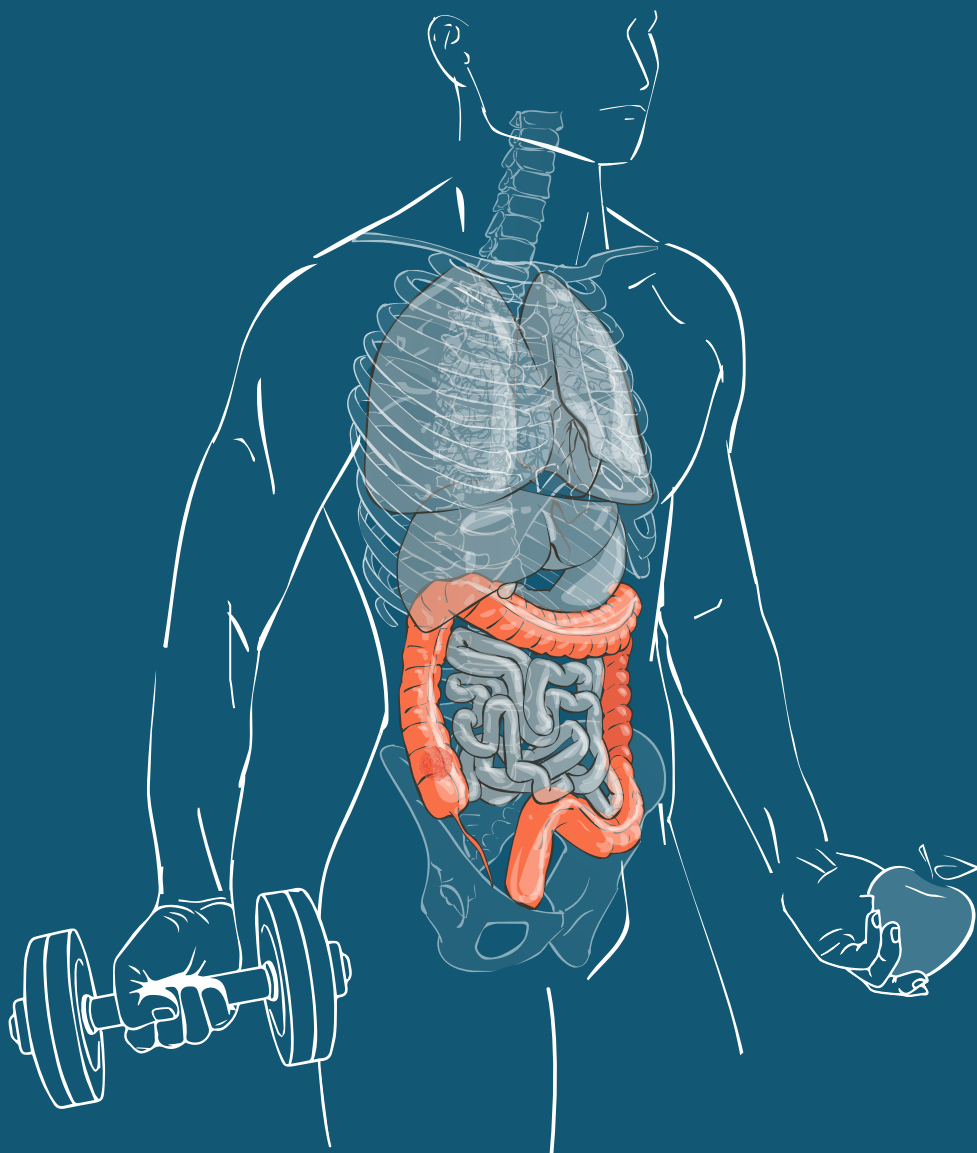


COLORECTAL CANCER SURVIVORSHIP

STEPS TOWARDS INTEGRATIVE ONCOLOGY
AND PATIENT-CENTERED CANCER CARE



JEROEN DERKSEN

Colorectal Cancer Survivorship

Steps towards integrative oncology and
patient-centered cancer care

Hiëronymus W.G. Derksen

Colorectal Cancer Survivorship:

Steps towards integrative oncology and patient-centered cancer care

Thesis with a summary in Dutch, Utrecht University

Proefschrift met een samenvatting in het Nederlands, Universiteit Utrecht

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Steps towards integrative oncology and
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Leven met en na darmkanker

Stappen in de richting van integratieve oncologie en
patiëntgerichte kankerzorg
(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de
Universiteit Utrecht
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Hiëronymus Wilhelmus Gijsbertus Derksen

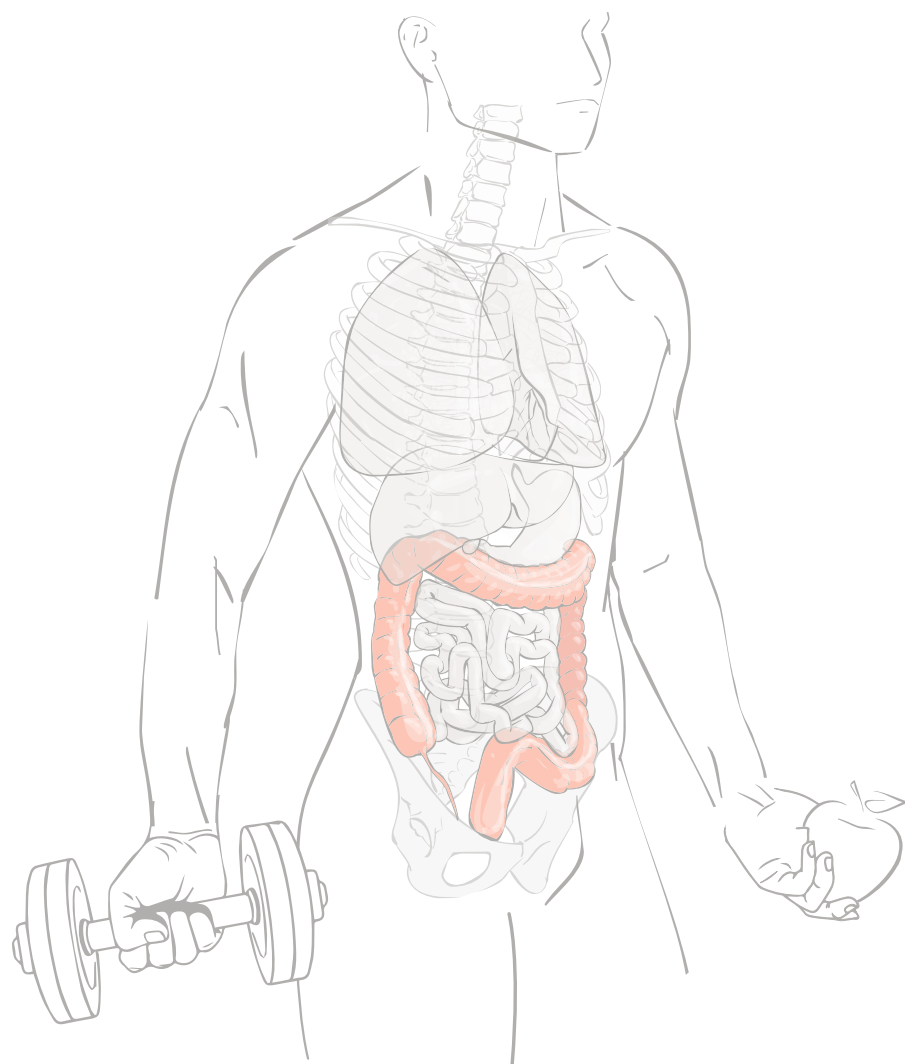
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1

GENERAL INTRODUCTION

Despite the significant progress in research on colorectal cancer (CRC) etiology, it remains the third most frequently diagnosed cancer worldwide ¹. Based on trend estimates produced by the International Agency for Research on Cancer (IARC), the global burden of CRC is expected to rise, from 1.8 million new cases in 2018 to more than 2.2 million in 2030 ². As a result of improvements in understanding CRC genetics, early detection through screening programs, local and systemic treatments and supportive care, the 5-year relative survival has increased substantially from 53 to 62% for colon cancer and from 51 to 65% for rectal cancer over the past three decades in the Netherlands ³. The number of cancer survivors, i.e. people living with and beyond cancer, is steadily growing, which inevitably results in an increasing need for health-related quality of life (HRQoL), supportive care and tertiary prevention research.

Colorectal carcinogenesis

Approximately 90% of CRC cases are sporadic, while less than 10% have an inherited predisposition. The development of a colorectal carcinoma is a slow, continuous, and multi-step process involving several genetic and epigenetic alterations to normal intestinal epithelial cells. These changes disturb the natural balance between cell proliferation (growth and division) and programmed cell death (apoptosis). In 1990, Fearon and Vogelstein were the first to present a model for the genetic basis of colorectal neoplasia that described the genetic mutations associated with the adenoma–carcinoma sequence in CRC (Figure 1) ⁴. The majority of cancers in the colon and rectum develop through this conventional pathway, which generally comes with increased chromosomal instability (CIN), whereas a minority of tumors is related to microsatellite instability (MSI) ^{5, 6}.

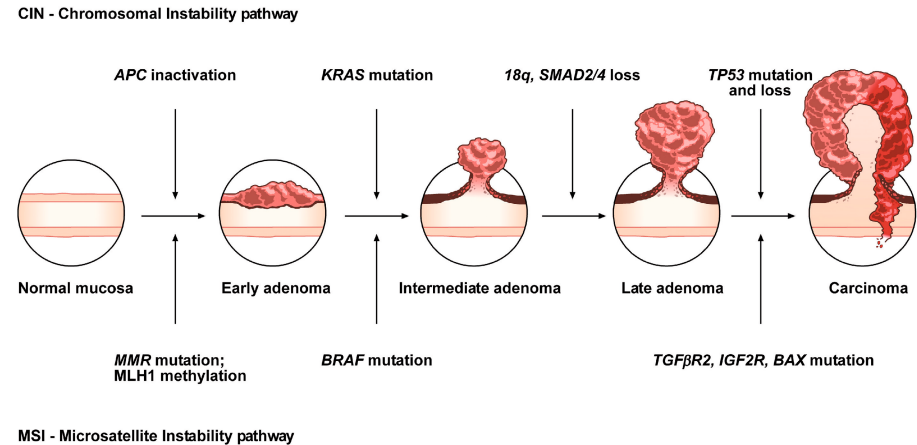


Figure 1. The adenoma–carcinoma sequence and associated genetic mutations (adapted from De Palma et al.⁷)

CIN tumors are primarily recognized by mutations in a number of oncogenes and tumor suppressor genes - most prominently the *APC*, *KRAS*, *SMAD4*, and *TP53* genes ⁵. Tumors that present with MSI as a result of impaired DNA mismatch repair (MMR), usually progress through different genetic mutation patterns ⁸. Together, the accumulation of these genetic alterations contributes to the transformation of normal epithelial tissue into adenomatous polyps which can progress to malignant carcinoma.

Tumor staging

After diagnosis, the extent of CRC progression is an important prognostic factor. The Union for International Cancer Control (UICC) has developed and maintains the TNM classification of Malignant Tumors, which is globally the most commonly used method to classify progression of solid tumors ⁹. This classification consists of three indicators, i.e. T(umor), N(ode), and M(etastasis) and is used to determine the clinical or pathological tumor stage, ranging from stage I to IV (Table 1). The T category describes the size of the primary tumor and whether it has invaded into adjacent tissue, the N category describes the degree of spread to regional lymph nodes, and the M category describes the presence of distant metastasis.

Table 1. The 5th TNM classification for colorectal cancer.

Stage	T	N	M
0	Tis	N0	M0
I	T1	N0	M0
	T2	N0	M0
II	T3	N0	M0
	T4	N0	M0
III	Tis-T4	N1-2	M0
IV	Tis-T4	N0-2	M1

Colorectal cancer treatment

Early-stage malignant polyps can mostly be resected by endoscopic polypectomy ¹⁰. If advanced CRC is confirmed after histological examination, surgery may be indicated to perform a wide local excision of the involved segment of colon together with the removal of surrounding lymph nodes. In individuals with an endoscopically unresectable polyp or a clinical suspicion of stage I-III CRC - i.e. without suspicion of distant metastasis - based on imaging, surgery is the first treatment option. In rectal cancer, surgery is preceded by neoadjuvant (chemo-)radiotherapy for patients with an intermediate to high-risk tumor ¹¹. In colon cancer, adjuvant chemotherapy is indicated for patients with high-risk

stage II or stage III tumor¹⁰. In stage IV disease – i.e. presence of distant metastasis at diagnosis – between 10 to 20% of the patients can still be treated with curative intent, using a combination of local and systemic treatment modalities. Palliative treatment will be considered for the other 80-90% of patients with the intention to prolong life expectancy, control symptoms including pain, and/or maintain quality of life¹².

Lifestyle-related risk factors

The World Health Organization (WHO) defines the term risk factor as any attribute, characteristic or exposure that is associated with an increased risk of a person to develop a certain disease¹³. In cancer epidemiology, lifestyle-related risk factors include modifiable exposures and behaviors related to a person's lifestyle that have the potential to lower the risk of developing cancer. Established potentially modifiable risk factors for cancer include: tobacco use, alcohol consumption, excess body fatness, diet, physical (in)activity, infectious agents, UV radiation, medical ionizing radiation, and radon exposure¹⁴. The World Cancer Research Fund (WCRF) concluded that for primary prevention of CRC specifically, there is strong convincing evidence that physical activity is related to a decreased risk and that body fatness and height, as well as the consumption of processed meat and alcohol is related to an increased risk¹⁵. To date, there is insufficient evidence to provide recommendations for patients after a cancer diagnosis, but the WCRF recommends cancer survivors to adhere to the primary prevention recommendations¹⁵.

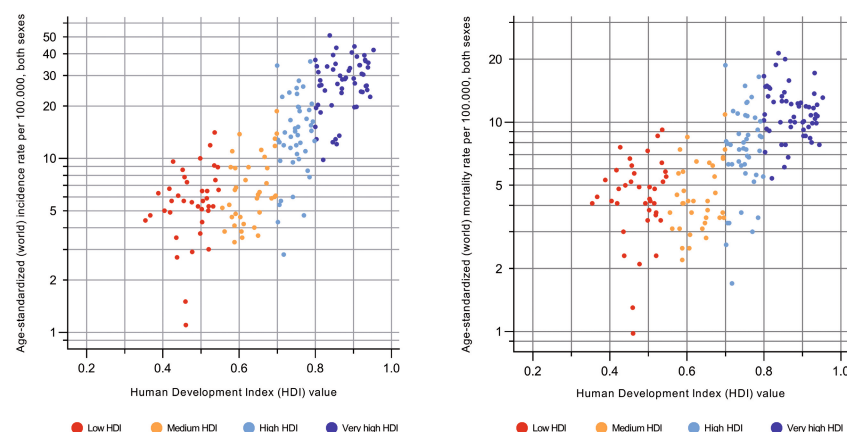


Figure 2. The correlation between age-standardized (world) CRC incidence (left) and mortality rates (right) and the human development index (HDI) for both sexes combined (updated from Arnold M. *et al.* 2015²; data of 174 countries obtained from GLOBOCAN 2018¹⁶ and United Nations Development Programme¹⁷).

Of all cancers, CRC is one of the most preventable cancers globally and one of the clearest examples of a malignancy related to human development¹⁸. As shown in Figure 2, CRC incidence and mortality rates are significantly higher in countries with a high human development index (HDI). This gradient – although biased by the presence of national screening programs and differences in cancer treatment – reflects to a certain extent the effects of lifestyle-altering westernization on CRC burden. Economic growth in low-income countries has shifted dietary patterns towards higher intake of fat, sugar and animal-source foods, paralleled by reductions in physical activity and increases in sedentary behavior^{19, 20}. This phenomenon implies that people themselves may have the opportunity to make major contributions to preventing this disease, but also to influencing the prognosis after a CRC diagnosis.

Body composition

Although body weight and body mass index (BMI) were the first measures used to determine health and nutritional status in patients with cancer and remain commonly used measures in clinical practice, they are inaccurate and do not allow for the differentiation between various tissue types²¹. In the past decade, CT images obtained as part of routine care in oncology have increasingly been used for body composition measures including visceral, subcutaneous, and intramuscular adipose tissue, and skeletal muscle mass. CT imaging usually relies on a single slice at the third lumbar vertebrae (L3) to estimate total body composition and has many advantages such as high accuracy and integration of measures in daily clinical practice²².

