electronic patient-reported outcomes (ePRO) was associated with increased level of PA and PI.

Method:

Study design and setting

The study was carried out as an interventional feasibility study in the period from February 2017 to January 2019 including patients with advanced cancer (i.e. peritoneal metastases from colorectal, appendiceal, and ovarian origin, and pseudomyxoma peritonei) treated with curative intent with complex cancer surgery at two different departments at Aarhus University Hospital. Both departments were national treatment centers for CRS+HIPEC. At Department of Surgery, the procedure was offered as standard treatment, whereas the treatment was performed as a part of a clinical trial at Department of Gynecology[21].

As depicted in Figure 1, the routine follow-up was scheduled according to specific cancer disease of interest, and thus, unequal at the two departments.

At Department of Surgery, according to national guidelines, the routine follow-up included a visit in the outpatient clinic at 3, 6, 12, 18, 24, 36, 48, and 60 months postoperatively. The standard follow-up included blood samples and a Computer Tomography (CT) of the thorax, abdomen and pelvis, with a subsequently physical follow-up visit containing results of the CT and a clinical examination.

At Department of Gynecology, the standard follow-up included blood samples (tumor marker), and a pelvic examination. Imaging was only performed if recurrence was suspected.

Participants

Patients from the two departments who had undergone complex surgery with curative intent (i.e. CRS+HIPEC) were considered eligible for study inclusion, and were included continuously, irrespective of time since the complex surgery, in the outpatient clinic or by telephone prior to each follow-up visit. Informed written consent was signed on-site or sent by e-mail and returned either personally or by mail.

Patients were not included in case of the following: 1) unable to speak and read Danish, 2) the forthcoming consultation was the last (48 months postoperatively), 3) no digital e-mail solution reached by public authorities and/or e-mail, 4) informed of recurrence at the consultation subjected to inclusion and 5) in a diagnostic process of recurrence.

Among the patients included in the study period, patients were divided into three groups according to the period of time and type of follow-up (Figure 2). Patients who only completed routine follow-up without ePRO was referred to as '-ePRO', whereas patients who participated in the intervention

was referred to as '+ePRO'. Patients receiving both routine and interventional follow-up were included in the '-/+ePRO' group.

Intervention

The purpose of the intervention was to improve and increase PA and PI by implementing patient-centered follow-up supported by electronic patient-reported outcomes. Patients screened themselves for a priori defined clinical important patient symptoms, ability of function and needs, which subsequently were presented to the clinician prior to each follow-up visit, aiming to facilitate the patient activation and involvement in each follow-up. The screening was performed with an ePRO, including validated questionnaires: The European Organization for Research and Treatment of Cancer (EORTC) quality of life questionnaire (QlQ) C30 [22], C29 [23] and OV28 [24], and item 6 and 11 from the Hospital and Anxiety Depression scale [25]. Further, the ePRO provided opportunity for patients to state three issues to be prioritized in the consultation. Each patient response was flagged with colors illustrating the severity according to the original response algorithm developed for each questionnaire [26]. The patient's ePRO response was graphically presented to the clinician. After the consultation, clinicians were required to document the use of the e-PRO, either technically in the electronic system or with a comment in the Electronic Medical Record.

Prior to implementation, a small, selected group of patients and clinicians evaluated the sensitivity and feasibility of the ePRO. Further, all clinicians were provided with a one-page manual of how to prepare for, undergo and document an e-PRO-based consultation, supplied by a one-hour training session. The development and feasibility of the e-PRO based follow-up is described in details elsewhere [26].

Outcomes measurements

The primary outcome was PI and PA. These outcomes were measured with an electronic questionnaire sent out 2-4 days after each follow-up visit to all study patients, before and during the intervention (Figure 1)

PI was measured by five questions developed and tested as indicators of PI by DEFACTUM, a department in the Central Region of Denmark dealing with social services, health care and labor market issues. The questions were as followed:

I. The health care provider asked about my own experiences with my illness / condition

II. I talked to the health care provider about the questions or concerns I had

III. The health care professional encouraged me to ask questions or talk about concerns

IV. I was on advice when deciding what was to happen and

V. I have had appropriate conversations with healthcare professionals about how to best manage my illness / condition.

Patients had following response categories "Not at all", "Less", "Some", "Much" and "very much", to increase the simplicity we categorized them into "Little", "Some" and "Much".

PA was measured by the Danish validated 13-item Patient Activation measurement (PAM) questionnaire[27], which was developed and validated by Hibbard et al. to evaluate the patient's ability to self-manage [13, 28]. The PAM scores from 0-100, where a higher score indicates a higher level of activation.

Statistical methods

Apart from the disease characteristics and date of surgery, which was retrieved from a local database, patient characteristics were collected at inclusion by an online questionnaire. Patient and disease characteristics are presented as frequencies and percentages for categorical variables, while continuous variables are presented as median with ranges or interquartile ranges (IQR). Patient characteristics are presented for each group (-ePRO, +ePRO and -/+ePRO), and for the total population.

Since the five questions regarding patient involvement was used to monitor PI in the follow-up consultation, each response was considered independent, and stratified by routine (-ePRO) and interventional (+ePRO) follow-up. Therefore, it should be noticed that some patients occur with repeated measurements.

A mean PAM score along with 95% confidence intervals was presented for 1st, 2nd and 3rd response in each period (-ePRO period and +ePRO period). The PAM score ranges from 0-100 introducing ceiling and floor effects that affect the normal distribution of data. Currently, no guidelines exist on the presentation of PAM, and PAM is often presented as means with 95% confidence intervals despite its distribution. We presented PAM data both as medians (with ranges) and means scores (with 95% confidence intervals). The Danish validated version of the 13-item PAM does not recommend the presentation of 4 levels[27], thus we restrained from this.

All analyses were performed as complete case analyses, thus only patients who answered outcome measurements were included in the analysis. Further, patient data were analyzed according to the assigned group (-ePRO, -/+ePRO or +ePRO). The statistical analysis was performed using STATA statistical software (STATA, release IC15, STATACorp, Texas, USA).

Ethical consideration

The collection and storage of data was approved by the Danish Data Protection Agency (Project ID: 1-16-02-572-16). All study participants delivered an informed written consent in accordance with the ethical standards of the Helsinki Declaration. The National Committee on Health Research Ethics assessed that notification of the study was not required.

The intervention was implemented in accordance to the already existing follow-up program for patients treated with complex surgery for advanced cancer, as we did not attend to create an extra burden for this vulnerable cohort of patients.

Results

In total, 255 patients were followed in the outpatient clinic in the study period from 2017-2019. Among these, 218 patients were eligible for inclusion, and 187 (86%) patients accepted participation in the study (Figure 3).

Baseline characteristics are presented according to group, and summed in Table 1. Overall, the majority of patients were female, aged < 65 years. A large part of the patients had PM originating from a gastrointestinal location (colorectal cancer and pseudomyxoma peritonei). In total, around 75% of the study population were in a relationship / married. The level of education was equally distributed between groups (-ePRO, +ePRO and -/+ePRO), with nearly 50% having 2-4 years additional education in each group. At least 50% of patients in each group were not attached to the labor market (senior citizens / sick leave).

Patient involvement

Patients' assessment of PI in the consultation is presented in Figure 4. Irrespective of the question (I-V), a larger proportion of patients in the +ePRO group evaluated themselves as "much" involved in consultation.

Patient activation measurement

For all groups, the median PAM score was at same level as the mean PAM score, thus only the mean PAM score is presented.

Comparing the -ePRO group with +ePRO group, patients with a +ePRO consultation did not report a higher mean PAM score (Figure 5, 5a).

Considering the -/+ePRO group, i.e. patients subjected both to –ePRO and +ePRO, no difference in the mean PAM score between the routine (-ePRO) and interventional follow-up (+ePRO) was found. However, patients tended to report a higher mean PAM score in the +ePRO period, though insignificant (Figure 5, 5b).

Stratified by time since surgery, there was no correlation between a mean PAM score and time since surgery (Figure 6). As demonstrated in Figure 6, there was a large interpersonal variance in mean PAM score, irrespective of -ePRO or +ePRO period.

Discussion

We performed a descriptive interventional study, aiming to improve PI and increase PA by implementing patient-centered follow-up supported by electronic patient-reported outcomes. Overall, patients tended to assess a high degree of PI in all consultations, yet, PI tended to be more frequent in +ePRO consultations. Follow-up consultations supported by ePRO did not change PA.

Patient involvement

Our results demonstrated that some aspects of PI in an outpatient clinical cancer setting may be improved by ePRO. Regarding question I-III (I.*The health care provider asked about my own experiences with my illness / condition*, II. *I talked to the health care provider about the questions or concerns I had* and III. *The health care professional encouraged me to ask questions or talk about concerns*), patients demonstrated the highest level of PI in favour of the +ePRO consultations. The answers to these questions (I-III) indicates that the use of ePRO may provide a wider scope of dialogue and encourage patients to ask questions and share their experiences and concerns during follow-up visits, which is also reported from other studies [18, 29].

Patient activation
It has previously been demonstrated that PA is a function of contextual factors and multiple patient and clinician characteristics[30].

Several contextual factors may increase the complexity of the implementation of e-PRO, thus impact its effect on PA. Due to ethical considerations the intervention was made to meet the requirements of the already existing follow-up program. Therefore, the intervention was confined to the specific times of follow-up for each patient (i.e. continuously inclusion at follow-up times at 3, 6, 12, 18, 24, 48 and 36 months), and 3 months, as a minimum, existed between each interventional follow-up. This interval between the +ePRO consultations could potentially affect the patient's level of activation, as learning strategies in both technical [31], and cognitive competences have the highest effect when executed intensively during a short period of time [27, 32]. In general, the implementation of a new set-up is affected by the existing organizational structure, and not automatically incorporated [33]. An organization must be capable of the development, integration and costs of structures that support technical solutions measuring and presenting health information [33]. In current setting, the ePRO was developed in collaboration with Ambuflex, which specializes in PRO as an electronic option. Therefore, the system was easily integrated in the Electronic

Medical Record. Despite this being an electronic solution, the implementation of the ePRO, and the operation of the system and each patient was managed by the first author. In case of future implementation, organizations must earmark costs for the electronic solution and its everyday operation.

The PAM was primarily developed and reported in populations with chronic diseases (i.e. diabetes, ischemic heart disease, rheumatic diseases and asthma) [34], which differs from patients with advanced cancer. A lack of change in PA may be due to particular characteristics present in patients surgically treated for advanced cancer. It has been described that patients with PM experience severe preoperative mental pressure, affecting their ability to process health-care information in the peri-operative period[35]. Further, despite intended curative surgery, recurrence is frequent [36, 37]), and introduces fear. The impaired ability to process health-care information in combination with potential fear of recurrence might affect patient activation, since the patient's ability to manage their health-care is dependent also on their emotional state [38]. On the other hand, the initial mean PAM measurements were high (PAM score between 55 and 59, Figure 5), and large changes in the PAM measurement have primarily been demonstrated in patients with initial low PAM scores [14, 39, 40]. Finally, as demonstrated in Figure 6, the majority of PAM measurements were between 250-500 days, indicating that the majority of responses were from patients far away from their complex surgery. It may be the case that, these patients already had accomplished sufficient knowledge, skills and confidence with respect to self-management[14].

It has previously been demonstrated that the use of PRO in clinical follow-up does not automatically enhance PI, and therefore the clinician's role is important. In general, the clinician's attitude towards PRO's in a consultation (i.e. main component in current intervention) has been described as ambivalent [18, 41, 42], and highly depend on the clinicians' day-to-day management of the system[43]. The lack of action from the health professionals to a problem reported by the patient in the PRO, induces unfilled patient expectations, and potentiates implementation barriers [18].

To summarize, an intervention with ePRO did not influence PA, presumably due to contextual factors, and clinician and patient characteristics (e.g. severe mental pressure and fear of recurrence). Hypothetically, the use of ePRO in itself is not sufficient to change self-management strategies.

Strengths and limitations

Overall, our results should be interpreted with caution, because of its descriptive nature. Both the intervention and outcome were measured with validated PRO, yet never validated in such a cohort of patients undergoing complex surgery. Clinicians' knowledge and familiarity with PRO's is important, and education/training may be needed to allow clinicians to utilize these instruments correctly and apply their data beneficially to their clinical practice. In this study, only a brief one-hour training session was provided (Skovlund et al, manual). We did not assess in which way, and to which extent the clinicians applied the ePRO. Finally, in current study patients were included at different times of follow-up, which potentially could affect the outcomes. However, we anticipated this by stratifying patient activation measurements with time since surgery, and demonstrated no correlation between a mean PAM score and time since surgery.

Conclusion

The implementation of electronic patient-reported outcomes in the follow-up of advanced cancer patients after complex surgery, tends to increase patient involvement by offering a wider scope of dialogue, and encourage patients to ask questions and share their experiences and concerns during follow-up visits.

1. Sugarbaker, P.H., *Management of peritoneal metastases - Basic concepts.* J BUON, 2015. **20 Suppl 1**: p. S2-11.
2. Klaver, Y.L., et al., *Peritoneal carcinomatosis of colorectal origin: Incidence, prognosis and treatment options.* World J Gastroenterol, 2012. **18**(39): p. 5489-94.
3. Baratti, D., et al., *Progress in treatments for colorectal cancer peritoneal metastases during the years 2010-2015. A systematic review.* Crit Rev Oncol Hematol, 2016. **100**: p. 209-22.
4. Verwaal, V.J., et al., *Randomized trial of cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy and palliative surgery in patients with peritoneal carcinomatosis of colorectal cancer.* J Clin Oncol, 2003. **21**(20): p. 3737-43.
5. Elias, D., et al., *Complete cytoreductive surgery plus intraperitoneal chemohyperthermia with oxaliplatin for peritoneal carcinomatosis of colorectal origin.* J Clin Oncol, 2009. **27**(5): p. 681-5.
6. Mahteme, H., et al., *Improved survival in patients with peritoneal metastases from colorectal cancer: a preliminary study.* Br J Cancer, 2004. **90**(2): p. 403-7.
7. Geng, Y. and S. Myneni, *Patient Engagement in Cancer Survivorship Care through mHealth: A Consumer-centered Review of Existing Mobile Applications.* AMIA Annu Symp Proc, 2015. **2015**: p. 580-8.
8. Denlinger, C.S., et al., *Survivorship: introduction and definition. Clinical practice guidelines in oncology.* J Natl Compr Canc Netw, 2014. **12**(1): p. 34-45.
9. Reb, A., et al., *Empowering survivors after colorectal and lung cancer treatment: Pilot study of a Self-Management Survivorship Care Planning intervention.* Eur J Oncol Nurs, 2017. **29**: p. 125-134.
10. Drury, A., S. Payne, and A.M. Brady, *Cancer survivorship: Advancing the concept in the context of colorectal cancer.* Eur J Oncol Nurs, 2017. **29**: p. 135-147.
11. Clayton, J.M., et al., *Randomized controlled trial of a prompt list to help advanced cancer patients and their caregivers to ask questions about prognosis and end-of-life care.* J Clin Oncol, 2007. **25**(6): p. 715-23.
12. Wright, A.A., et al., *Associations between end-of-life discussions, patient mental health, medical care near death, and caregiver bereavement adjustment.* JAMA, 2008. **300**(14): p. 1665-73.
13. Hibbard, J.H., et al., *Development and testing of a short form of the patient activation measure.* Health Serv Res, 2005. **40**(6 Pt 1): p. 1918-30.
14. van der Hout, A., et al., *Role of eHealth application Oncokompas in supporting self-management of symptoms and health-related quality of life in cancer survivors: a randomised, controlled trial.* Lancet Oncol, 2020. **21**(1): p. 80-94.