Cancer cachexia – a multifactorial syndrome that leads to systemic inflammation and substantial weight loss – is characterized by an accelerated loss of skeletal muscle²³. In oncology, sarcopenia is often defined as having a low skeletal muscle mass as compared to threshold values defined by their association with low survival²⁴. Depending on the definition deployed and patient population, sarcopenia is prevalent in 11-74% of adults with cancer²⁵ and strongly associated with adverse outcomes, independent of body weight^{24, 26, 27}. Currently, interventions that target muscle mass, including nutritional support, exercise programs, and some combination thereof, are being studied. From studies on nutritional supplements that contain components such as vitamins, protein, fatty acids, and/or essential amino acids, results suggest beneficial effects of ω -3 fatty acids on muscle mass, but inconclusive results indicate the need for additional evidence²⁸. Moreover, the ESPEN guidelines currently state that “In all patients – with the exception of end of life care – energy and substrate requirements should be met by offering in a step-wise manner

nutritional interventions from counseling to parenteral nutrition”²⁹. Regarding exercise interventions, resistance training in which the limbs are pushed against resistance provided by either body weight, gravity, bands or dumbbells, seems promising in counteracting the loss of muscle mass, strength and physical performance in cancer survivors³⁰⁻³². However, how nutritional and exercise interventions – during and after treatment – impact oncologic outcomes such as post-surgical complications and recovery, chemotherapy-related toxicity and survival, is an area of ongoing research.

Tertiary prevention

Tertiary prevention focuses on patients living with and beyond cancer. The goal is to improve quality of life and long-term outcomes by reducing disability, limiting or delaying complications, and restoring function. This is done by treating the disease, providing rehabilitation therapy, and focusing on the patient’s lifestyle habits. Research on the effects of changing an unhealthy lifestyle factor, or the combination of multiple factors simultaneously, on oncologic outcomes was recently highlighted as a research priority³³. In general, behavioral changes related to lifestyle are difficult to achieve, however, the likelihood of success is thought to be much higher after the ‘teachable moment’ of a cancer diagnosis. Limited but increasing evidence from epidemiological studies indeed shows that several lifestyle factors, including no or quitting smoking^{34, 35}, low alcohol consumption³⁶ and physical activity^{37, 38}, are associated with improved prognosis and quality of life in patients with CRC. Nevertheless, additional evidence is needed to advance the knowledge in this field, to provide guidelines for cancer survivors, and to improve evidence-based practice. Traditionally, evidence obtained from a properly designed randomized clinical trial and systematic reviews thereof are considered the highest level of scientific evidence. However, given the high cost of trials, methodological challenges, and limited generalizability, aspects such as study population, recruitment, randomization, outcome measures, and data collection should critically be considered in study designs.

Research infrastructures

From unselected to unselected

The first clinical trial within the era of modern clinical research originates from 1747 when surgeon James Lind conducted a comparative trial for the cure of scurvy³⁹. This trial was followed by a series of important milestones in the history of modern clinical trials; the introduction of “placebo” in 1863⁴⁰, the first double-blinded trial in 1943⁴¹, and the first randomized control trial of streptomycin in pulmonary tuberculosis in 1946⁴². Although preceding studies were of “ad hoc” nature in unselected populations, the streptomycin

trial was one of the first to use systematic enrollment criteria. Contemporary randomized clinical trials (RCT), primarily used for assessing the effect of an intervention on a certain outcome, are typically conducted under idealized and rigorously controlled conditions which may compromise their external validity. There is a current need to improve the external validity of RCTs in a way that physicians treating patients in their daily clinic have the appropriate evidence to base their clinical decisions on. This could be achieved by returning to using data from unselected populations – data generated from large observational studies or registries – to supplement trial-based evidence, as well as by modifying trial designs to pragmatic clinical trials in which interventions are tested in a more “real world” clinical practice setting. Moreover, large real-world datasets reflecting daily clinical practice allow for the evaluation of (new) treatments in everyday patients and contribute to a learning healthcare system.

Ongoing research

In The Netherlands, the Prospective Dutch Colorectal cancer (PLCRC) cohort is a modern observational population-based initiative of the Dutch Colorectal Cancer Group (DCCG) that allows for a wide range of research on CRC outcomes. This cohort is linked with the Netherlands Cancer Registry (NCR) and collects additional patient-reported outcomes and biospecimens to facilitate CRC research and ultimately aims to improve clinical outcomes by optimizing treatments to the individual patient. Furthermore, the infrastructure of PLCRC allows for studies to be incorporated within the cohort, and since 2015 two studies focusing on nutrition have been initiated. First, the “*Dietary intake after diagnosis and colorectal cancer outcomes (PLCRC-PROTECT)*” study, in which we assess dietary patterns, dietary supplement use, and sensory perception in 1,000 patients diagnosed with stage I-IV CRC, with the primary objective to investigate the association between diet and CRC survival. Second, the “*Lean body mass and treatment toxicities in adjuvant chemotherapy-receiving colon cancer patients (PLCRC-PROTECT-Plus)*” study, in which additional CT scans are made in 150 patients with high-risk stage II or stage III colon cancer with the primary objective to investigate the association between changes in lean body mass and overall grade 2-4 treatment-related toxicity from adjuvant chemotherapy. Lastly, the NUTRACT study investigates the tolerability of a medical nutrition supplement during first line treatment in patients with metastatic CRC. This product is specifically developed to support the nutritional needs of patients during their treatment, and eventually contribute to maintaining or increasing muscle mass in order to improve clinical outcomes.

Aim and outline of this Thesis

The overall aim of this thesis is to add further evidence to the integrative oncology program in which additional, patient-specific factors are considered to improve CRC outcomes. In fact, the definition of integrative oncology is “a *patient-centered, evidence-informed field of cancer care that utilizes mind and body practices, natural products, and/or lifestyle modifications from different traditions alongside conventional cancer treatments. Integrative oncology aims to optimize health, quality of life, and clinical outcomes across the cancer care continuum and to empower people to prevent cancer and become active participants before, during, and beyond cancer treatment.*”⁴³. Within this broad approach we focus on lifestyle-related factors, i.e. body composition and smoking behavior. Both are becoming of increasing relevance besides conventional treatments and have the potential to enhance patient empowerment by providing options to the patient to contribute to better outcomes themselves.

The first part of this thesis focuses on methodologies and the role of “real-world data” in contemporary cancer research. In **Chapter 2**, we describe the development of the Prospective Dutch Colorectal Cancer (PLCRC) Cohort towards a nationwide platform for CRC research and study the representativeness of the first 5,744 participants as compared to the general Dutch CRC population.

In response to a comprehensive review article on the use of real-world data (RWD) in oncology, we wrote a Correspondence which can be found in **Chapter 3**. Here, the overlooked opportunities for using alternative trial designs to enhance the “real-world” nature of the data within RCTs is addressed. The emphasis is on the Trials within Cohorts (TwICs) design and how the implementation of TwICs in large cohort studies could improve the generalizability of trial results.

The second part of this thesis focuses on research on lifestyle factors, body composition and quality of life. In **Chapter 4**, we provide an overview of methods for ambulant monitoring of potentially modifiable lifestyle factors in large-scale prospective studies in cancer survivors, including dietary intake, body composition, alcohol consumption, smoking behavior and physical activity. Measuring lifestyle factors non-invasively could help to increase its feasibility and ultimately improve our understanding of the individual and synergistic effects of lifestyle factors on quality of life and long-term clinical outcomes.

Increasing evidence indicates that loss of muscle mass is associated with adverse outcomes in metastatic CRC. In **Chapter 5**, we report the results of a study in which we investigate the association between changes in muscle mass during first-line palliative systemic treatment and health-related quality of life (HRQoL), daily functioning, as well as several disease-specific symptoms. This contributes to the identification of a potentially modifiable factor related to the patients’ HRQoL, which is valuable input to future intervention studies. In **Chapter 6** we describe which demographic, lifestyle- (smoking), tumor-, and treatment-related factors are associated with muscle loss in patients with metastatic CRC. Understanding the determinants may help to better identify patients who are at risk of losing muscle mass during first-line treatment.

Lastly, **Chapter 7** shows the results of a survey among European oncologists on their beliefs regarding tobacco use after a cancer diagnosis, current practice patterns in smoking cessation support, and barriers to facilitating cessation support. Results of this survey may help identifying future opportunities to enhance smoking cessation support which might be justified given its expected cost-effectiveness in oncology.

This thesis is completed by a General Discussion in **Chapter 8**, in which the main results and conclusions of the presented studies are discussed, followed by potential future applications and a general conclusion.

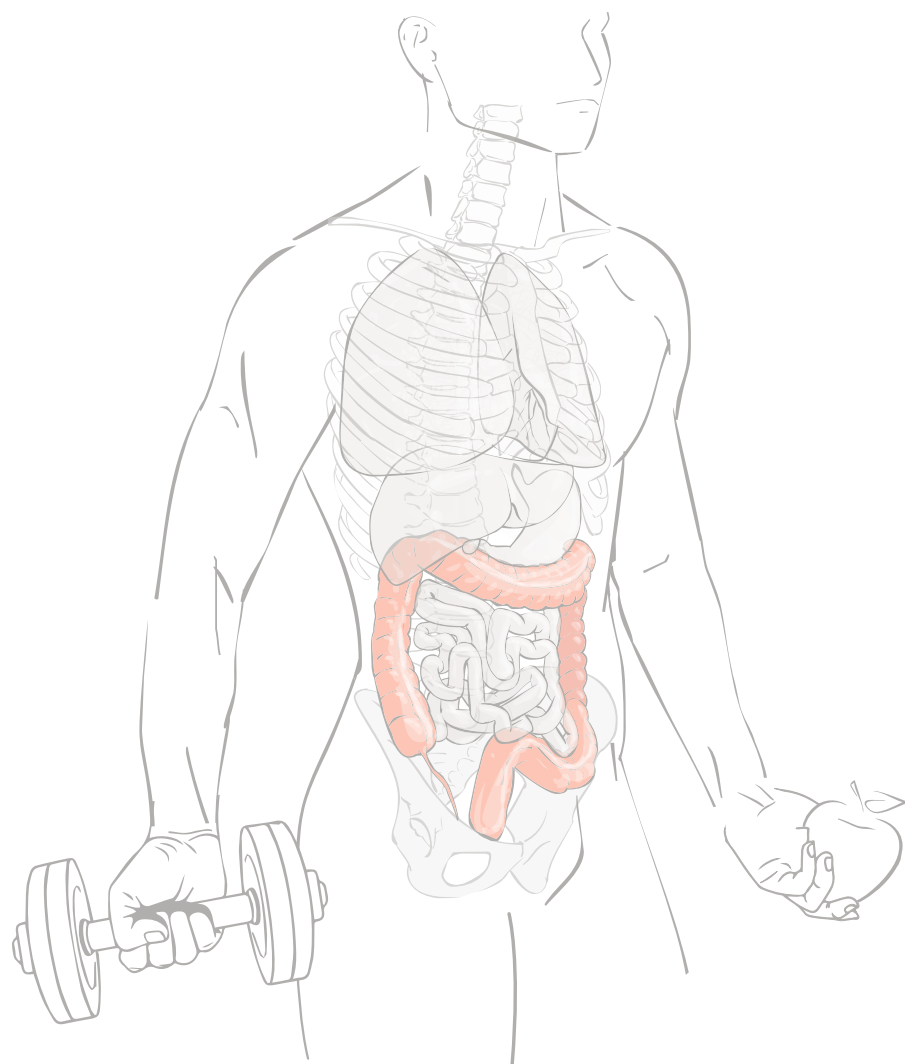
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PART I

RESEARCH METHODOLOGIES
IN ONCOLOGY



2

THE PROSPECTIVE DUTCH
COLORECTAL CANCER (PLCRC)
COHORT: “REAL-WORLD” DATA
FACILITATING RESEARCH AND
CLINICAL CARE.

SUBMITTED

J.W.G. Dersken, G.R. Vink, M.A.G. Elferink, J.M.L. Roodhart, H.M. Verkooijen, W.M.U. van Grevenstein, P.D. Siersema, A.M. May †, and M. Koopman †, on behalf of the PLCRC study group *.

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Abstract

Background

Real-world data (RWD) sources are important to advance clinical oncology research and evaluate treatments in daily practice. Since 2013, the Prospective Dutch Colorectal Cancer (PLCRC) cohort, linked to the Netherlands Cancer Registry, serves as an infrastructure for scientific research collecting additional patient-reported outcomes (PRO) and biospecimens. Here we report on cohort developments and investigate to what extent PLCRC reflects the “real-world”.

Methods

Clinical and demographic characteristics of PLCRC participants were compared with the general Dutch CRC population (n=74,692, Dutch-ref). To study representativeness, standardized differences between PLCRC and Dutch-ref were calculated, and logistic regression models were evaluated on their ability to distinguish cohort participants from the Dutch-ref (AU-ROC 0.5 = preferred, implying participation independent of patient characteristics). Stratified analyses by stage and time-period (2013-2016 and 2017-Aug 2019) were performed to study the evolution towards RWD.

Results

In August 2019, 5,744 patients were enrolled. Enrollment increased steeply, from 129 participants (1 hospital) in 2013 to 2,136 (50 of 75 Dutch hospitals) in 2018. Low AU-ROC (0.65, 95%CI: 0.64–0.65) indicates limited ability to distinguish cohort participants from the Dutch-ref. Characteristics that remained imbalanced in the period 2017-Aug’19 compared with the Dutch-ref were age (65.0 years in PLCRC, 69.3 in the Dutch-ref) and tumor stage (40% stage-III in PLCRC, 30% in the Dutch-ref).

Conclusions

PLCRC approaches to represent the Dutch CRC population and will ultimately meet the current demand for high-quality RWD. Efforts are ongoing to improve multidisciplinary recruitment which will further enhance PLCRC’s representativeness and its contribution to a learning healthcare system.

Introduction

Global colorectal cancer (CRC) incidence is expected to increase in the coming decades¹, which emphasizes the need to fulfill current knowledge gaps and improve clinical outcomes. In the current era of precision medicine, smaller treatment-eligible target populations are both an advancement as well as a challenge in cancer research^{2,3}. Due to the large amount of CRC subgroups defined by clinical characteristics in combination with the many (low-frequency) molecular markers⁴⁻⁶, the enrollment of sufficiently large sample sizes in studies evaluating the safety and efficacy of new therapeutic agents is a growing challenge. In addition, selective enrollment in most phase III randomized clinical trials (RCTs) may affect the generalizability of trial results and limits our understanding of the “true” treatment’s benefit-risk profile in the broader patient population. This is a constraint in clinical cancer research, given that international clinical guidelines are often based on results from strongly selected trial populations.

As advocated by both the research community and regulators such as the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA), the development of high quality population-based studies in cancer patients that provide real-world data (RWD) is a major research priority to overcome challenges in research methodologies, complement RCT data, and ultimately improve patient outcomes^{7,8}. A learning healthcare system approach, defined as a circular system in which “science, informatics, incentives, and culture are aligned for continuous improvement and innovation, with best practices seamlessly embedded in the delivery process and new knowledge captured as an integral by-product of the delivery experience”⁹, uses RWD to accelerate knowledge generation and its translation into clinical practice. RWD mainly distinguishes itself from trial-based evidence by being population-level data originating from sources outside of the typical clinical research setting, such as electronic health records (EHRs) or cancer registries, with the potential to efficiently answer research questions relevant to the broader patient population¹⁰. To warrant high quality RWD, ascertaining a high quality of primary data (i.e. completeness and accuracy of EHRs), linkage of data sources, and quality of derived variables, is paramount^{11,12}. Altogether, a prospective “real-world” cohort requires longitudinal patient, treatment (sequences), and outcome data from an unselected and representative patient population.

Since 2013, the Prospective Dutch Colorectal Cancer (PLCRC) cohort collects extensive longitudinal clinical data, together with blood, (tumor) tissue, and repeated patient-

reported outcomes (PROs) in patients with stage I to IV CRC that are prospectively followed from primary diagnosis until death ¹³. PLCRC serves as an infrastructure for a wide variety of research projects including etiological, biomarker, basic, (epi)genetic, and interventional (according to the Trials within Cohorts (TwICs) design ¹⁴), as well as health-care policy and cost-effectiveness studies. In order for results to be generalizable, and for accurate evaluation of cancer treatments, it is important to obtain a cohort that consists of a demographically and clinically representative patient population. Therefore, the aims of this manuscript are to (1) describe developments towards a nationwide cohort, (2) provide baseline characteristics, including PROs, of the first 5,722 participants, and (3) investigate to what extent PLCRC reflects the “real-world” - over time and by tumor stage - by comparing PLCRC cohort participants with the general Dutch CRC population as registered in the Netherlands Cancer Registry (NCR).

Methods

PLCRC is an initiative coordinated by the Dutch Colorectal Cancer Group (DCCG) and is registered at Clinicaltrials.gov (NCT02070146). The ‘Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)’ guidelines were taken into account when the cohort was designed ¹⁵. The study protocol was approved by the Institutional Review Board of the University Medical Center Utrecht (The Netherlands). We here describe the cohort briefly since the detailed design is published elsewhere ¹³.

Textbox 1. Informed consent options and main objectives of PLCRC.

IC options within the PLCRC cohort

Mandatory:

- 1. Informed consent for longitudinal observational clinical data collection.

Optional:

- 2. Informed consent for providing PRO (hard-copy or electronic).
 - a. In case of electronic patient-reported outcomes (ePRO), patients can choose to receive a summarized evaluation of their HRQoL (incl. optional comparisons with average scores of sex- and age-matched CRC patients and/or the non-cancer population) and share these data with their healthcare professional.
- 3. Informed consent to approach the patient for future studies and to use their data in comparative research according to the Trials within Cohorts (TwICs) design.
- 4. Informed consent for biobanking of (tumor) tissue.

- 5. Informed consent for providing additional blood samples during routine blood withdrawal for observational studies or biobanking.
- 6. Informed consent to receive information in case of new relevant DNA abnormalities.

Objectives of the PLCRC cohort

- To prospectively collect detailed data on medical history, serious comorbidities, basic physical examination, imaging results, pathology results, tumor characteristics, treatments, treatment outcomes, hospital stays, interventions and adverse events.
- To collect blood and (tumor) tissue material, obtained during routine practice, for ongoing and future research.
- To provide more accurate treatment data, and clinical and patient-reported outcomes of CRC in daily clinical practice.
- To create a continuous basis for a large variety of research purposes including, but not limited to:
 - Etiologic, diagnostic, and prognostic research.
 - Basic and (epi)genetic research.
 - Interventional studies according to TwICs designs.
 - Healthcare policy and cost-effectiveness studies.

The PLCRC population

PLCRC consists of patients diagnosed with a malignancy of the colon and/or rectum (ICD-10, C18-20) in the Netherlands. Each patient with histologically proven, or a strong suspicion of CRC without pathological confirmation, who is ≥ 18 years of age is eligible. The informed consent procedure preferably is performed shortly after diagnosis and before treatment starts. However, patients can also be enrolled during treatment or follow-up. Consent for longitudinal clinical data collection is mandatory for participation. In addition, patients can choose to consent to other optional items as shown in Textbox 1. Patients enrolled before August 1, 2019 of whom complete clinical data of the initial diagnosis and treatment period were available - to ascertain correct classification of tumor stage - were included in the analyses. Of these patients, baseline demographic and clinical data were retrieved and reported, as well as self-reported physical activity, fatigue, quality of life, BMI, presence of chronic comorbidities, smoking behavior, alcohol consumption, education level, and living situation at baseline.

The Netherlands Cancer Registry (NCR)

The Netherlands Cancer Registry (NCR) contains an extensive set of clinical data - from diagnosis onwards - of individuals diagnosed with cancer in the Netherlands and has a national coverage of over 95% ¹⁶. Clinical data of the complete treatment trajectory are retrieved from EHRs and entered into the NCR. The NCR’s high quality is assured by thorough training of data managers and computerized consistency checks. PLCRC’s

informed consent allows for linkage with the NCR and thus ensures the availability of clinical data over the complete cancer trajectory.

For the current analysis, only data of the initial data registration phase, i.e. at diagnosis, were used. We compared characteristics of PLCRC participants with the general Dutch CRC population (Dutch-ref) from the NCR with incidences between January 1, 2013 and December 31, 2017.

Statistical Analysis

Descriptive statistics were used to describe baseline patient characteristics, including baseline PROs. Standardized differences (d) were calculated to quantify the magnitude of differences in patient characteristics between PLCRC participants and the Dutch-ref. Values greater than 0.20 indicate a large imbalance, while values between 0.10 and 0.20 indicate a small imbalance, and standardized differences less than 0.10 indicate a negligible imbalance^{17,18}. Results are shown for the total group and stratified by tumor stage and time of enrollment. Two time-periods (enrolled between 2013-’16 and 2017-August ’19) were evaluated to assess whether PLCRC participants became more representative of the Dutch-ref over time. Logistic regression models were used to investigate to what extent, based on the available patient characteristics (i.e. age, sex, primary tumor location and tumor stage), cohort participation could be predicted¹⁹. Model performance was assessed based on calibration and discrimination²⁰. Calibration - the goodness of fit - was evaluated using the Hosmer-Lemeshow test²¹. Discrimination refers to the ability to distinguish cohort participants from non-participants, and was quantified by the area under the receiver operating characteristic curve (AU-ROC)²⁰. The AU-ROC ranges from 1, corresponding to perfect discrimination, to 0.5, corresponding to a model with no discrimination ability, here preferred and defined as cohort participation independent of patient characteristics (0.5 = random chance, 0.5-0.7 = poor, 0.7-0.8 = good, 0.8-1.0 = strong, 1.0 = perfect prediction)²². Statistical analyses were performed using STATA (Release 15, Stata Corp LLC, College Station, TX) and SPSS (version 25.0, IBM Corp, Armonk, NY).

Results

The flowchart for the selection of individuals for the current analyses is shown in Figure 1. On August 1, 2019, a total of 5,744 patients were enrolled. A complete TNM tumor stage could not be retrieved for 22 patients, who were therefore not included in the analyses.

Figure 1.

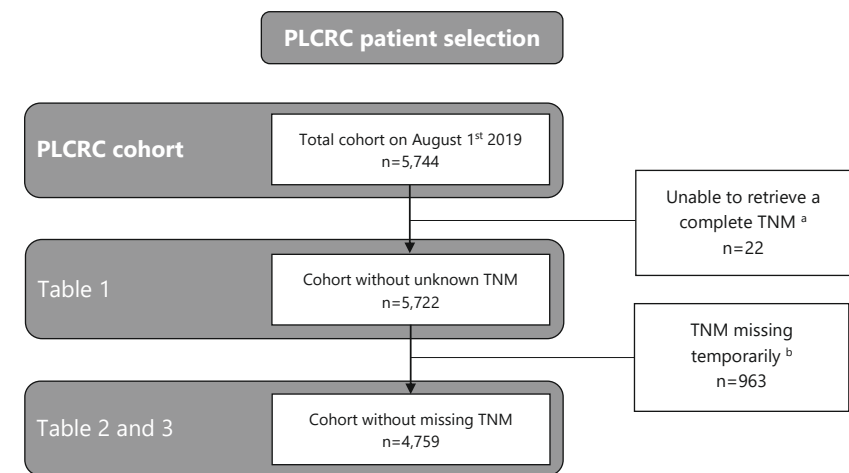


Fig. 1. Flow diagram of the selection of individuals for the current analyses. ^a Insufficient data in patient’s EHRs for the NCR to collect a complete TNM stage. ^b Missing due to time-lag in NCR clinical data collection. This number is higher than presented in Table 1, as for some cases sufficient staging information was available to classify into TNM stage.

Developments towards a nationwide cohort

PLCRC has continuously strengthened its infrastructure to improve the enrollment rate. In August 2019, patients were enrolled in 50 of 75 Dutch hospitals including 7 (of 8) academic hospitals, 22 (of 26) top clinical hospitals that focus on education and research, and 21 (of 41) regular hospitals (Fig. 2). This led to an improved annual enrollment-rate, from 129 participants from 1 recruiting hospital in 2013 to 2,136 from 50 recruiting hospitals in 2018 (note that there are approx. 14,000 incident cases annually). At enrollment, 100% of patients consented for using their clinical data obtained from the NCR, which was mandatory, 81% consented to receive repeated PRO questionnaires, 83% for blood withdrawals, 95% for use of tissue for scientific research, 83% for contact when relevant DNA abnormalities are found, and 78% for future research and trials according to the TwiCs design (Fig. 3). Once consented to receive questionnaires for PROs, 77% of patients returned their baseline questionnaire, and completion rates remained above 60% in the first three years after

enrollment (Fig. 4). Interestingly, patients who received paper-based questionnaires had consistently higher completion rates compared to electronic questionnaires (85% vs. 72% at baseline, respectively).

Figure 2.

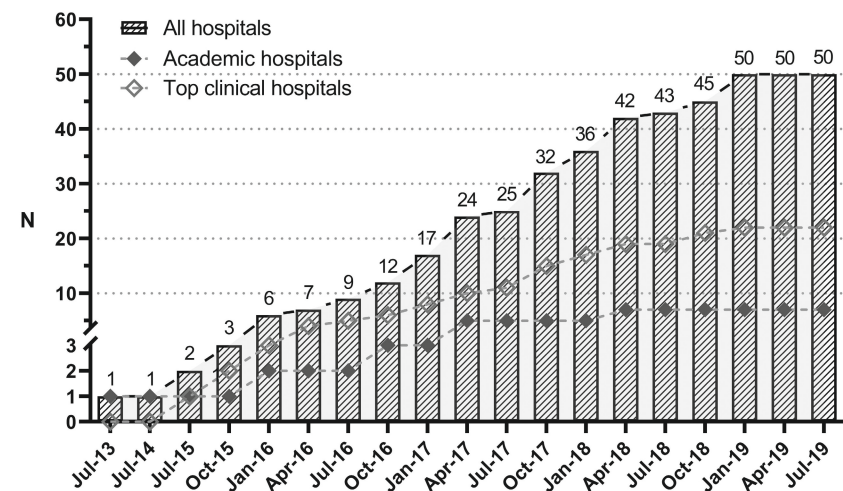


Fig. 2. PLCRC recruiting hospitals (academic, non-academic, and top clinical hospitals) over time. Note: In The Netherlands there is a total of 75 hospitals, of which 8 academic hospitals and 26 top-clinical hospitals.

Figure 3.

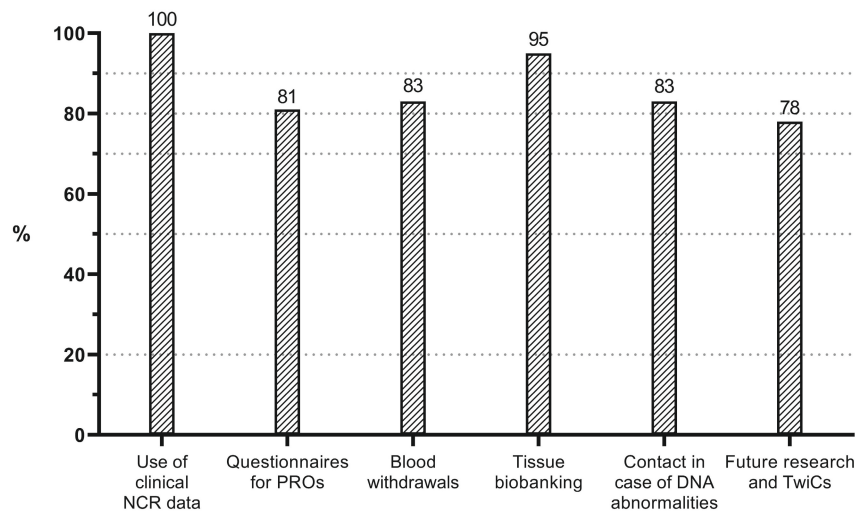


Fig 3. Baseline informed consent percentages per item. The use of clinical NCR data is 100% since this item is mandatory for participation. NCR, Netherlands Cancer Registry, PROs, patient-reported outcomes, TwiCs, Trials within Cohorts.

Figure 4.

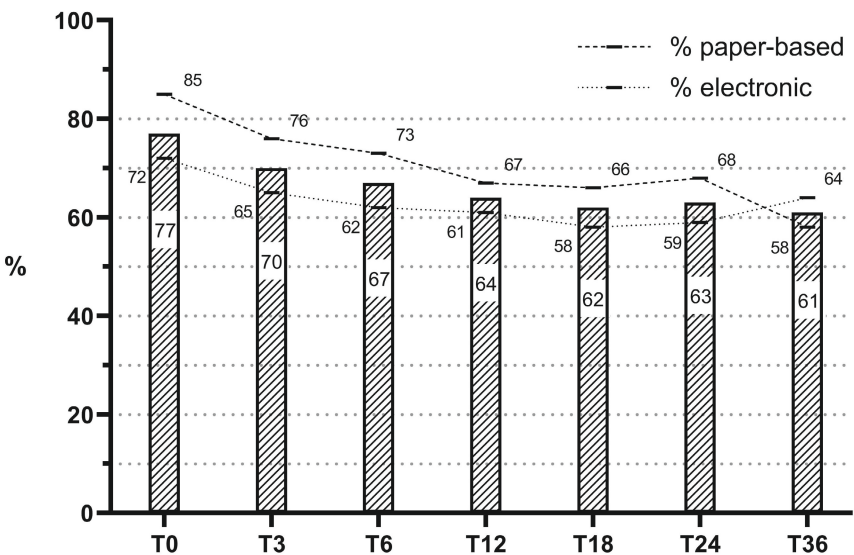


Fig. 4. Completion rates of questionnaires until three years after enrollment. Overall completion rates are presented in the bars, and electronic and paper-based percentages at the dashed lines. Time-points (T) are months since enrollment.

Baseline patient characteristics

The cohort contained 851 patients with stage I CRC, 1,079 with stage II, 1,960 with stage III, 946 with stage IV, and 886 patients of whom data on tumor stage is still being collected (Table 1). The median number of days from diagnosis until enrollment was 18 (IQR: 1 to 131) for the total cohort, and was similar for all stages except for stage IV patients, who were enrolled much later in the cancer trajectory (188 [IQR: 23 to 670] days). The percentage of males was higher than females for all stages, and 61% of the patients had a primary tumor located in the colon, and 39% in the rectum. Of the 946 stage IV patients, 79% had synchronous liver, 22% lung, and 17% peritoneal metastases. On average, PLCRC participants were overweight at enrollment with a mean BMI of $26,3 \pm 4,5$ kg/m². Regarding molecular diagnostics at diagnosis, *RAS* status was available in 596 (10%) patients, *BRAF* in 570 (10%), and microsatellite instability (MSI) in 2,600 (45%). In terms of physical and psychological wellbeing at enrollment (supplementary Table 1), patients reported to experience impaired psychosocial functioning, and high levels of fatigue, appetite loss and diarrhea as compared to reference populations (refs).

Table 1. Baseline descriptive demographic and clinical characteristics at PLCRC enrollment, stratified by tumor stage.