15. Street, R.L., Jr. and P. Haidet, *How well do doctors know their patients? Factors affecting physician understanding of patients' health beliefs.* J Gen Intern Med, 2011. **26**(1): p. 21-7.

16. Lindsay, A., et al., *Patient Activation Changes as a Potential Signal for Changes in Health Care Costs: Cohort Study of US High-Cost Patients.* J Gen Intern Med, 2018. **33**(12): p. 2106-2112.

17. Hibbard, J.H., et al., *Do increases in patient activation result in improved self-management behaviors?* Health Serv Res, 2007. **42**(4): p. 1443-63.

18. Mejdahl, C.T., et al., *Patient-reported outcome measures in the interaction between patient and clinician - a multi-perspective qualitative study.* J Patient Rep Outcomes, 2020. **4**(1): p. 3.

19. Bennett, A.V., R.E. Jensen, and E. Basch, *Electronic patient-reported outcome systems in oncology clinical practice.* CA Cancer J Clin, 2012. **62**(5): p. 337-47.

20. Franko, J., et al., *Treatment of colorectal peritoneal carcinomatosis with systemic chemotherapy: a pooled analysis of north central cancer treatment group phase III trials N9741 and N9841.* J Clin Oncol, 2012. **30**(3): p. 263-7.

21. Mikkelsen, M.S., et al., *Morbidity after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy with carboplatin used for ovarian, tubal, and primary peritoneal cancer.* J Surg Oncol, 2019. **120**(3): p. 550-557.

22. Aaronson, N.K., et al., *The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology.* J Natl Cancer Inst, 1993. **85**(5): p. 365-76.

23. Whistance, R.N., et al., *Clinical and psychometric validation of the EORTC QLQ-CR29 questionnaire module to assess health-related quality of life in patients with colorectal cancer.* Eur J Cancer, 2009. **45**(17): p. 3017-26.

24. Greimel, E., et al., *An international field study of the reliability and validity of a disease-specific questionnaire module (the QLQ-OV28) in assessing the quality of life of patients with ovarian cancer.* Eur J Cancer, 2003. **39**(10): p. 1402-8.

25. Zigmond, A.S. and R.P. Snaith, *The hospital anxiety and depression scale.* Acta Psychiatr Scand, 1983. **67**(6): p. 361-70.

26. Skovlund, P.C., et al., *The development of PROmunication: a training-tool for clinicians using patient-reported outcomes to promote patient-centred communication in clinical cancer settings.* J Patient Rep Outcomes, 2020. **4**(1): p. 10.

27. Maindal, H.T., I. Sokolowski, and P. Vedsted, *Translation, adaptation and validation of the American short form Patient Activation Measure (PAM13) in a Danish version.* BMC Public Health, 2009. **9**: p. 209.

28. Hibbard, J.H., et al., *Development of the Patient Activation Measure (PAM): conceptualizing and measuring activation in patients and consumers.* Health Serv Res, 2004. **39**(4 Pt 1): p. 1005-26.

29. Schougaard, L.M.V., et al., *Patient-initiated versus fixed-interval patient-reported outcome-based follow-up in outpatients with epilepsy: a pragmatic randomized controlled trial.* J Patient Rep Outcomes, 2019. **3**(1): p. 61.

30. Street, R.L., Jr., et al., *Patient participation in medical consultations: why some patients are more involved than others.* Med Care, 2005. **43**(10): p. 960-9.

31. Zimmerman, H., et al., *Intensive laparoscopic training course for surgical residents: program description, initial results, and requirements.* Surg Endosc, 2011. **25**(11): p. 3636-41.

32. Uutela, A., et al., *Health psychological theory in promoting population health in Paijat-Hame, Finland: first steps toward a type 2 diabetes prevention study.* J Health Psychol, 2004. **9**(1): p. 73-84.

33. Santana, M.J., et al., *How to practice person-centred care: A conceptual framework.* Health Expect, 2018. **21**(2): p. 429-440.

34. Harkness, J., *Patient involvement: a vital principle for patient-centred health care.* World Hosp Health Serv, 2005. **41**(2): p. 12-6, 40-3.

35. Thaysen, H.V., K. Lomborg, and L. Seibaek, *Patient involvement in comprehensive, complex cancer surgery: Perspectives of patients, relatives and health professionals.* Eur J Cancer Care (Engl), 2019. **28**(4): p. e13071.

36. Feferman, Y., et al., *Sites of Recurrence After Complete Cytoreduction and Hyperthermic Intraperitoneal Chemotherapy for Patients with Peritoneal Carcinomatosis from Colorectal and Appendiceal Adenocarcinoma: A Tertiary Center Experience.* Ann Surg Oncol, 2019. **26**(2): p. 482-489.

37. Verwaal, V.J., et al., *Recurrences after peritoneal carcinomatosis of colorectal origin treated by cytoreduction and hyperthermic intraperitoneal chemotherapy: location, treatment, and outcome.* Ann Surg Oncol, 2004. **11**(4): p. 375-9.

38. Rottenberg, J., J.J. Gross, and I.H. Gotlib, *Emotion context insensitivity in major depressive disorder.* J Abnorm Psychol, 2005. **114**(4): p. 627-39.

39. Couture, E.M., et al., *The relationship between health literacy and patient activation among frequent users of healthcare services: a cross-sectional study.* BMC Fam Pract, 2018. **19**(1): p. 38.

40. Napoles, T.M., et al., *Assessing Patient Activation among High-Need, High-Cost Patients in Urban Safety Net Care Settings.* J Urban Health, 2017. **94**(6): p. 803-813.

41. Berry, D.L., et al., *Enhancing patient-provider communication with the electronic self-report assessment for cancer: a randomized trial.* J Clin Oncol, 2011. **29**(8): p. 1029-35.

42. Boyes, A., et al., *Does routine assessment and real-time feedback improve cancer patients' psychosocial well-being?* Eur J Cancer Care (Engl), 2006. **15**(2): p. 163-71.