Baseline characteristics		Stage I (n=851)	Stage II (n=1,079)	Stage III (n=1,960)	Stage IV (n=946)	Stage missing * (n=886)
Total § (n=5,722)						
Demographic and clinical characteristics †						
Year of enrollment (n=5,722)						
2013–2016						
2017	1,088 (19%)	160 (19%)	213 (20%)	462 (24%)	253 (27%)	0 (0%)
2018	1,343 (24%)	240 (28%)	326 (33%)	512 (26%)	264 (28%)	1 (<1%)
2019 (until August)	2,128 (37%)	369 (43%)	421 (39%)	759 (39%)	314 (33%)	265 (30%)
Age at enrollment (n=5,722)	1,163 (20%)	82 (10%)	119 (11%)	227 (12%)	115 (12%)	620 (70%)
66.3 ± 10.6	67.7 ± 8.9	68.2 ± 10.3	65.7 ± 10.5	63.8 ± 10.9	66.7 ± 11.6	
< 55 years						
55 – 64 years	720 (13%)	49 (6%)	95 (9%)	263 (13%)	196 (21%)	117 (13%)
65 – 74 years	1,652 (29%)	240 (28%)	290 (27%)	582 (30%)	286 (30%)	254 (29%)
75 – 84 years	2,040 (36%)	372 (44%)	386 (36%)	708 (36%)	308 (33%)	266 (30%)
≥ 85 years	1,117 (20%)	165 (19%)	249 (23%)	365 (19%)	140 (15%)	198 (22%)
193 (3%)	25 (3%)	59 (6%)	42 (2%)	16 (2%)	51 (6%)	
Days from diagnosis to enrollment (n=5,722)	18 (1,131)	14 (0.45)	13 (2.66)	23 (3.156)	188 (23.670)	4 (10.20)
< 31 days	3,397 (59%)	595 (70%)	719 (67%)	1,087 (56%)	269 (28%)	727 (82%)
31 – 90 days	693 (12%)	109 (13%)	112 (10%)	255 (13%)	106 (11%)	111 (13%)
91 – 365 days	637 (11%)	61 (7%)	79 (7%)	239 (12%)	211 (22%)	47 (5%)
> 365 days	995 (17%)	86 (10%)	169 (16%)	379 (19%)	360 (38%)	1 (<1%)
Sex (n=5,722)						
Male	3,526 (62%)	532 (63%)	685 (64%)	1,196 (61%)	583 (62%)	530 (60%)
Female	2,196 (38%)	319 (38%)	394 (36%)	764 (39%)	363 (38%)	356 (40%)
Primary tumor location (n=5,722)						
Rectum (C19.9, C20.9)	2,231 (39%)	321 (38%)	347 (32%)	1,023 (52%)	364 (38%)	176 (20%)
Colon (C18.0–18.9)	3,491 (61%)	530 (62%)	732 (68%)	937 (48%)	582 (62%)	710 (80%)
Right colon (C18.0–18.4)	1,403 (40%)	254 (48%)	410 (56%)	432 (46%)	253 (44%)	54 (8%)
Left colon (C18.5–18.7)	1,564 (45%)	270 (51%)	309 (42%)	489 (52%)	315 (54%)	181 (25%)
Colon unspecified (C18.8–18.9)	524 (15%)	6 (1%)	13 (2%)	16 (2%)	14 (2%)	475 (67%)
Location synchronous metastases (n=5,722)						
Liver	746 (13%)				746 (79%)	
Lung	212 (4%)				212 (22%)	
Peritoneal	163 (3%)				163 (17%)	
Molecular diagnostics (n=570–2,600, missing 55–90%)						
RAS mutation status determined	596 (10%)	9 (1%)	30 (3%)	119 (6%)	438 (46%)	0 (0%)
BRAF mutation status determined	570 (10%)	14 (2%)	48 (4%)	121 (6%)	387 (41%)	0 (0%)
Microsatellite instability (MSI) determined	2,600 (45%)	436 (51%)	582 (54%)	1,097 (56%)	483 (51%)	2 (<1%)

Table 1. (Continued)

Baseline characteristics		Stage I (n=851)	Stage II (n=1,079)	Stage III (n=1,960)	Stage IV (n=946)	Stage missing * (n=886)
Total § (n=5,722)						
BMI at enrollment, kg/m² (n=3,108, missing 46%) †						
Underweight (<18.5)	26.3 ± 4.5	27.1 ± 4.6	26.3 ± 4.6	26.1 ± 4.2	25.8 ± 5.0	26.2 ± 4.3
Normal weight (18.5–25)	37 (1%)	2 (<1%)	7 (1%)	11 (1%)	7 (1%)	10 (2%)
Overweight (25–30)	1,313 (42%)	170 (37%)	198 (39%)	466 (43%)	261 (48%)	218 (41%)
Obese (>30)	1,254 (40%)	185 (40%)	214 (43%)	435 (40%)	199 (37%)	221 (42%)
50.4 (16%)	101 (22%)	83 (17%)	165 (15%)	74 (14%)	81 (15%)	
Past 12 months treated for chronic disease, at enrollment (n=2,986, missing 48%) †						
Cardiac disease or stroke	313 (11%)	59 (13%)	42 (9%)	114 (11%)	44 (9%)	54 (11%)
Diabetes	290 (10%)	38 (9%)	58 (12%)	117 (11%)	27 (5%)	50 (10%)
Liver disease	184 (6%)	11 (3%)	18 (4%)	35 (3%)	112 (22%)	8 (2%)
Kidney disease	38 (1%)	5 (1%)	6 (1%)	13 (1%)	7 (1%)	7 (1%)
Smoking status at enrollment (n=3,140, missing 45%) †						
Current	231 (7%)	23 (5%)	54 (11%)	74 (7%)	46 (8%)	34 (6%)
Former	1,840 (59%)	293 (63%)	286 (56%)	646 (59%)	298 (55%)	317 (59%)
Never	1,069 (34%)	149 (32%)	168 (33%)	368 (34%)	200 (37%)	184 (34%)
Past month average alcohol consumption at enrollment (n=3,111, missing 46%) †						
0 units per day	1,167 (38%)	134 (29%)	165 (33%)	403 (37%)	259 (48%)	206 (39%)
0 – 1 units per day	1,223 (39%)	195 (42%)	211 (42%)	400 (37%)	196 (36%)	221 (42%)
1 – 2 units per day	464 (15%)	82 (18%)	75 (15%)	182 (17%)	58 (11%)	67 (13%)
> 2 units per day	257 (8%)	50 (11%)	52 (10%)	94 (9%)	26 (5%)	35 (7%)
Living situation at enrollment (n=3,144, missing 45%) †						
Living alone	530 (17%)	74 (15%)	87 (17%)	183 (17%)	90 (17%)	96 (18%)
Living with partner, without children	1,965 (63%)	324 (70%)	322 (63%)	679 (62%)	313 (57%)	327 (61%)
Living with partner and children	537 (17%)	51 (11%)	82 (16%)	189 (17%)	120 (22%)	95 (18%)
Living alone with children	69 (2%)	8 (2%)	12 (2%)	26 (2%)	12 (2%)	11 (2%)
Other	43 (1%)	8 (2%)	5 (1%)	13 (1%)	11 (2%)	6 (1%)
Educational level (n=3,108, missing 46%) †						
≤ High school	1,206 (39%)	201 (44%)	194 (39%)	401 (37%)	192 (36%)	218 (41%)
Trade / college / other non-university	1,548 (50%)	212 (46%)	256 (51%)	539 (50%)	278 (51%)	263 (49%)
University	354 (11%)	45 (10%)	53 (10%)	135 (13%)	70 (13%)	51 (10%)

Descriptives are presented as count (%), mean (±SD), or median (IQR). § N = 22 patients with permanently unknown tumor stage are not included in the analysis. † In case of missing data, the descriptive statistics of complete cases are presented. ‡ Self-reported. * PLCRC is a dynamic cohort with continuous new enrollment and data-linkage. The high percentage of missing data, is due to the time-lag between enrollment and data linkage from the NCR to PLCRC, which is continuously updated.

PLCRC vs. the general Dutch CRC population

While the logistic regression model including age, sex, primary tumor location, and tumor stage overestimates the probability of participation ($p < 0.001$), the low discriminative power (AU-ROC 0.65, 95%CI: 0.64-0.65) indicates limited ability to distinguish cohort participants from the Dutch-ref, based on available data (full ROC curves in supplementary Figure 1). This discrimination decreased over time from an AU-ROC of 0.70 (95%CI: 0.68 - 0.71) in PLCRC's initial phase (2013-'16) to 0.64 (95%CI: 0.63 - 0.64) in the most recent phase (2017-Aug'19).

Between PLCRC participants ($n=4,759$) and the Dutch-ref ($n=72,685$), large imbalances were found for age at diagnosis (64.9 years in PLCRC, 69.3 in the Dutch-ref, d_{age} 0.41), primary tumor location (43% rectum in PLCRC and 31% in the Dutch-ref, $d_{pr.tumor}$ 0.24) and TNM stage (41% stage III in PLCRC and 30% in the Dutch-ref, d_{tnm} 0.24), a small imbalance in sex (62% male in PLCRC and 57% in the Dutch-ref, d_{sex} 0.11), and negligible imbalances in BMI at diagnosis (26.6 in PLCRC and 26.6 in the Dutch-ref, d_{bmi} 0.01) and in location of synchronous metastasis (15% liver in PLCRC and 15% in the Dutch-ref, d_{meta} between 0.01 and 0.08), Table 2.

When the two time-periods were compared with the Dutch-ref to study PLCRC's evolution, a large imbalance remained for age at diagnosis and tumor stage (d_{age} from 0.45 to 0.40, d_{tnm} from 0.33 to 0.22). The distribution of sex, BMI at diagnosis, and primary tumor location improved to imbalances classified as small or negligible (d_{sex} from 0.17 to 0.09, d_{bmi} from 0.16 to 0.03, $d_{pr.tumor}$ from 0.53 to 0.16). For location of synchronous metastases, e.g. liver metastasis, the imbalance compared with the Dutch-ref was negligible in both time periods (d_{liver} from 0.08 to 0.04).

Table 2. Characteristics of PLCRC participants at diagnosis (2013-Aug'19), compared with the general Dutch CRC population (2013-'17), and stratified by time-period (2013-'16, and 2017-Aug'19).

Baseline characteristics	Dutch population with CRC between 2013-'17 (n=72,685)	All PLCRC participants 2013-Aug'19 (n=4,759)	Standardized difference (d) †	PLCRC's initial phase 2013-'16 (n=1,088)	Standardized difference (d) †	PLCRC's most recent phase 2017-Aug'19 (n=3,671)	Standardized difference (d) †
Age at diagnosis	69.3 ± 10.8	64.9 ± 10.5	0.41	64.6 ± 10.2	0.45	65.0 ± 10.6	0.40
< 55 years	6,476 (9%)	733 (15%)		170 (16%)		563 (15%)	
55 - 64 years	15,248 (21%)	1,470 (31%)		350 (32%)		1,120 (31%)	
65 - 74 years	26,602 (37%)	1,722 (36%)		395 (36%)		1,327 (36%)	
75 - 84 years	19,482 (27%)	729 (15%)		153 (14%)		576 (16%)	
≥ 85 years	4,877 (7%)	105 (2%)		20 (2%)		85 (2%)	
Sex			0.11		0.17		0.09
Male	41,115 (57%)	2,949 (62%)		704 (65%)		2,245 (61%)	
Female	31,570 (43%)	1,810 (38%)		384 (35%)		1,426 (39%)	
BMI at diagnosis, kg/m² *	26.6 ± 4.6	26.6 ± 4.8	0.01	25.9 ± 4.0	0.16	26.7 ± 4.9	0.03
Underweight (<18.5)	228 (2%)	10 (1%)		1 (1%)		9 (1%)	
Normal weight (18.5-24.9)	5,252 (38%)	502 (40%)		78 (47%)		424 (39%)	
Overweight (25-29.9)	5,625 (41%)	503 (40%)		61 (37%)		442 (41%)	
Obese (≥30)	2,691 (20%)	229 (18%)		26 (16%)		203 (19%)	
Primary tumor location **			0.24		0.53		0.16
Rectum (C19.9, C20.9)	22,426 (31%)	2,025 (43%)		610 (56%)		1,415 (39%)	
Colon (C18.0-18.7)	50,259 (69%)	2,734 (57%)		478 (44%)		2,256 (61%)	
Right colon (C18.0-18.4)	24,244 (48%)	1,330 (49%)		200 (42%)		1,130 (50%)	
Left colon (C18.5-18.7)	24,634 (49%)	1,359 (50%)		269 (56%)		1,090 (48%)	
Colon unspecified (C18.8-18.9)	1,381 (3%)	45 (2%)		9 (2%)		36 (2%)	
TNM			0.24		0.33		0.22
Stage I	17,686 (24%)	849 (18%)		160 (15%)		689 (19%)	
Stage II	17,951 (25%)	1,063 (22%)		213 (20%)		850 (23%)	
Stage III	21,707 (30%)	1,929 (41%)		462 (42%)		1,467 (40%)	
Stage IV	15,341 (21%)	918 (19%)		253 (23%)		665 (18%)	
Location synchronous metastases							
Liver	11,218 (15%)	722 (15%)	0.01	202 (19%)	0.08	520 (14%)	0.04
Lung	3,954 (5%)	209 (4%)	0.05	58 (5%)	0.00	151 (4%)	0.06
Peritoneal	3,673 (5%)	162 (3%)	0.08	42 (4%)	0.06	120 (3%)	0.09

† Standardized differences (d) are differences in means or proportions divided by standard error; $d > 0.20$ indicate a large difference, $d > 0.10 - 0.20$ indicate a small difference, and $d < 0.10$ indicate a negligible difference ^{17,18}. * BMI at diagnosis for PLCRC only available when participants were enrolled at diagnosis and provided PROs ($n=1,244$); the NCR only collected height and weight in 2015; thus the reference values for BMI originate only from patients diagnosed in 2015 ($n=13,796$). ** Standardized differences calculated over the proportion rectum vs. colon tumors.

Table 3. Characteristics of the PLCRC participants at diagnosis (2013-Aug'19), compared with the general Dutch CRC population (2013-17), stratified by tumor stage.

Baseline characteristics	Dutch population with CRC between 2013-17 (n=849)	PLCRC participants 2013-Aug'19 Stage I (n=849)	Standardized difference (d) †	Dutch population with CRC between 2013-17 Stage II (n=1,063)	PLCRC participants 2013-Aug'19 Stage II (n=1,063)	Standardized difference (d) †	Dutch population with CRC between 2013-17 Stage III (n=2,170)	PLCRC participants 2013-Aug'19 Stage III (n=1,929)	Standardized difference (d) †	Dutch population with CRC between 2013-17 Stage IV (n=15,344)	PLCRC participants 2013-Aug'19 Stage IV (n=918)	Standardized difference (d) †
Age at diagnosis												
< 55 years	69.3 ± 9.1	66.8 ± 9.0	0.28	71.2 ± 10.6	66.9 ± 10.4	0.41	68.4 ± 11.2	64.2 ± 10.6	0.38	68.4 ± 11.8	62.2 ± 11.0	0.55
55 - 64 years	910 (5%)	64 (8%)		1,205 (7%)	123 (12%)		2,440 (11%)	326 (17%)		1,921 (13%)	220 (24%)	
65 - 74 years	3,861 (22%)	258 (30%)		3,117 (17%)	302 (28%)		4,929 (23%)	607 (31%)		3,341 (22%)	303 (33%)	
75 - 84 years	7,486 (42%)	367 (43%)		6,362 (35%)	385 (36%)		7,656 (35%)	689 (36%)		5,098 (33%)	281 (31%)	
≥ 85 years	4,674 (26%)	143 (17%)		5,612 (31%)	211 (20%)		5,341 (25%)	273 (14%)		3,855 (25%)	102 (11%)	
	755 (4%)	17 (2%)		1,655 (9%)	42 (4%)		1,341 (6%)	34 (2%)		1,126 (7%)	12 (1%)	
Sex			0.08			0.19			0.08			0.11
Male	10,411 (59%)	531 (63%)		9,695 (54%)	675 (64%)		12,340 (57%)	1,176 (61%)		8,669 (57%)	567 (62%)	
Female	7,275 (41%)	318 (37%)		8,256 (46%)	388 (36%)		9,367 (43%)	753 (39%)		6,672 (43%)	351 (38%)	
BMI at diagnosis, kg/m² *			0.01			0.08			0.08			0.06
Underweight (<18.5)	27.2 ± 4.6	27.2 ± 4.8		26.5 ± 4.7	26.9 ± 5.0		26.6 ± 4.6	26.3 ± 4.4		25.6 ± 4.4	25.9 ± 5.7	
Normal weight (18.5-24.9)	28 (1%)	1 (0%)		72 (2%)	4 (1%)		62 (1%)	5 (1%)		66 (3%)	0 (0%)	
Overweight (25-29.9)	1,134 (32%)	119 (40%)		1,323 (39%)	103 (35%)		1,606 (37%)	216 (42%)		1,189 (46%)	64 (50%)	
Obese (≥ 30)	1,532 (44%)	112 (37%)		1,367 (40%)	129 (43%)		1,774 (41%)	214 (41%)		952 (37%)	48 (37%)	
	798 (23%)	68 (23%)		668 (19%)	61 (21%)		855 (20%)	83 (16%)		370 (14%)	17 (13%)	
Primary tumor localization **			0.14			0.25			0.24			0.23
Rectum (C19.9, C20.9)	5,543 (31%)	321 (38%)		3,836 (21%)	342 (32%)		8,813 (41%)	1,008 (52%)		4,234 (28%)	354 (39%)	
Colon (C18.0-18.7)	12,143 (69%)	528 (62%)		14,115 (79%)	721 (68%)		12,894 (59%)	921 (48%)		11,107 (72%)	564 (61%)	
Right colon (C18.0-18.4)	4,686 (39%)	253 (48%)		7,757 (55%)	406 (56%)		6,314 (49%)	425 (46%)		5,487 (49%)	246 (44%)	
Left colon (C18.5-18.7)	7,245 (60%)	269 (51%)		6,040 (43%)	304 (42%)		6,326 (49%)	481 (52%)		5,023 (45%)	305 (54%)	
Colon unspecified (C18.8-18.9)	212 (2%)	6 (1%)		318 (2%)	11 (2%)		254 (2%)	15 (2%)		597 (5%)	13 (2%)	

† Standardized differences (d) are differences in means or proportions divided by standard error; d > 0.20 indicate a large difference, d 0.10 - 0.20 indicate a small difference, and d < 0.10 indicate a negligible difference.
*, BMI at diagnosis for PLCRC only available when participants were enrolled at diagnosis and provided PROs (n=1,244); the NCR only collected height and weight in 2015, thus the reference values for BMI originate only from patients diagnosed in 2015 (n=13,796). **, Standardized differences calculated over the proportion rectum vs. colon tumors.

Table 3 shows stratified analyses in which PLCRC participants were compared with the Dutch-ref by tumor stage. Age at diagnosis was lower for PLCRC participants in all stages, and discrepancies increased by stage (d_{age} from 0.28 in stage I to 0.55 in stage IV). For all disease stages, PLCRC contained relatively more patients with a primary tumor in the rectum and fewer patients with a primary tumor in the colon, compared with the Dutch-ref (d_{pr.tumor} between 0.14 and 0.25). The proportions of sex and BMI at diagnosis were comparable to the ref. population in all stages (d_{sex} between 0.08 and 0.19, d_{bmi} between 0.01 and 0.08).

Discussion

Over the past six years, the increased number of PLCRC recruiting centers has resulted in a steep increase in participating patients, with excellent consent rates for PROs, blood and tissue biobanking, and participation in future research within PLCRC. Although we found an overall shift towards the Dutch-ref for patients enrolled between 2017 - Aug 2019, PLCRC participants were still younger and more often had stage III disease, as compared to the total Dutch CRC population.

Besides common discrepancies such as performance status and number of comorbidities, clinical trial participants are notably younger than the real-world population, which for now might hamper the applicability of trial results in daily clinical practice. It was recently shown that phase-III RCT patients were on average seven years younger than the general CRC population²³. Similarly, patients within PLCRC are younger compared to the Dutch-ref, however, this difference only is 4 years (mean age 65 years). Standardized differences for age increased by tumor stage with stage IV patients showing a mean age comparable to phase-III clinical trials in metastatic CRC²⁴. This emphasizes the need to focus on the enrollment of (stage IV) patients that are diagnosed at older age. Although important factors such as comorbidities and performance status are currently unknown, we believe that PLCRC has the potential to serve as a research platform that fulfills the current demand for RWD as advocated for by regulators and research community. The additional advantage of PLCRC is the large collection of biospecimen, which is intertwined with routine clinical care, and longitudinal PROs from diagnosis onwards. Moreover, the incorporation of PROs that describe the impact of treatment on quality of life, daily activities and symptoms is increasingly recognized as an essential component of real-world evidence and has the potential to improve cancer care, shared decision making, and clinical outcomes²⁵⁻²⁷.

Dutch CRC guidelines recommend, in line with the European guidelines, to determine both mismatch repair status in stage II-IV tumors, and *RAS* and *BRAF* mutation status in tumor of patients with metastatic CRC prior to the start of systemic treatment ²⁸⁻³⁰. Although our percentages may be an underestimation as mutation status could become available during NCR updates after the initial data registration, the amount of missing data on molecular diagnostics is noteworthy. A limitation that is currently inevitable within PLCRC is that completeness of the NCR depends on daily clinical practices. In contrast to the above mentioned national guidelines, molecular markers are not routinely measured in all patients in the clinic. This means that currently, PLCRC is missing opportunities to optimally use tumor mutation status for research purposes. Efforts are ongoing to perform retrospective molecular profiling within PLCRC to supplement existing molecular pathology data with the aim to be able to tailor treatment options to the individual patient in the future. Next to the identification of predictors for treatment response and clinical outcomes, this will also contribute to the development of a unique cohort that could provide “external” controls for future single arm clinical trials in uncommon CRC subtypes with high unmet medical need ^{31, 32}.

Given the large variety of available data, i.e. longitudinal clinical data, blood and tissue samples, and patient-reported outcomes such as treatment-related side-effects and HRQoL, PLCRC will allow for comprehensive analyses on CRC. However, future improvements are required to optimize two fundamental elements of RWD sources: completeness of cases and completeness of clinical data. Based on our experience, over 90% of patients provide informed consent once the study aim is explained. Enhanced integration of research into daily clinical practice and the development of local infrastructures that lead to increased willingness and availability of personnel to inform the patient about PLCRC are crucial to further improve the completeness of cases and create a true RWD cohort. Second, completeness of clinical data mainly depends on how well clinicians document clinical data in EHRs. Regardless of the list of items to be collected in the NCR, unmeasured or undocumented data will never become available to the research community. Moreover, EHR data are often unstructured and inconsistent due to large variation between clinicians and differences in EHR software systems. Nationwide harmonization and standardization of clinical data entries in EHRs and subsequent implementation of electronic data-capture systems to enable real-time data transfer from EHRs to the NCR, will significantly enhance the completeness and quality of clinical data.

Despite the establishment of a unique CRC cohort, focus should be given to reach and enroll older patients and to enhance involvement of the gastroenterology departments to enroll patients with early stage tumors. Moreover, especially stage IV patients should be enrolled closer to diagnosis to standardize time points for PROs and avoid potential survivor bias. This can be achieved by an optimal research-focused infrastructure and implementation of research-specific consultations for all cancer patients shortly after diagnosis. During this consultation, the patient is informed about the specific components of PLCRC (textbox 1), as well as on the main aim to optimally evaluate treatments, accelerate innovation, and learn from each individual patient. Besides the aforementioned suggestions, we need to create a societal change with respect to clinical research. All stakeholders should be aware that, in order to improve oncology practice, research needs to become an integrated part of clinical care and that contributions to clinical research are self-evident. Lastly, PLCRC is a platform to centralize national CRC research to maximize its potential and minimize patient burden. Access to cohort resources for collaborative research projects may be requested through the Scientific Committee [<https://plcrc.nl/for-international-visitors>] that reviews all research projects for approval.

To conclude, PLCRC is establishing a unique and steeply growing national RWD cohort that allows for a wide range of research. Data from the general patient population enables a learning healthcare system that provides insight into the care and outcomes of patients that are usually underrepresented in RCTs, e.g. the very young and older patients and the ones with multiple comorbidities. Comprehensive analyses within PLCRC are facilitated by the extensive amount of clinical data covering the complete treatment trajectory and additional patient-reported outcomes. Further improvements in recruitment methodologies and multidisciplinary enrollment of patients will contribute to the aim of enrolling all newly diagnosed CRC patients in the Netherlands. This will continue to enhance PLCRC's representation of the real-world and its ability to improve both scientific research and daily clinical practice.

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SUPPLEMENTARY MATERIAL

Supplementary Table 1. Mean scores (± standard deviations) of patient-reported physical activity, fatigue, and quality of life of all respondents at any time of PLCRC enrollment, and in a subgroup enrolled at diagnosis.

	PLCRC participants at any time of enrollment (n=4,759)		PLCRC participants enrolled at diagnosis (n=2,615)		Reference population *	
	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD
Physical activity (SQUASH)						
Light intensity (<3 MET) in min/wk	2,481	1,298 ± 1,048	1,220	1,396 ± 1,093		
Moderate intensity (3-6 MET) in min/wk	2,481	582 ± 695	1,220	662 ± 762		
Vigorous intensity (≥6 MET) in min/wk	2,481	24 ± 90	1,220	31 ± 101		
Adherence to Dutch guideline ‡	2,481	893 (36%)	1,220	486 (40%)	3,527	1,633 (46%)
Fatigue (MFI-20, range 4-20)						
General fatigue	2,494	11.2 ± 4.9	1,220	10.6 ± 4.9	2,037	8.7 ± 3.6
Physical fatigue	2,496	10.9 ± 4.8	1,221	10.3 ± 4.8	2,037	8.4 ± 4.1
Reduced activity	2,489	11.4 ± 4.6	1,216	11.1 ± 4.6	2,037	8.0 ± 3.3
Reduced motivation	2,491	9.8 ± 4.1	1,221	9.6 ± 4.1	2,037	8.4 ± 3.8
Mental fatigue	2,495	8.7 ± 4.2	1,219	8.5 ± 4.1	2,037	7.7 ± 3.3
Health-related quality of life (QLQ-C30, range 0-100)						
Functional scales						
Overall quality of life	2,854	71 ± 20	1,440	73 ± 19	1,731	78 ± 17
Physical functioning	2,861	86 ± 17	1,445	88 ± 16	1,731	90 ± 15
Role functioning	2,857	74 ± 30	1,442	78 ± 30	1,731	89 ± 21
Emotional functioning	2,859	80 ± 19	1,444	80 ± 19	1,731	89 ± 16
Cognitive functioning	2,859	87 ± 18	1,444	88 ± 17	1,731	92 ± 15
Social functioning	2,859	80 ± 23	1,444	83 ± 22	1,731	94 ± 16
Symptoms						
Fatigue	2,858	29 ± 25	1,444	26 ± 25	1,731	17 ± 20
Nausea and vomiting	2,859	7.1 ± 16	1,444	6.2 ± 16	1,731	2.7 ± 10
Pain	2,861	17 ± 24	1,445	16 ± 23	1,731	15 ± 22
Dyspnea	2,851	12 ± 21	1,441	10 ± 20	1,731	7.1 ± 17
Insomnia	2,858	23 ± 29	1,444	23 ± 29	1,731	14 ± 23
Appetite loss	2,857	14 ± 25	1,443	12 ± 24	1,731	3.3 ± 12
Constipation	2,851	11 ± 21	1,442	12 ± 22	1,731	4.8 ± 14
Diarrhea	2,846	18 ± 26 †	1,438	19 ± 27 †	1,731	3.9 ± 14

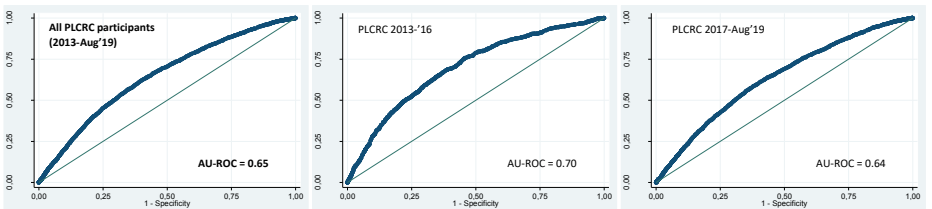
Baseline PROs for the complete cohort of respondents, and for a subset of patients enrolled at diagnosis (<31 days), obtained from the EORTC QLQ-C30, SCQ, SQUASH, and the MFI-20 ³³⁻³⁶. To put PROs into perspective, outcomes were evaluated based on pre-determined minimal clinically relevant differences relative to normative data, i.e. 2 points difference in fatigue ³⁷ and 10 points difference in HRQoL ³⁸. Clinically relevant difference are shown in bold. Absolute HRQoL scores were also evaluated based on recently published thresholds for identification of clinically important symptoms and functional health impairments ³⁹.

† Above the absolute threshold for clinically important impairments. * Reference physical activity levels originate from Statistics Netherlands ⁴⁰ (to obtain a reference group of comparable age, subjects with an age ranging between the 5th and 95th percentile of the age within the PLCRC cohort [i.e. 48-83 years] were selected and individuals living with and beyond cancer were excluded), reference values for fatigue originate from Schwarz *et al.* ⁴¹, and HRQoL from van de Poll-Franse *et al.* ⁴².

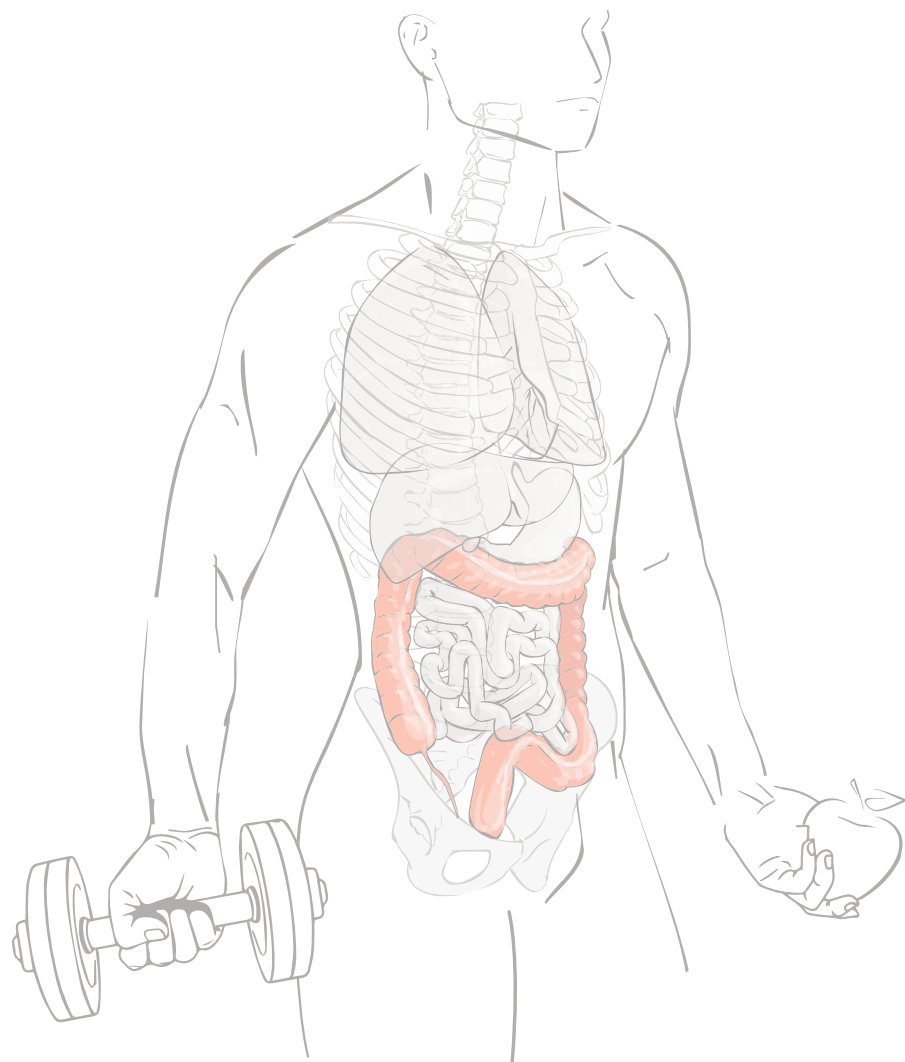
‡ 2017 Dutch Physical Activity Guideline ⁴³. Note: HRQoL scores and standard deviations ≥ 10 are rounded.

MET, metabolic equivalent of task (1 MET is equivalent to the consumption of 3.5 ml of oxygen per kilogram of body mass per minute).

Supplementary Figure 1.



Suppl. Fig. 1. Area under the ROC curves (AU-ROC) as a predictive performance measure to evaluate the logistic regression models' ability to discriminate between PLCRC participants and non-participants, based on age at diagnosis, sex, primary tumor location, and tumor stage.



3

THE ERA OF ALTERNATIVE
DESIGNS TO CONNECT
RANDOMIZED CLINICAL TRIALS
AND REAL-WORLD DATA

NATURE REVIEWS
CLINICAL ONCOLOGY
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In their Review published in the May 2019 issue of this journal (Real-world data: towards achieving the achievable in cancer care. *Nat. Rev. Clin. Oncol.* 16, 312–325 (2019))¹, Booth *et al.* address challenges and future perspectives relating to the use of real-world data (RWD) in oncology. They describe the quality, and current and future applications of RWD, and the pitfalls of studies of comparative effectiveness using RWD. We acknowledge the authors' efforts to provide this comprehensive overview and appreciate the future perspectives they present. In light of the authors' appeal for increasing focus to be placed in the implementation of randomized clinical trials (RCTs) in real-world settings, herein we would like to address overlooked opportunities for using alternative trial designs to enhance the real-world nature of the data within RCTs. Owing to the length limitations of this Correspondence, we cannot define each modality but provide supporting references.

Pragmatic trial designs, such as registry-based RCTs (R-RCTs), have become of increasing interest globally as efficient and cost-effective tools that combine the advantages of a prospective RCT with the strengths of large-scale clinical registries. R-RCTs are characterized by low cost, enhanced generalizability of findings, rapid consecutive enrolment and the high potential for completeness in the follow-up management of participants, especially hard end points^{2,3}. Although R-RCTs retain methodological limitations (for example, a dependence on the quality of the registry) and could face ethical challenges given the differences in national ethical guidelines³, such studies can be designed to efficiently address research questions about comparative effectiveness in real-world settings.