43. Mejdahl, C.T., et al., *Exploring organisational mechanisms in PRO-based follow-up in routine outpatient care - an interpretive description of the clinician perspective.* BMC Health Serv Res, 2018. **18**(1): p. 546.

Table 1. Baseline characteristics presented for each group (-ePRO, -/+ePRO and +ePRO) and the total population. Groups are based on the type of follow-up

Variable	Groups according to type of follow-up *Total: n=187*			
	- ePRO *n= 48*	-/+ ePRO *n= 57*	+ ePRO *n= 82*	Total n = 187
Sex				
Female	35 (73)	32 (56)	44 (54)	111 (59)
Male	13 (27)	25 (44)	38 (47)	76 (41)
Age (median, range)	57 (28 – 76)	61 (39 – 77)	59 (26 – 75)	59 (26 – 77)
Age				
<60	29 (60)	23 (40)	42 (51)	94 (50)
60-65	6 (13)	11 (19)	10 (12)	27 (14)
65-70	10 (21)	14 (25)	19 (23)	43 (23)
>70	3 (6)	9 (16)	11 (13)	23 (12)
Disease				
Pseudomyxoma Peritonei	13 (27)	20 (35)	21 (26)	54 (29)
Colorectal Cancer[1]	28 (59)	31 (54)	49 (60)	108 (58)
Ovarian	4 (8)	4 (7)	10 (12)	18 (10)
Malignant mesothelioma	3 (6)	2 (4)	2 (2)	7 (4)
Civil status				
Married / relationship	39 (81)	47 (82)	54 (67)	141 (75)
Divorced / Single	7 (15)	9 (16)	11 (14)	27 (14)
Other	0	0	1 (1)	1 (1)
Missing	2 (4)	1 (2)	15 (18)	18 (10)
Education				
Primary school	4 (8)	10 (18)	10 (12)	24 (13)
High school / training	10 (21)	8 (14)	10 (12)	28 (15)
+ 2-4 years education	24 (50)	33 (58)	37 (45)	94 (50)
+ > 4 years education	8 (17)	5 (9)	10 (12)	23 (12)
missing	2 (4)	1 (2)	15 (18)	18 (10)
Labor				
Full-time	10 (21)	11 (19)	14 (17)	35 (19)
Reduced time	7 (15)	8 (14)	12 (15)	27 (14)
Senior citizen	13 (27)	27 (47)	24 (29)	64 (34)
Sick leave	12 (25)	10 (18)	16 (20)	38 (20)
Unemployed	1 (2)	0 (0)	0 (0)	1 (1)
Unknown / Missing	5 (10)	1 (2)	15 (18)	22 (12)

[1] Including appendix cancer (n=11) and Goblet Cell carcinoma (n=9)
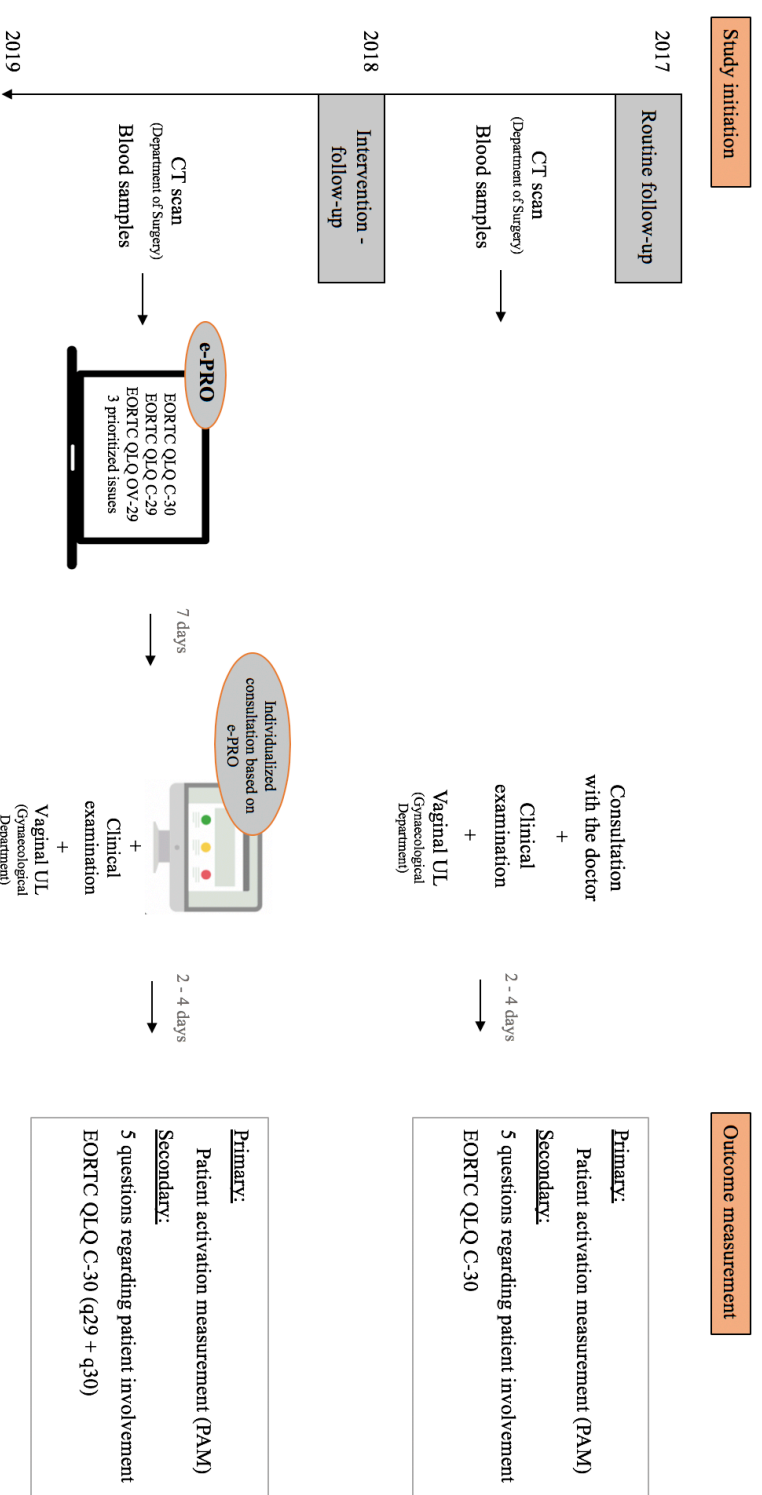
Figure 1. The setting

Study initiation

2017

Routine follow-up

CT scan
(Department of Surgery)
Blood samples

2018

Intervention - follow-up

CT scan
(Department of Surgery)
Blood samples

e-PRO

EORTC QLQ C-30
EORTC QLQ C-29
EORTC QLQ OV-29
3 prioritized issues

2019

Consultation
with the doctor
+
Clinical
examination
+
Vaginal UL
(Gynaecological
Department)

7 days

Individualized
consultation based on
e-PRO

Clinical
examination
+
Vaginal UL
(Gynaecological
Department)

2 - 4 days

2 - 4 days

Outcome measurement

<u>Primary:</u>
Patient activation measurement (PAM)
<u>Secondary:</u>
5 questions regarding patient involvement
EORTC QLQ C-30