The trials within cohorts (TwICs) design, also referred to as cohort multiple RCT (cmRCT), is another innovative trial design of interest^{4,5}. In oncology RCTs, this design enables the incorporation of methodological advantages, such as high recruitment rates, avoiding disappointment bias, improved generalizability of trial results and improved ethical acceptability when a two-stage informed consent procedure is applied⁶. The implementation of TwICs in nationwide cohorts of patients with cancer brings researchers one step closer to achieving the achievable by using prospective RCT designs together with real-world follow-up data from cancer registries. Recently, several ongoing or completed TwICs have been described^{7–10}. Owing to the brevity of this correspondence piece, we highlight only the Prospective Dutch Colorectal Cancer (PLCRC) cohort, which serves as an infrastructure for a broad body of cancer registry-based research including (but not limited to) aetiological, biomarker, basic and (epi)genetic, interventional (TwICs), and health-care policy and cost-effectiveness studies¹¹. Additionally, tumour biospecimens and repeated population-based patient-reported outcomes (PROs) are collected within

the PLCRC. PROs are enriched follow-up RWD available for TwICs, as well as an important element that enables the implementation of learning health-care systems¹².

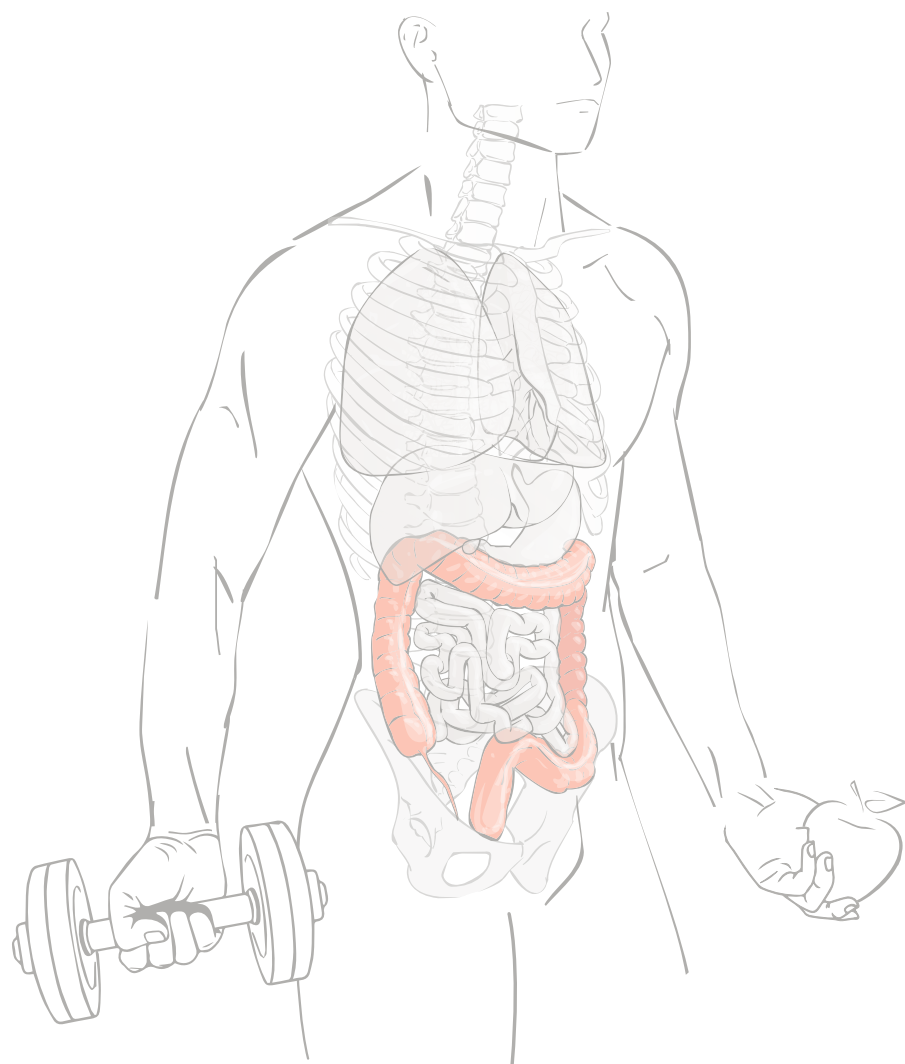
Future logistic developments (such as obtaining the patient's informed consent at hospital entry) will enable a closer integration of medical services into clinical research. Finally, innovations in clinical oncology practice by standardizing nation-wide entry of clinical data in electronic health records (EHRs) and subsequent implementation of electronic data-capture systems, which enable real-time data transfer from EHRs to national cancer registries, will support further improvements in quality and efficiency of RWD and cohort-embedded RCTs.

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PART II

LIFESTYLE FACTORS,
BODY COMPOSITION
AND QUALITY OF LIFE



4

MONITORING POTENTIALLY
MODIFIABLE LIFESTYLE FACTORS IN
CANCER SURVIVORS: A NARRATIVE
REVIEW ON CURRENTLY AVAILABLE
METHODOLOGIES AND INNOVATIONS
FOR LARGE-SCALE SURVEILLANCE

EUROPEAN JOURNAL OF CANCER
2018, VOLUME 103, PAGES 327-340

Abstract

In most European countries, the prevalence of cancer has increased from 1–3% in the 1990's to 4–5% in the 2010's. This increase is largely due to earlier detection and improved treatment. The number of cancer patients who survive longer than 5 years after their primary diagnosis is increasing, emphasizing the need for research in cancer survivors focussing on improving quality of life and cancer prognosis. In this narrative review, we provide an overview of the current and novel methodologies for the ambulant assessment of potentially modifiable lifestyle factors in large-scale prospective studies and discuss future innovations for optimal surveillance of cancer survivors.

Lifestyle factors described are potentially modifiable and include dietary intake, body composition, alcohol consumption, smoking behaviour and physical activity. To date, mostly questionnaires are used, but many monitoring tools are already available that allow ambulant measurements. However, technological improvements are still needed to longitudinally measure lifestyle factors on a large scale from diagnosis onwards.

Measuring lifestyle factors non-invasively in a home setting could help to increase its feasibility and ultimately improve our understanding of the individual and synergistic effects of lifestyle factors on quality of life and long-term outcomes. In the process of developing such surveillance programmes, several aspects should be taken into account including, but not limited to, methodological considerations, study design optimisation, patient perspectives, privacy issues and information and communications technology solutions to capture, store and analyse big data.

Future large-scale lifestyle surveillance studies in cancer survivors will, in addition to questionnaires, increasingly include ambulant monitoring using sensors and wireless tools as this lowers patient burden, provides objective information and facilitates longitudinal data collection.

Introduction

In most European countries, the prevalence of cancer has increased from 1–3% in the 1990's to 4–5% in the 2010's^{1,2}. About 10 million people in Europe have been diagnosed with cancer in the past 5 years³. Owing to the ageing of the population and improvements in early detection, treatment, follow-up and supportive care, the number of cancer survivors (any person diagnosed with cancer from the time of initial diagnosis until the end of life) is growing steeply. More than half of the European cancer patients survive 5 years or longer after their primary diagnosis, leading to more cancer survivors experiencing long-term or latent side-effects as a result of cancer treatment⁴. Besides functional limitations and psychosocial problems related to cancer (treatment), cancer survivors are at an increased risk of second cancers and the occurrence of comorbidities such as diabetes and cardiovascular disease^{5,6}.

In the last decades, evidence is emerging that lifestyle of cancer survivors (a healthy diet⁷, increased physical activity⁸ and as a consequence, a healthy body weight and body composition^{9,10,11}, as well as not smoking¹²) positively influences cancer prognosis. Current evidence for the role of lifestyle after a cancer diagnosis, however, remains inconclusive, partly due to heterogeneity in study populations and assessment methodology and the complexity of lifestyle–disease relationships. Moreover, most studies so far focussed on the most frequently occurring cancers.

To date, recommendations for an optimal lifestyle after diagnosis contributing to prolonged survival and reduced risk of second primary tumours are limited and only available from breast cancer prevention research. The World Cancer Research Fund (WCRF) Continuous Update Project's panel concluded that current evidence is not strong enough to make specific recommendations for cancer survivors¹³. Therefore, it is recommended that cancer survivors should, as far as possible, adhere to the general recommendations for cancer prevention as described by the WCRF Cancer Prevention Recommendations^{14,15} and the European Code against Cancer, 4th Edition (Textbox 1)¹⁶. This is based on the assumption that the cancer patient at least will not suffer but likely benefit from eating a healthy diet, being physically active, maintaining a healthy weight, limited or no alcohol consumption and no (second-hand) smoking or use of other tobacco products. In addition, studies have shown that adherence to these guidelines is associated with lower mortality and better quality of life among cancer survivors^{17,18}.

Textbox 1. Recommendations regarding modifiable factors to reduce cancer risk according to European Code Against Cancer and World Cancer Research Fund.

European Code Against Cancer - 12 ways to reduce your cancer risk
J. Schuz et al. 2015 ¹⁶, and www.cancercode.eu

1. Do not smoke, and do not use any form of tobacco.
2. Make your home smoke free. Support smoke-free policies in your workplace.
3. Take action to be a healthy body weight.
4. Be physically active in everyday life. Limit the time you spend sitting.
5. Have a healthy diet¹.
6. Limit alcohol intake. Not drinking alcohol is better for cancer prevention.
7. Avoid too much sun, especially children. Use sun protection. Do not use sunbeds.
8. In the workplace, protect yourself against cancer-causing substances.
9. Reduce radiation from naturally high radon levels.
10. For women: breastfeed your baby and limit use of hormone replacement therapy.
11. Vaccinate children for Hepatitis B and human papillomavirus.
12. Take part in cancer screening programs.

¹ see reference for further specification

World Cancer Research Fund - Cancer Prevention Recommendations
WCRF/AICR, 2018 ¹⁴, and www.dietandcancerreport.org

1. Be a healthy weight.
2. Be physically active.
3. Eat a diet rich in wholegrains, vegetables, fruit and beans.
4. Limit consumption of 'fast foods' and other processed foods high in fat, starches or sugars.
5. Limit consumption of red and processed meat.
6. Limit consumption of sugar sweetened drinks.
7. Limit alcohol consumption.
8. Do not use supplements for cancer prevention.
9. For mothers: breastfeed your baby, if you can..
10. After a cancer diagnosis: follow our Recommendations, if you can.

To refine our knowledge on the associations between lifestyle factors and cancer outcomes and to create opportunities for interventions aimed at beneficial lifestyle changes, it is important to have optimal large-scale lifestyle surveillance for cancer survivors. The aim of this narrative review is to provide an overview of the current and novel methodologies for the assessment of potentially modifiable lifestyle factors in large-scale prospective studies and discuss future innovations for optimal surveillance of cancer survivors. The primary focus in this review will be on the application of repeated measures in (large-scale) cohort studies consisting of either a fixed or a dynamic population of cancer survivors to follow cancer survivors' lifestyle and health over time and investigate risk relations. Literature for this narrative review has been searched in PubMed, using keywords pertaining to each lifestyle factor in this review. For example, keywords such as current, new, innovative, non-invasive, epidemiological, diet, dietary, nutrition, nutritional, intake, assessment and method were used for the dietary intake section. Recent reviews per lifestyle factor served as basis, and their reference lists were screened for relevant articles. Lifestyle factors described include dietary intake, body composition including body weight, alcohol consumption, smoking behaviour and physical activity, of which an overview is provided in Table 1. We will only focus on ambulant assessments that are feasible to perform on a large scale without the need for the patient to visit a research centre.

Dietary intake, nutritional status and body composition

In the last decade, clinical researchers have become increasingly aware of the impact of diet during and after cancer treatment. Nutritional status (including body weight and body composition) is now often being highlighted as an important factor in cancer prognosis. Adequate assessment of dietary intake and body composition is a challenging field because these variables are highly diverse and multifactorial. Here, we describe commonly used methods for the assessment of dietary intake, body composition and nutritional status and propose approaches to overcome current limitations.

Dietary intake

Design of data collection

Classical methods to determine self-reported dietary intake can be divided into prospective (real-time recording in diaries) and retrospective (recall) methods. Dietary records that suffer less from memory limitations are not often used in large-scale epidemiological studies due to higher costs, time-consuming coding and calculations, higher patient burden, reactivity (changed behaviour due to awareness of measurements) and low compliance¹⁹. Dietary recall methods, although susceptible to recall bias, intentional and unintentional misreporting leading to potential misclassifications^{20,21}, are the most commonly used tools to assess dietary intake. In large-scale epidemiological studies, food frequency questionnaires (FFQs) have been the favoured method to estimate the population's long-term habitual intake, primarily from a cost and logistic point of view. The 24-h dietary recall (24HDR) method has been used for surveys and nutrition surveillance studies to estimate the population's current intake and identify vulnerable subgroups in need of dietary guidance or intervention^{22,23}.

As a result of the valid concerns about the impact of long and extensive surveys on response rates, short FFQs (SFFQs) have been developed to collect dietary information from large populations. SFFQs differ in number of items and type of foods included and are overall rated as a reasonably valid instrument²⁴⁻²⁸.

Finally, also indexes are available to assess the dietary quality, such as the Dutch Healthy Diet index (DHD-index)²⁹. Recently, the DHD-FFQ was developed to be used as a basis for calculating the DHD-index score³⁰. The DHD-index score classifies adherence to the Dutch dietary recommendations as an indication of diet quality³¹.

To date, there is no gold standard method for measuring dietary intake in nutritional epidemiology. The combination of assessment methods can contribute to reducing the measurement error³², for example, combining data from multiple 24HDRs (4–6 measures)³³ or combining short-term dietary intake data from 24HDRs and long-term intake from FFQ data³³. Next to patient-reported dietary assessments, biomarkers also provide information regarding dietary intake and nutritional status. The emerging field of metabolomics might lead to the identification of new metabolites that can potentially be used as biomarkers for dietary intake, metabolism or nutritional status in future cohort studies on diet–disease relationships³⁴. Biomarker analysis does not replace dietary

assessment methods but is intended to be complementary to measure diet intake in large nutritional epidemiologic studies³⁵. However, the use and implementation of biomarkers in nutritional epidemiological studies is beyond the scope of our article.

Usage of new innovative technologies

Novel technologies seem to have potential to improve dietary assessment by reducing patient burden and recall bias. These include existence of web-based applications, mobile phone applications, personal digital assistant technologies, interactive computer-based technologies, camera-based and tape recorder-based technologies and scan- and sensor-based technologies³⁶.

In Europe, several web-based 24HDR tools are developed, of which 'myfood24' (UK) and 'NutriNet Santé' (France) have been extensively described and validated^{37,38}. Compared with interviewer-administered 24HDR, both myfood24 and NutriNet Santé showed strong correlations for energy intake and most nutrients^{39,40}. Furthermore, it was shown that web-based tools are appreciated by the patient and lead to substantial simplification of logistics and cost reduction compared with interview-based assessment, which is beneficial for large-scale surveys⁴⁰. For further simplification of 24HDRs, abbreviated (closed-ended) web-based 24HDRs are developed, for example, the 'short 24-hour food list' and 'the Oxford WebQ'^{41,42}. The use of WebQ in the UK Biobank also showed strong correlations for energy and nutrient intake, compared with interviewer-administered 24HDRs, and proved acceptability for repeated assessments in population-based studies. Whether comparable results can be obtained in cancer survivors remains to be explored.

Nowadays, mobile phones contain several potential features for nutritional research such as built-in cameras, high-speed microprocessors and (wireless) connectivity to external devices and networks via Bluetooth and Wi-Fi. Dietary assessment methods using mobile phones can be categorised into self-reported dietary intake methods (electronic food diary), analysis of food photographs by trained dietitians and automated food photograph or video analysis⁴³. Regarding mobile phone dietary assessment methods, studies have shown high levels of satisfaction and preference. Together with the low research costs from web-based and mobile phone applications through automated coding and calculation of nutrient content, the use of mobile phones seems promising. Implementation of mobile phone photographs still needs to overcome limitations such as problems with photo quality and angle, incompleteness to required photographs and inadequate descriptive information for foods contained within photographs⁴⁴⁻⁴⁶.