<u>Primary:</u>
Patient activation measurement (PAM)
<u>Secondary:</u>
5 questions regarding patient involvement
EORTC QLQ C-30 (q29 + q30)

Figure 2. Classification of the study cohort

- ePRO	+ ePRO
STUDY PERIOD 1	STUDY PERIOD 2

February 2017   March 2018   February 2019

-ePRO group	-/+ePRO group	+ePRO group
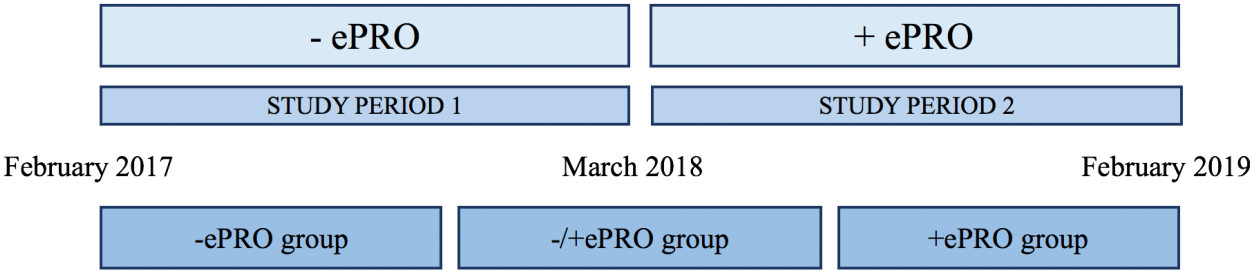
Figure 3. Flowchart – inclusion of patients

Patients followed in the outpatient clinic after advanced cancer surgery

n = 255

Not eligible for inclusion

Last follow-up (n=16)
Recurrence (n=10)
No electronic mail (n=6)
Linguistic (5)

Patients eligible for study inclusion

n = 218

Not included

N/A (n=16)
Not interested (n=14)
Medical disease at inclusion (n=1)

Included patients

n = 187

-ePRO

n = 48

-/+ ePRO

n = 57

+ ePRO

n = 82
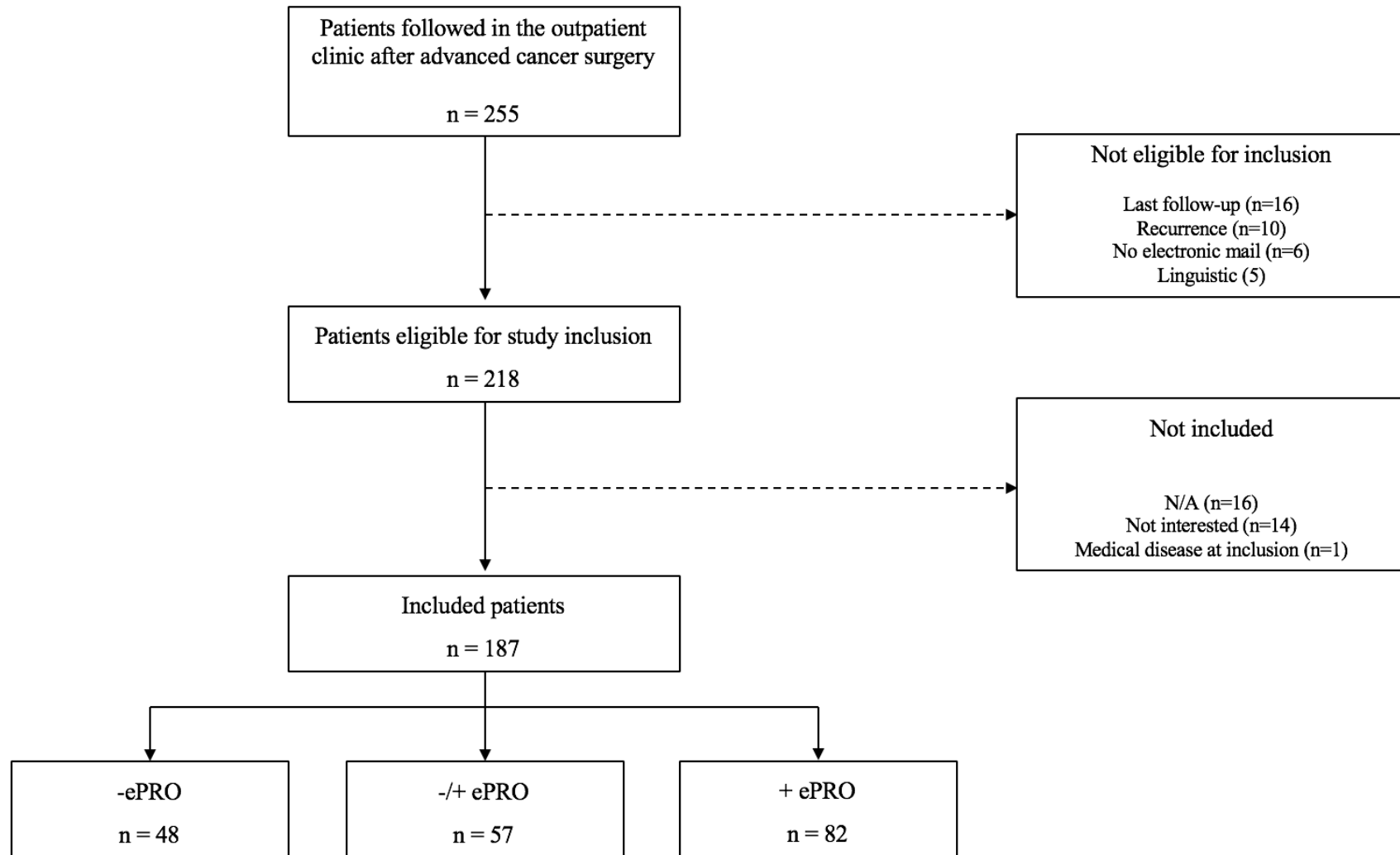
Figure 4. Patient involvement stratified by -ePRO consultations and +e-PRO consultations.
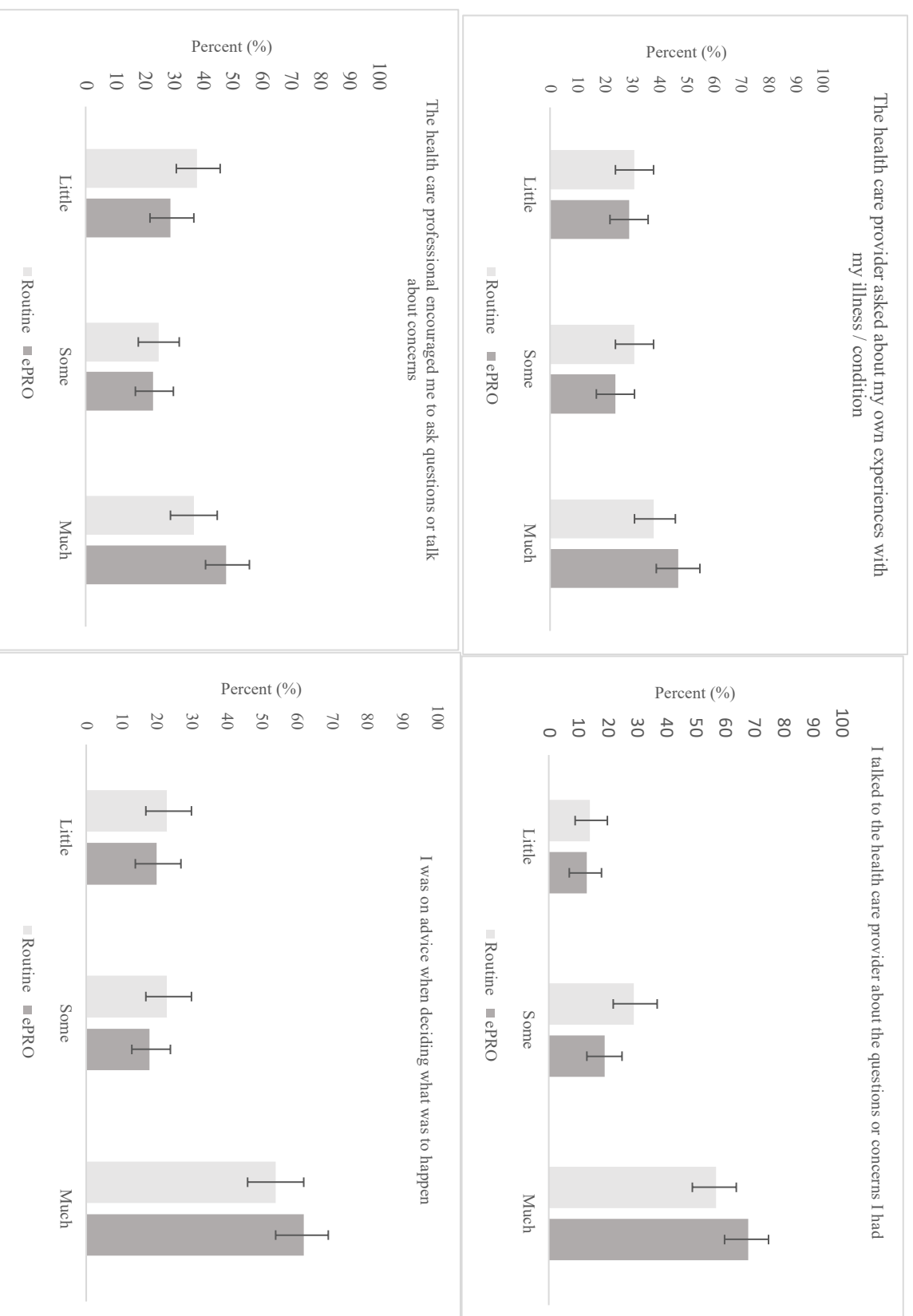
Percent (%)