Nutritional status and body composition

Cancer survivors often experience malnourishment and/or cancer cachexia, which complicates treatment and negatively affects survival and quality of life ⁴⁷. Multiple screening tools are available and used for quick identification of patients at risk or with malnutrition. The Patient-Generated Subjective Global Assessment (PG-SGA) is an internationally used tool and serves as the reference method to screen and/or monitor nutritional status in patients with cancer. This tool was shown to be accurate at discriminating between well-nourished and malnourished cancer patients ⁴⁸, also in the outpatient oncology setting ⁴⁹. Importantly, the abridged version of the PG-SGA (consisting of weight history, food intake, symptoms and activities and function) can be filled in by the patient and has been proven to be a practical, informative and valid tool for detecting malnutrition and predicting outcomes of cancer cachexia ^{50,51}.

Anthropometric measurements are used in cancer survivor surveillance to determine the relationship between various simple body measurements (e.g. height, weight, waist-hip circumference) and clinical outcomes. Obesity is a well-known risk factor for many cancers, and associations between obesity and survival in patients with cancer are also shown. However, these associations are inconsistent between the types of cancer. For example, obesity (body mass index [BMI] > 30) has been associated with lower breast cancer survival ⁵², while in colorectal cancer, this association is less evident ⁵³. Clearly, BMI does not give enough information on the individual patient as obese patients can vary in body composition and sarcopenic status ^{54,55}. Therefore, recent research has focussed more on tissue quantification, in particular skeletal muscle and adipose tissue.

Design of data collection

Bioelectric impedance analysis (BIA) is an indirect method to analyse body composition, which estimates total body water, fat-free mass (FFM) and fat mass by measuring the resistance of the body as a conductor to a very small alternating electrical current ⁵⁶. Sex-specific BIA prediction equations have been published that show excellent precision and are recommended for use in epidemiologic studies to describe normal levels of body composition ⁵⁷. Body composition can also be measured using techniques that measure body properties, such as density (e.g. hydrodensitometry or the more modern air displacement plethysmography method), or describe amounts and distributions of skeletal, adipose and muscle tissues using ultrasound, dual-energy X-ray absorptiometry, computed tomography or magnetic resonance imaging. All techniques suffer from two types of error:

methodological error when collecting raw data and error in the assumptions by which raw data are converted to final values. The relative magnitude of these errors varies between techniques.

Opportunities from existing technologies

Apart from simple anthropometrics, BIA is the only method that allows measurements from the patient's home as leg-to-leg and arm-to-leg analysis can be implemented in weighing scales. Despite the high interpatient variability, BIA may be a valuable tool to monitor FFM longitudinally, if used under constant conditions ⁵⁸⁻⁶⁰. Even in situations of acute weight loss, leg-to-leg BIA is a highly reproducible, simple and rapid tool for the clinical monitoring of body composition changes ⁶¹.

Implementation of Bluetooth-connected or Wi-Fi-connected scales with built-in BIA to be used at home in large-scale surveillance studies would allow researchers to measure the evolution of body composition and body weight over time. Via Bluetooth and Wi-Fi connectivity, data can be sent to compatible devices as smartphones or computers and subsequently be uploaded to a platform for cloud storage and data analysis. The limitation of commercially available scales is that predefined (usually unknown) algorithms are used to calculate measured values. It is, therefore, recommended to use scales from which raw bioimpedance data can be obtained.

Alcohol consumption

A recent review on the association between alcohol consumption and prognosis after a diagnosis of breast cancer including 29,239 breast cancer patients showed that moderate alcohol consumption after diagnosis is unlikely to have major adverse effect on survival ⁶². Comparable results were found for colorectal cancer patients, although there are suggestions for an association between higher amount (≥ 2 drinks/day) consumers, and an increased risk of colorectal cancer-specific mortality ⁶³. As alcohol is known to be an important health determinant, it is of interest to optimise surveillance techniques to be able to study to which extent the patient changes his/her alcohol consumption after diagnosis and whether this is associated with response to treatment and cancer outcomes. A recent European initiative is the Standardized Measurement of Alcohol-Related Troubles project that aims to develop standardised alcohol use and drinking pattern survey methodology ⁶⁴. Because data on alcohol consumption after cancer diagnosis are

sparse, further confirmation is warranted in large prospective studies collecting detailed information during a long-term follow-up.

Design of data collection

Traditionally, alcohol intake is measured using recall methods. Alcohol consumption questions are incorporated in most FFQs, a method that has shown good relative validity but also has its limitations⁶⁵⁻⁶⁷. A major concern is social desirability, that is, respondents might understate their alcohol use to be represented in a more favourable way⁶⁸. Even though the assessment of social desirability is a common way to control for this self-reporting bias, it remains a limitation of this method.

Besides FFQs, alcohol consumption can also be measured using specifically developed questionnaires. Currently, there are three main approaches for measuring alcohol consumption. First, short-term recall methods that ask participants to recall their alcohol intake of a recent short period of time, such as the previous week. It is assumed that because of the short recall period, participants will correctly remember their consumption. To avoid misqualification of infrequent drinkers, this method should be used in large-scale surveillance studies only⁶⁹. Second, the quantity-frequency (QF) method records both the frequency and quantity of drinking alcohol and allows for volume calculations. Also, extended or adapted versions are available, for example, addition of binge drinking or episodically heavy-drinking questions and a beverage-specific version. The QF method can capture patterns over varying periods, ranging from a week to a year. Third, the graduated frequency method also aims to capture the total drinking volume but is developed in such a way that it systematically examines intake of all alcoholic drinks consumed on occasions. The respondent's drinking frequency is asked for different levels of drinking (number of drinks) in the last year for combined beverage types.

Different survey modes for alcohol consumption research are possible, for example, face-to-face interviews, telephone interviews and self-administered questionnaires (usually paper-based). Comparative studies have shown that mail or self-administered questionnaires yield comparable, if not better quality, data on alcohol consumption than face-to-face or telephone interviews^{70,71}. Despite the development of web-based approaches, which can reduce patient's burden and research costs, this does not improve alcohol consumption estimates⁷². Furthermore, a long reference period, that is, time frame of recall, is needed when associations between alcohol consumption and health outcomes are studied⁷³.

Future applications

In contrast to data acquired using recall methods, more objective measures would provide more valid estimations of alcohol consumption. Breath or blood alcohol concentrations (BACs) can objectively measure alcohol consumption but only provide indices of very recent consumption, given the rapid metabolism and early BAC peaks⁷⁴. A method that allows for long-term objective and continuous measurement of both the frequency and the quantity of alcohol consumption is transdermal alcohol sensors. This non-invasive tool provides valuable objective data about alcohol. Several transdermal alcohol sensors are described in research settings, but two devices are developed to detect transdermal alcohol concentrations (TACs) in human, the Secure Continuous Remote Alcohol Monitor (Alcohol Monitoring Systems, Inc., Littleton, CO) and the Wrist Transdermal Alcohol Sensor (Giner, Inc., Newton, MA)⁷⁵. Both devices use an electrochemical sensor that detects ethanol vapour near the skin, allowing blood alcohol levels to be indirectly estimated. Limitations of these biomonitoring devices are the relatively high cost, their size and the quality of the devices, and their TAC readouts need to be improved before it can be implemented in larger studies⁷⁶.

Although even further from being applied in epidemiologic studies, researchers recently developed a microneedle sensor that allows continuous minimally invasive alcohol monitoring⁷⁷. This sensor can be worn on the skin and measures subcutaneous alcohol levels via low-cost micron-sized microneedles⁷⁷. It penetrates through the epidermis to access the interstitial fluid (ISF) with negligible damage or pain⁷⁸. To date, these microneedle sensors are only tested in ex-vivo mice skin models with artificial ISF, where a wide alcohol detection range and high sensitivity ($r = 0.98$) were reached⁷⁷. Once this device is further developed, it has huge potential for real-time remote alcohol monitoring and can potentially be used in future large-scale studies, while avoiding self-reporting and eliminating blood sampling complications.

Table 1. Overview of current methods that can be used ambulatory to measure lifestyle-related risk factors in large-scale prospective studies, and new innovative methods that are currently used or have potential for future ambulant use.

Lifestyle-related risk factor	Current methods	New innovative methods
Dietary intake	Food Frequency Questionnaires (FFQ)	Web-based applications
	24-Hour dietary recalls (24HDR)	Mobile phone applications
	Dietary records	PDA applications
	Biomarker analysis	Interactive computer-based technologies
		Camera- and tape-recorder-based technologies
Body composition		Scan- and sensor-based technologies
	Anthropometric measures	Bluetooth- or WiFi-connected scales with built-in BIA
Alcohol consumption	Bioelectric impedance analysis (BIA)	
	Incorporated in FFQs	Transdermal alcohol sensors
Smoking behavior	Short-term recall	Microneedle sensors
	Quantity-frequency (QF) method	
	Graduated frequency (GF) method	
	Tobacco use Questionnaires (TUQ)	Cotinine-levels in dried blood spots
Physical activity	Biomarker analysis	Wearable sensors
	Physical activity Questionnaires (PAQ)	Wearable physical activity trackers
	Pedometers	Multi-sensor patches (biosensors)
	Accelerometers	

PDA, personal digital assistant.

Smoking behavior

Continued smoking after a cancer diagnosis increases the risk of second primary tumours, cancer recurrence and cancer-specific mortality ⁷⁹⁻⁸¹. Furthermore, smoking decreases the effectiveness of cancer treatment and increases cancer treatment toxicity for almost every cancer site and treatment regimens ⁸²⁻⁸⁴. Despite this, a substantial proportion of cancer survivors continue to smoke after diagnosis ⁸⁵⁻⁸⁷.

Design of data collection

Measuring tobacco use in cancer patients comes with several limitations. First of all, most of the current evidence is based on cigarette smoking, whereas there is a growing variety of tobacco- and nicotine-containing products ^{88,89}. Second, as smoking behaviour is highly addictive and relapses can be expected, repeated measures are needed to capture the behaviour over time.

To date, postdiagnostic longitudinal data on smoking patterns of cancer survivors are sparse, and future epidemiological studies in cancer turing the smoking behaviour. The National Cancer Institute and American Association for Cancer Research Cancer Patient Tobacco Use Assessment Task Force also recognised this research priority and has recently developed and published a Cancer Patient Tobacco Use Questionnaire (C-TUQ) ⁹⁰. This questionnaire is developed for cancer patients and survivors, consisting of a ‘core’ set to be used routinely in cancer care and an ‘extension’ set to provide more detailed information ⁹⁰. The C-TUQ is currently available in English and Spanish, but future work will provide translations into other languages. Based on the core set, pack-years (i.e. the number of cigarette packs smoked per day multiplied by the number of years smoking) can be calculated.

While nicotine - the main constituent of tobacco - has a biological half-life of 0.5-3 h, its primary metabolite, cotinine, has a biological half-life of 15-20 h. Thus, cotinine is the preferred biomarker for estimating tobacco smoke exposure in blood samples ⁹¹⁻⁹³. Recently, a comprehensive overview of cotinine cut-off values was published to distinguish smokers from passive or non-smokers ⁹⁴. Saliva, urine and blood cotinine levels are used to validate self-reported smoking status and/or compute corrected smoking prevalence rates ⁹⁵.

Future applications in research

For exposure to tobacco smoke, a new validated and highly sensitive method has recently been described to measure cotinine levels in dried blood spot (DBS) samples ⁹¹. These DBS samples are blood drops from a simple heel or finger prick, collected and dried on a paper card. It is even suggested that whole blood, as collected by DBS samples, may provide a better estimate of tobacco smoke exposure than plasma or serum. Using DBS samples is a simple, high-throughput and minimally invasive method that can be applied in large epidemiological studies to measure tobacco exposure but should always be used complementary to self-reported data that recall over a longer reference period.

Another tool to measure smoking behaviour is wearable sensors, such as the Personal Automatic Cigarette Tracker (PACT) ⁹⁶. The PACT is developed to record smoke inhalation by continuously monitoring breathing patterns and hand-to-mouth gestures. Besides the PACT, several other methods and modelling techniques have been described ^{97,98}. These wearable systems can potentially be applied to monitor smoking behaviour but are currently still under development ⁹⁹.

Physical activity

In breast and colorectal cancer survivors, positive associations are shown between physical activity and survival⁸. Furthermore, it is also shown that physically active breast cancer survivors have a reduced risk of recurrences¹⁰⁰. In addition, randomised controlled trials (RCTs) in cancer survivors show beneficial effects of physical exercise on body composition, physical fitness, quality of life, anxiety and self-esteem¹⁰¹.

Design of data collection

Main types of physical activity include occupational, household, transportation and recreational physical activity. Of these types, the frequency, intensity and duration of physical activity need to be measured to estimate the dose of physical activity¹⁰². The absolute intensity is the rate of energy expenditure and is usually expressed as the metabolic equivalent of task (MET). Activities are categorised into light-, moderate- and vigorous-intensity activities with corresponding MET values of 1.6–2.9, 3.0–5.9 and ≥ 6 METs, respectively. METs between 1.0 and 1.5 represent sedentary behaviours¹⁰².

Surveillance of physical activity in populations is most often undertaken using questionnaires as these are relatively inexpensive and easy to administer compared with objective measurement techniques. A widely used tool is the International Physical Activity Questionnaire that is developed and validated to monitor health-related physical (in)activity across countries¹⁰³. In addition, for every country, specifically designed and validated physical activity questionnaires (PAQs) are available usually for multiple reference periods, for example, past week, past month or past year. The main disadvantage of subjective methods is impaired reporting quality and recall-related issues, which limits the validity of the measurement and could lead to misinterpretation of the true effect of physical activity on cancer. The use of objective measurement methods, such as pedometers or accelerometers, can reduce misclassification of physical activity levels. For population-based surveillance of physical activity, the use of accelerometers in addition to PAQs is recommended^{104,105}. From previous research with repeated physical activity measurements in patients with colorectal cancer, it was shown that measuring for 3 valid days is sufficient for an accurate assessment of physical activity¹⁰⁶.

Future applications in research

Recent developments in wearable technologies have provided researchers the opportunity to collect real-time, objective physical activity data. Several technologies are available, such

as smart watches, fitness bands and jewellery-like accessories that record physical activity patterns. These wearables create new opportunities as they can be worn continuously and are used together with a tablet/smartphone application or website to collect and store data.

There is an abundance of consumer-based physical activity monitors available. In a recent validation study, four commonly used consumer-based physical activity monitors (Fitbit One, Fitbit Zip, Fitbit Flex, and Jawbone UP24) were compared with a research-grade accelerometer (ActiGraph GT3X+)¹⁰⁷. It was concluded that consumer monitors underestimate, but are equally accurate as the ActiGraph for step count, energy expenditure and active minutes, which is in line with other studies^{108–111}. Together with their ease of use, low-cost and real-time data collection, consumer monitors could be used for monitoring long-term physical activity behaviour in large-scale studies. Built-in GPS functionality could, together with heart rate measurements, provide a more comprehensive understanding of the type of activity performed.

One of the limitations of regular accelerometers and physical activity monitors is that they can be forgotten by the patient, which leads to missing data. The development of integrated multisensor patches (biosensors) that can be applied to the skin has led to the ability to measure physical activity patterns for multiple days, without actively wearing a noticeable device. There are several clinically oriented and research-oriented biosensors available that monitor a broad range of vital signs, including single-lead electrocardiography, heart rate, heart rate variability, respiratory rate, skin temperature, body posture, fall detection and physical activity (step count). Body posture monitoring is especially useful in discriminating among standing, sitting and lying down. So far, the battery capacity is limited to 36–96 h, but physical activity monitoring for 3 consecutive days is sufficient to accurately measure physical activity¹⁰⁶.

Previously described physical activity monitors and patches mainly monitor behaviour and vital signs, whereas in some situations, it can be desirable to collect more information on the patient's physiological state. For this reason, a wearable flexible integrated sensing array was developed for *in situ* perspiration analysis¹¹². This wearable sensor enables non-invasive monitoring of human sweat and is a powerful tool to advance large-scale studies, where physiological biomarkers of physical activity are of interest. Data from the sensor are sent wirelessly to a Bluetooth-enabled mobile handset that contains an application for uploading data to cloud servers.

Discussion

The growing awareness of the role of a healthy lifestyle after a cancer diagnosis asks for detailed knowledge on lifestyle–disease relationships to provide recommendations. In this narrative review, we described the current and novel methodologies for ambulant large-scale monitoring of potentially modifiable lifestyle factors in cancer survivors from the moment of diagnosis onwards. Even though the described methods can be used in many research settings, the primary focus within this population should be on (large-scale) cohort studies following cancer survivors' lifestyle and health over time to investigate the risk relations. Once established, population surveys can be conducted to monitor and evaluate population risk and health behaviour without the need of continuous follow-up.