I have had appropriate conversations with healthcare professionals about how to best manage my illness / condition

Routine
ePRO

Little
Some
Much
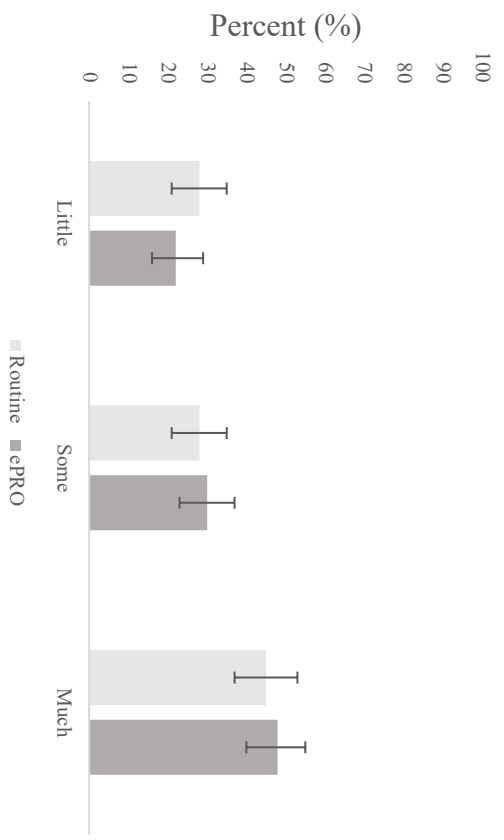
Figure 5. Mean Patient Activation Measurement (PAM) score for patients receiving routine follow-up (-ePRO), a follow-up supported by electronic Patient-reported measurements (+ePRO), and patients receiving both (-/+ePRO).

5a. Patients receiving only a -e-PRO follow-up compared to those receiving only a +e-PRO follow-up	5b. Patients receiving both a -e-PRO and a +e-PRO follow-up.
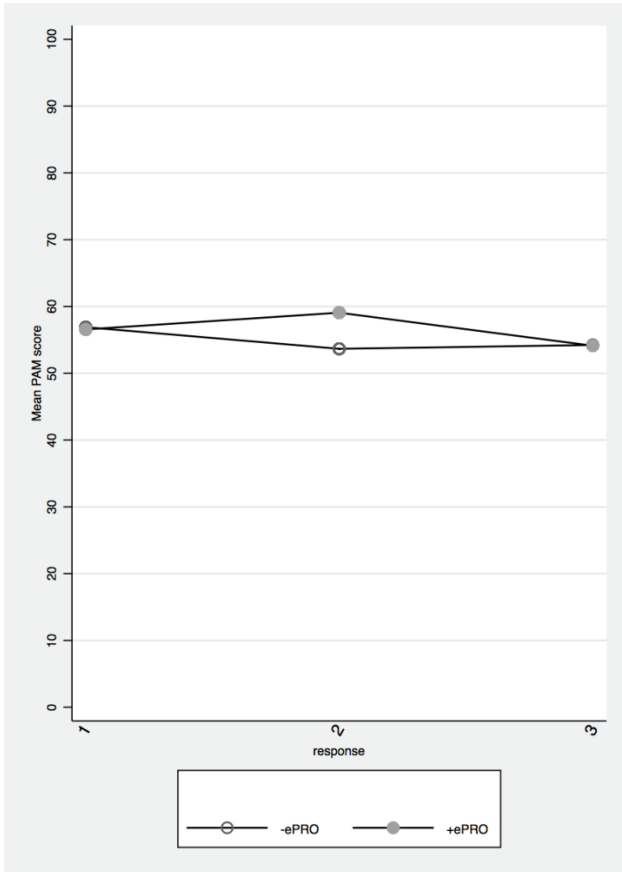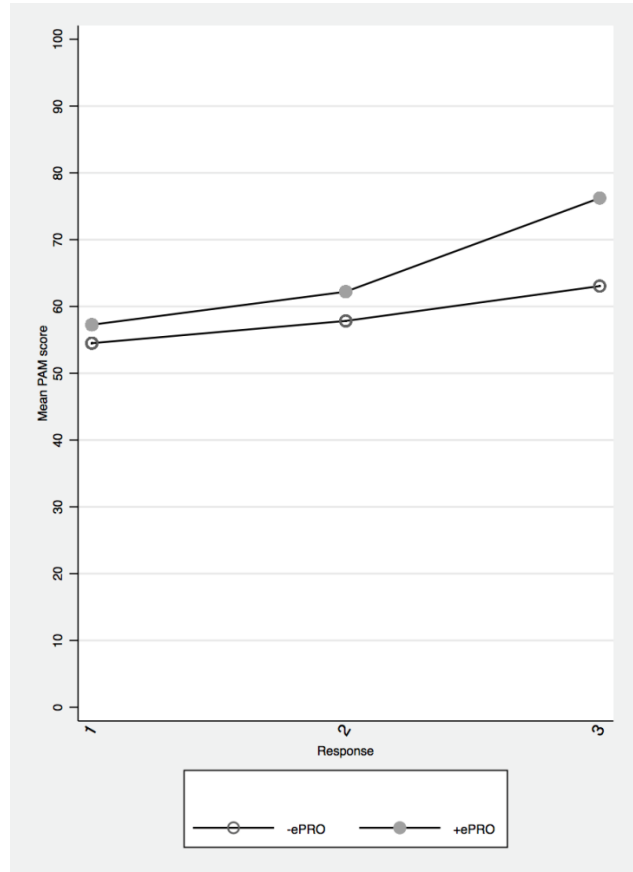
Figure 6.

Mean Patient Activation Measurement (PAM) score stratified by time since complex surgery. Presented for period -ePRO and period +ePRO.
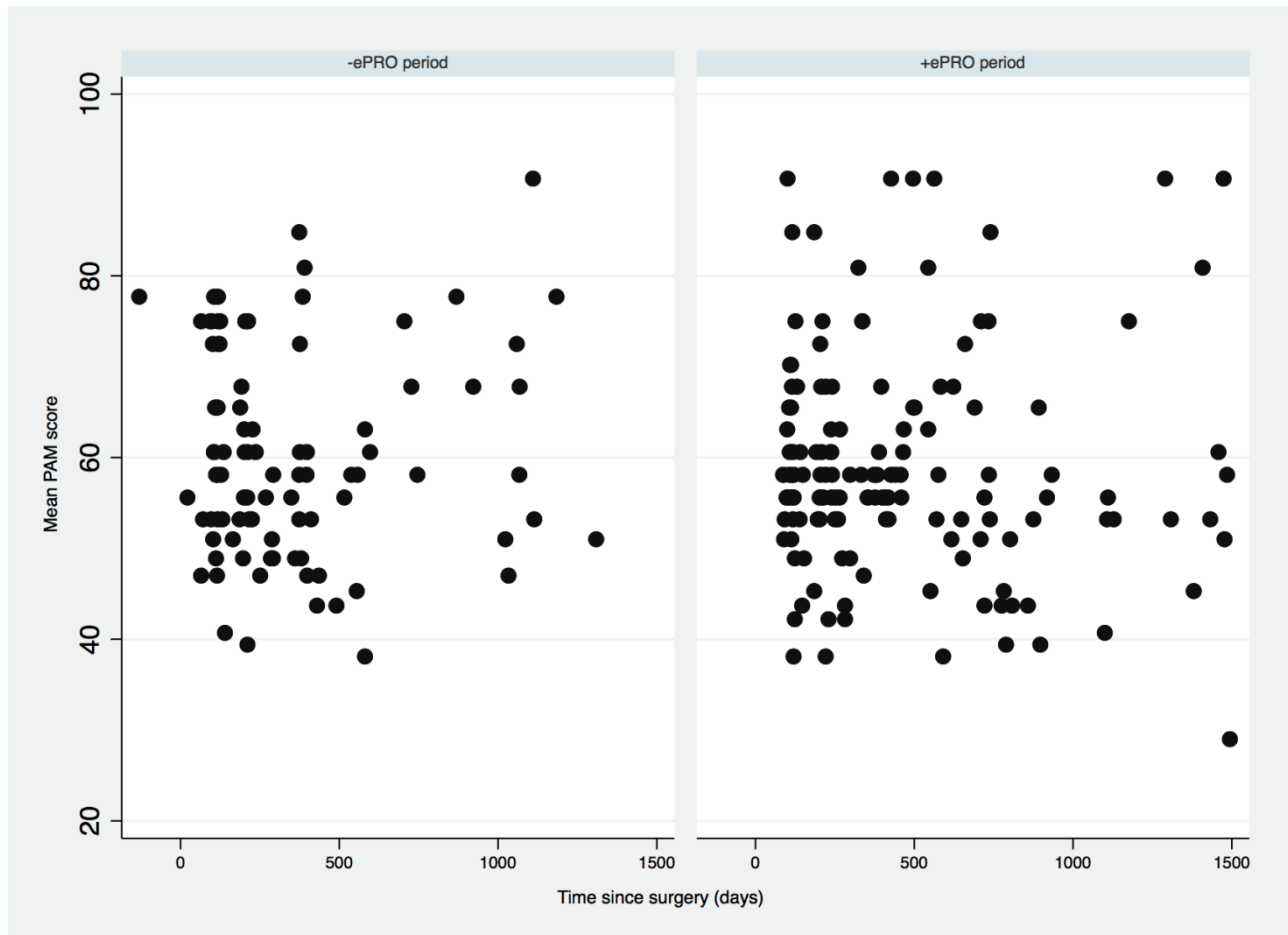
AARHUS UNIVERSITY

Declaration of co-authorship concerning <u>article for PhD dissertations</u>

Full name of the PhD student: Sissel Ravn

This declaration concerns the following article/manuscript:

Title:	The validity of registered synchronous peritoneal metastases from colorectal cancer in the Danish medical registries
Authors:	Sissel Ravn, Christian F. Christiansen, Rikke H. Hagemann-Madsen, Victor J. Verwaal, Lene H. Iversen.

The article/manuscript is: Published ☒ Accepted ☐ Submitted ☐ In preperation ☐

If published, state full reference: Ravn S, Christiansen CF, Hagemann-Madsen RH, Verwaal VJ, Iversen LH. The Validity of Registered Synchronous Peritoneal Metastases from Colorectal Cancer in the Danish Medical Registries. Clin Epidemiol. 2020;12:333-343
https://doi.org/10.2147/CLEP.S238193

If accepted or submitted, state journal:

Has the article/manuscript previously been used in other PhD or doctoral dissertations?

No ☒ Yes ☐ If yes, give details:

Your contribution

Please rate (A-F) your contribution to the elements of this article/manuscript, **and** elaborate on your rating in the free text section below.
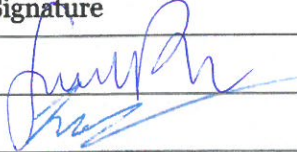
- A. Has essentially done all the work (>90%)
- B. Has done most of the work (67-90 %)
- C. Has contributed considerably (34-66 %)
- D. Has contributed (10-33 %)
- E. No or little contribution (<10%)
- F. N/A

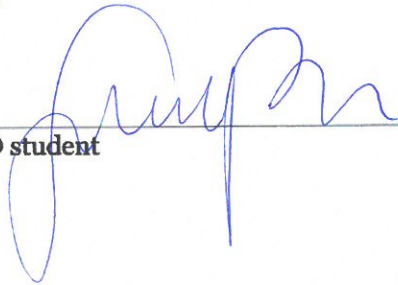| Category of contribution	Extent (A-F)
The conception or design of the work:	A
*Free text description of PhD student's contribution (**mandatory**)* The PhD student came across a discrepancy between the registration of peritoneal metastases in the Danish medical registries, and initiated the study protocol.	
The acquisition, analysis, or interpretation of data:	A
*Free text description of PhD student's contribution (**mandatory**)* The PhD student performed all analysis and interpretation of data. In collaboration with the main supervisor and the Clinical Epidemiological Department, results were discussed.	
Drafting the manuscript:	A
*Free text description of PhD student's contribution (**mandatory**)* The PhD student wrote the manuscript, and discussed corrections with the Main supervisor and collaborators at the Clinical Epidemiological Department	

Submission process including revisions:	A

*Free text description of PhD student's contribution (**mandatory**)*
The PhD student performed submission and point-to-point response with few inputs from Main supervisor and collaborators at the Clinical Epidemiological Department

Signatures of first- and last author, and main supervisor

Date	Name	Signature
28/08 2020	Sissel Ravn	
28/08 2020	Lene H. Iversen	

Date: 31/08/2020

_____

Signature of the PhD student

AARHUS UNIVERSITY

Declaration of co-authorship concerning article for PhD dissertations

Full name of the PhD student: Sissel Ravn

This declaration concerns the following article/manuscript:

Title:	Overall risk and risk factors for metachronous peritoneal metastasis after colorectal cancer surgery: a nationwide cohort study
Authors:	Sissel Ravn, Uffe Heide-Jørgensen, Christian F. Christiansen, Victor J. Verwaal, Rikke H. Hagemann-Madsen, Lene H. Iversen.

The article/manuscript is: Published ⊠ Accepted ☐ Submitted ☐ In preperation ☐

If published, state full reference: Ravn, S., Heide-Jørgensen, U., Christiansen, C.F., Verwaal, V.J., Hagemann-Madsen, R.H. and Iversen, L.H. (2020), Overall risk and risk factors for metachronous peritoneal metastasis after colorectal cancer surgery: a nationwide cohort study. BJS Open, 4: 284-292. doi:10.1002/bjs5.50247

If accepted or submitted, state journal:

Has the article/manuscript previously been used in other PhD or doctoral dissertations?

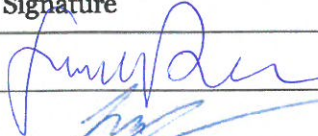No ⊠ Yes ☐ If yes, give details:

Your contribution

Please rate (A-F) your contribution to the elements of this article/manuscript, **and** elaborate on your rating in the free text section below.

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- D.   Has contributed (10-33 %)
- E.   No or little contribution (<10%)
- F.   N/A

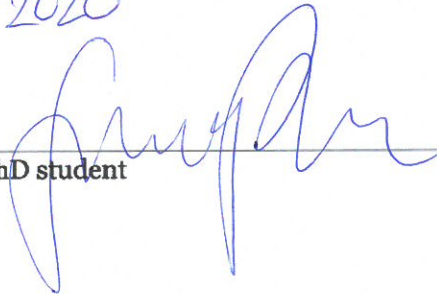| Category of contribution	Extent (A-F)
The conception or design of the work:	A
*Free text description of PhD student's contribution (**mandatory**)* The PhD student performed the study design with few inputs from collaborators at The Clinical Epidemiological Department and the main supervisor	
The acquisition, analysis, or interpretation of data:	A
*Free text description of PhD student's contribution (**mandatory**)* All analyses was performed by the PhD student and supervised/reviewed by a statiscian at the Clinical Epidemiological Department	
Drafting the manuscript:	A
*Free text description of PhD student's contribution (**mandatory**)* The PhD student performed the manuscript with few inputs from collaborators at The Clinical Epidemiological Department and the main supervisor	

Submission process including revisions:	A

*Free text description of PhD student's contribution (**mandatory**)*
The PhD student performed submission and point-to-point response with few inputs from Main supervisor and collaborators at the Clinical Epidemiological Department

Signatures of first- and last author, and main supervisor

Date	Name	Signature
28/08 2020	Sissel Ravn	
28/08 2020	Lene Hjerrild Iversen	

Date: 3/08 / 2020

_____
Signature of the PhD student

AARHUS UNIVERSITY

Declaration of co-authorship concerning article for PhD dissertations

Full name of the PhD student: Sissel Ravn

This declaration concerns the following article/manuscript:

Title:	Cancer follow-up supported by electronic patient-reported outcomes: Development and implementation.
Authors:	Sissel Ravn, Henriette V. Thaysen, HIPEC ePRO collaborative, Lene Seibaek, Victor J. Verwaal, Lene H. Iversen

The article/manuscript is: Published ☐ Accepted ☐ Submitted ☒ In preperation ☐

If published, state full reference:

If accepted or submitted, state journal: Journal of Patient-Reported Outcomes

Has the article/manuscript previously been used in other PhD or doctoral dissertations?

No ☒ Yes ☐ If yes, give details:

Your contribution

Please rate (A-F) your contribution to the elements of this article/manuscript, **and** elaborate on your rating in the free text section below.
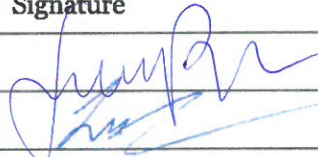
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- F. N/A

Category of contribution	Extent (A-F)
The conception or design of the work:	B
*Free text description of PhD student's contribution (**mandatory**)* The PhD student proposed the idea of a follow-up supported by patient-reported outcomes, and in collaboration with the supervisor group the details were discussed	
The acquisition, analysis, or interpretation of data:	A
*Free text description of PhD student's contribution (**mandatory**)* All data analyses and interpretation has primarily been done by the PhD student, and afterwards discussed in the supervisor group	
Drafting the manuscript:	B
*Free text description of PhD student's contribution (**mandatory**)* The PhD student performed the manuscript with input and feed-back from the supervisor group	
Submission process including revisions:	A

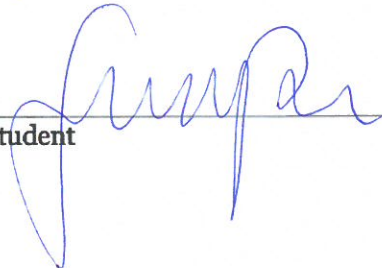Free text description of PhD student's contribution *(mandatory)*
Submission was performed solitary by the PhD student

Signatures of first- and last author, and main supervisor

Date	Name	Signature
28/08 2020	Sissel Ravn	
28/08/2020	Lene H. Iversen	

Date: 31/08/2020

Signature of the PhD student

AARHUS UNIVERSITY

Declaration of co-authorship concerning article for PhD dissertations

Full name of the PhD student: Sissel Ravn

This declaration concerns the following article/manuscript:

Title:	Cancer follow-up supported by Patient-Reported Outcomes in patients undergoing intended curative complex surgery for advanced cancer
Authors:	Sissel Ravn, Henriette V. Thaysen, HIPEC ePRO collaborative, Lene Seibaek, Victor J. Verwaal, Lene H. Iversen

The article/manuscript is: Published ☐ Accepted ☐ Submitted ☒ In preperation ☐

If published, state full reference:

If accepted or submitted, state journal: Journal of Patient-Reported Outcomes

Has the article/manuscript previously been used in other PhD or doctoral dissertations?

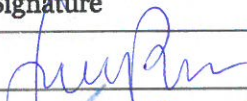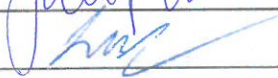No ☒ Yes ☐ If yes, give details:

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The acquisition, analysis, or interpretation of data:	B
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Drafting the manuscript:	B
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Submission process including revisions:	A

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Submission was performed solitary by the PhD student

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