Despite the presence of many tools that allow (objective) ambulant measurements of the discussed lifestyle factors, improvements are highly warranted to ascertain their applicability on a large scale. Novel tools that incorporate these improvements are under development. Furthermore, we want to highlight the importance of standardisation of data collection and processing methods to perform between-study comparisons or international pooling projects.

Methodological considerations

It is widely known that in prospective cohort studies, the relatively 'better' patients are recruited and/or respond to follow-up assessments, compared with the source population^{113,114}. To minimise this so called 'healthy volunteer effect', research groups should create an optimal research infrastructure during the early phase of designing the study. For example, at the department of radiation oncology of the University Medical Center Utrecht, research-specific consultations are planned with every patient 30 min before their first appointment with the radiation oncologist. During this consultation, the patient is offered any study that the patient is eligible for. The Utrecht cohort for multiple breast cancer intervention studies and long-term evaluation (UMBRELLA) makes use of this infrastructure and has thereby shown that it is feasible to have a high percentage (88% in UMBRELLA) of eligible patients sign for consent¹¹⁵. In addition, when patients are recruited around diagnosis, there will not be selection based on treatment outcomes and/or inclusion of patients who have a relative long survival. However, the bias caused by the fact that 'better' patients typically have a more complete and/or longer follow-up cannot be avoided, and needs to be taken into account in the phase of data analysis and interpretation.

Second, most researchers focus in their studies on individual lifestyle factors. To get a better understanding of the synergistic effect of multiple lifestyle factors on cancer prognosis, researchers should focus on studying the combined effects. Because there is insufficient knowledge on the evolution of (combined) lifestyle factors after cancer diagnosis and the associations with cancer outcomes, repeated measures over time are needed. The frequency of measurement mainly depends on the factor of interest and the patient's phase in the cancer trajectory, with increased frequencies in periods with major changes, for example, during treatment. Additionally, the concept of lifetime exposure should be considered when designing new cohort studies, so that data on habitual behaviour before diagnosis are available. In studies starting at the point of cancer diagnosis, only retrospective information can be collected, which is prone to recall bias. Ideally, prospective cohort studies with repeated lifestyle assessments in healthy populations convert to cancer survivor cohorts from a cancer diagnosis onwards to include precancer factors that may influence prognosis. Finally, owing to the increasing prevalence of comorbidities in cancer patients and its influence on cancer outcomes such as overall survival and quality of life, it is highly recommended to capture comorbidities in the study population^{116–118}.

So far, most evidence on the association between lifestyle and cancer prognosis is based on observational studies. As a next step, to establish causality as a basis for future recommendations, randomised intervention studies into the effect of lifestyle changes are of importance. However, in RCTs, investigating the effects of lifestyle interventions is challenging because, usually, group allocation could not be blinded, leading to contamination, drop out or disappointment bias¹¹⁹. A promising alternative is the cohort multiple RCT (cmRCT), of which the design has been described elsewhere^{120,121}. In brief, patients who enter an observational cohort are asked to provide 'broad consent for randomisation'¹²². Hereby, patients give permission for being offered an experimental (yet unknown) future intervention. When initial informed consent (first stage) for collecting observational lifestyle and medical data and future cmRCT is obtained shortly after diagnosis, interventions can be offered anytime during follow-up. Patients can accept the offered intervention (by second-stage informed consent) or refuse, whereas controls are not informed and are not offered the intervention. Regular cohort follow-up measures are used as outcome variables. The feasibility of the cmRCT design in exercise-oncology research is currently investigated within the Dutch UMBRELLA cohort¹²³.

Big data

Extended lifestyle monitoring including multiple measurements in cancer survivors at multiple time points during the cancer continuum in a home setting results in a large amount of various data. For the analysis of these data from different sources, with different formats, volumes and velocities of collection, integrated information and communications technology (ICT) platforms are needed. These platforms should capture and store big data including, but not limited to clinical variables, patient-reported outcomes, imaging, physical activity patterns and body composition data, combined with electronic case report forms. The 'Patient Reported Outcomes Following Initial treatment and Long term Evaluation of Survivorship' (PROFILES) registry is such a platform initiated to study the physical and psychosocial impact of cancer and its treatment from a dynamic, growing population-based cohort of both short- and long-term cancer survivors ¹²⁴. The PROFILES also includes a large web-based questionnaire component and is directly linked to clinical data from the Netherlands Cancer Registry. To successfully initiate and continue a web-based registry such as PROFILES, it is important to start with a few dedicated doctors in a few hospitals. Ensuring that the logistics will completely be managed by a team of research assistants will positively affect the willingness of busy clinicians to participate. Furthermore, it is recommended to first set up a limited data collection. The PROFILES started with questionnaires about quality of life, fatigue, depression and so forth but has recently broadened its data collection to include blood sampling, body composition, dietary information and physiological parameters as recorded by a biosensor. Other factors for success are a high penetration rate of internet access and efforts to enhance patient participation and response, for example, a digital newsletter, an up-to-date website, a help desk and reminder letters. When data collection runs smoothly, the number of hospitals and/or data can be expanded leading to simultaneous growth of the infrastructure. The PROFILES data are shared within the scientific community for free at www.profilesregistry.nl. It is important that these big databases are processed in a proper manner. To improve European harmonisation of big data in health research, recommendations for a European action plan have recently been published ¹²⁵. In addition, algorithms need to be developed and become publicly available to analyse the combined data.

Patient perspectives and privacy issues

A considerable point of attention is the privacy aspect of closely monitoring of patients. Per May 2018, new privacy legislation called the General Data Protection Regulation (GDPR) will be implemented throughout the European Union ¹²⁶. This legislation focusses on improved data protection and rights of those from whom data are collected. Improved privacy legislation will reassure patients that their data are stored and processed safely.

There are specific exceptions for (medical) research. Provided that appropriate technical and organisational measures have been taken, the implementation of certain rights of those involved may be waived, if required for the type of research (Art. 89, GDPR). These exceptions will be regulated per member state, on a national level. In addition, the importance of the possibility of linking data from registers for research purposes is recognised (Recital 156, GDPR). As a result of the research-specific exceptions and possibilities of data linking, it is expected that this type of research will not be impeded and that patients do not become more hesitant to provide informed consent. Further elaboration is beyond the scope of this article.

Another point of concern is the willingness of patients to be closely monitored. From a patient's perspective, it might be undesirable to contribute to long-term surveillance, given the constant reminder of the disease and the desire to live a normal life. Communication on the procedures and optimal integration of measurements into a patient's daily life during surveillance is crucial. In our opinion, future large-scale lifestyle surveillance studies should, therefore, be designed in close collaboration with cancer survivors and attention should be paid to incorporate facilitators for long-term retention. However, recent trends show that patients increasingly start tracking their own lifestyle and health status, with wearables such as physical activity trackers or BIA-containing weighing scales. In a movement such as 'the Quantified Self', people aim to improve self-knowledge through self-tracking using current technologies ¹²⁷. Although currently not applicable, these new and upcoming initiatives hold potential to be integrated in future lifestyle research. This trend also suggests that patients would prefer to receive feedback about their outcomes ¹²⁸. Although provision of feedback may methodologically interfere with the observational aims of cohort studies, it seems unethical not to do so. Insight into their own health may stimulate patients' long-term participation in longitudinal cohort studies.

To conclude, future large-scale surveillance of potentially modifiable lifestyle factors in cancer survivors will, in addition to questionnaires, increasingly include ambulant monitoring using sensors and wireless tools as this lowers patient burden, provides objective information and facilitates longitudinal data collection. Although multiple methodologies are already available, integration and technical improvements will allow easier usage of monitoring tools for lifestyle surveillance in large epidemiological studies.

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Physical Activity Section

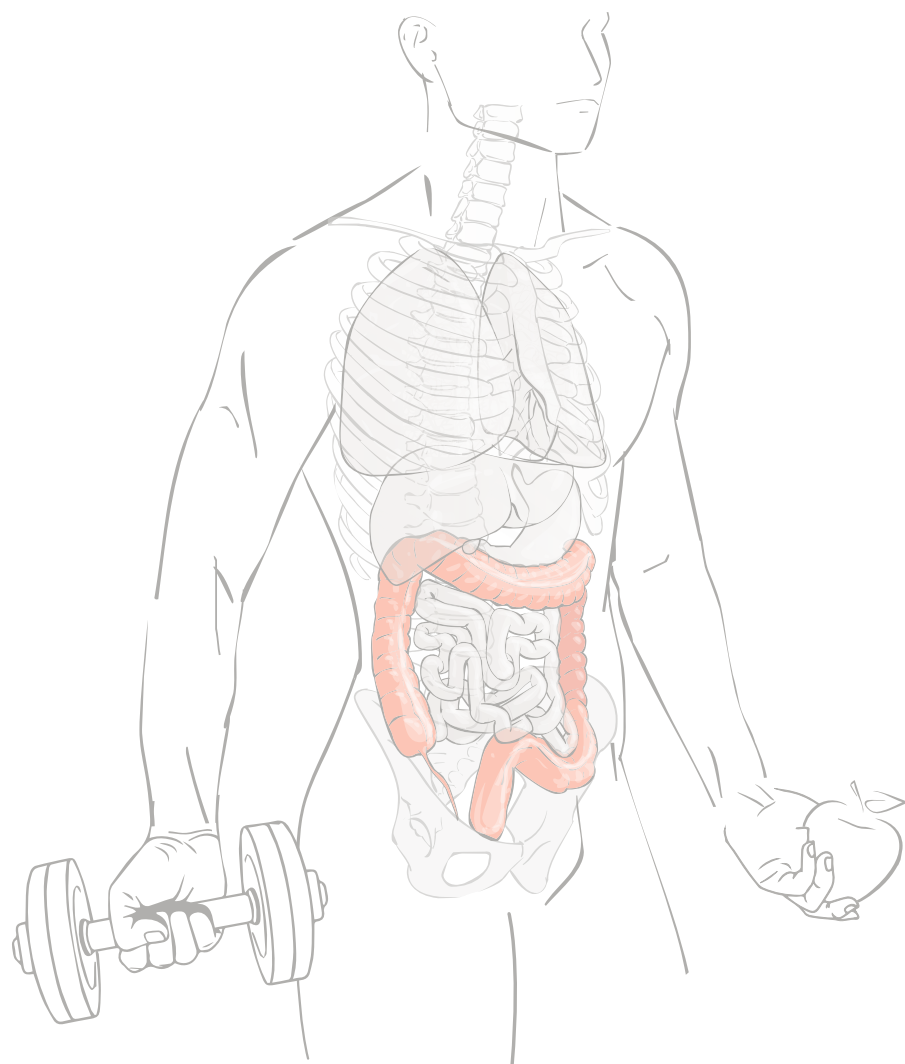
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5

THE ASSOCIATION BETWEEN
CHANGES IN MUSCLE MASS AND
QUALITY OF LIFE IN PATIENTS
WITH METASTATIC COLORECTAL
CANCER

JOURNAL OF CACHEXIA,
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Abstract

Background

Skeletal muscle mass (SMM) loss is common in metastatic colorectal cancer (mCRC) patients and associated with poor clinical outcomes, including increased treatment-related toxicities and reduced survival. Muscle loss may contribute to reduced health-related quality of life (HRQoL), including fatigue. Our aim was to study associations between changes in SMM and concomitant changes in patient-reported HRQoL.

Methods

This was a secondary analysis of mCRC patients in the CAIRO3 randomized clinical trial who were - after initial treatment - randomized between maintenance treatment with capecitabine plus bevacizumab (CAP-B) and observation until first disease progression (PD1). Included patients had computed tomography images for SMM quantification, together with HRQoL assessments available at randomization and PD1. Changes in SMM (categorized as >2% loss, stable, and >2% gain) and HRQoL were computed between randomization and PD1. Changes in HRQoL score >10 points were considered clinically relevant. Associations between SMM and HRQoL changes were studied by multiple linear regression models. We also investigated whether associations differed by treatment arm for global health and the 13 other HRQoL subscales.

Results

Of 221 patients included (mean age 63.5 ± 8.4 years), 24% lost, 27% remained stable, and 49% gained SMM. At randomization, mean global health status was 73.5 ± 15.9 in the CAP-B arm and 75.1 ± 17.5 in the observation arm ($P = 0.48$). A stable or gain in SMM was significantly associated with a clinically relevant improvement in global health status (9.9 and 14.7 points, respectively), compared with patients who lost SMM. From the subscales that did not show significant differences between the two treatment arms, we found significant and clinically relevant associations for stable or gain in SMM with improved role functioning (12.0 and 17.9, respectively) and with less fatigue (-10.0 and -15.0, respectively) and pain (-16.3 for SMM gain). From the subscales that did show significantly different associations with SMM between the two treatment arms, we only found significant results in the observation arm. Here, associations were found for stable or gain in SMM with clinically relevant improved physical (12.4 for SMM gain), cognitive (10.7 and 9.7, respectively), and social functioning (15.5 and 15.6, respectively) as well as reduced appetite loss (-28.5 and -30.7, respectively).

Conclusions

In mCRC, SMM preservation during CAP-B and observation treatment is associated with significant and clinically relevant improvements in global health status and multiple functional and symptom scales. Studies are warranted to investigate whether interventions targeting SMM lead to improved HRQoL, fewer symptoms, and better functioning.

Background

In approximately 20% of the patients with colorectal cancer, metastases are present at diagnosis, and another 20% of patients will eventually develop metachronous metastases^{1,2}. For the treatment of unresectable metastatic colorectal cancer (mCRC), chemotherapy, radiation therapy, and biologically targeted therapies may be given alone or in combination to relieve symptoms and prolong survival. During these treatments, clinicians aim to minimize patients' side effects to maintain physical functioning and quality of life. In research, quality of life is often assessed and expressed as health-related quality of life (HRQoL), which focuses on the impact of (physical or mental) health on a person's ability to live a fulfilling life. Extensive knowledge on potentially modifiable factors related to HRQoL during palliative systemic therapy can contribute to the development of strategies that potentially have a positive influence on HRQoL. This is especially important given the slow but steady improvements in median survival of patients with mCRC³.

Advanced cancer is associated with metabolic reprogramming and reduced food intake, which are two main drivers of cancer-associated cachexia. This phenomenon is characterized by an ongoing loss of skeletal muscle mass (SMM), independent of fat mass, that cannot be reversed by conventional nutritional support and leads to functional impairment³⁻⁵. The presence of cancer-associated cachexia in conjunction with often low levels of physical activity can enhance the ongoing loss of muscle mass. In patients with mCRC, malnutrition and SMM loss are highly prevalent^{6,7}. In the oncology setting, the analysis of routine computed tomography (CT) images is the preferred method to measure SMM and its changes over time⁸. Based on this approach, cross-sectional studies indicate that low SMM (sarcopenia) at start of treatment is associated with poor outcomes of systemic treatment in various cancers, including mCRC^{6,9,10}. Furthermore, SMM loss is associated with poor outcomes including reduced overall survival, increased treatment-related toxicities, and progressive functional impairment^{4,11-14}. This is in line with our previous findings from the same population used for the current analysis, because we observed that during capecitabine plus bevacizumab (CAP-B) treatment and observation, mCRC patients had the ability to gain muscle mass¹⁵. We also found that muscle loss occurring during CAP-B treatment and observation was associated with reduced survival¹⁶ and with increased treatment-related toxicities¹⁷. Additionally, loss of SMM may influence muscle function, possibly leads to loss of strength and increased disability, and thus potentially affect HRQoL.

Few studies have investigated the relation between SMM and HRQoL in cancer patients¹⁸⁻²². Three previous cross-sectional studies in patients with advanced cancer showed that higher levels of SMM at diagnosis or before start of palliative chemotherapy were associated with less cancer-related fatigue and better physical functioning, role functioning, and global quality of life¹⁸⁻²⁰. In a small cross-sectional study with stage IV CRC patients, low SMM before start of chemotherapy was negatively associated with physical functioning, but not with other HRQoL outcomes²¹. Another recent study in stage I–III CRC survivors found no significant associations between SMM at diagnosis and long-term HRQoL outcomes²². Although disease progression and oncologic treatment likely impact both SMM change^{14,15} and HRQoL²³, none of the studies investigated longitudinal changes in muscle mass and the association with HRQoL changes during systemic treatment for mCRC. Therefore, our objective was to investigate whether changes in SMM are associated with concomitant changes in HRQoL in mCRC patients, and we hypothesized that maintenance or gain of SMM during either CAP-B and observation treatment is associated with an improvement in HRQoL.

Methods

The current analysis is a post hoc secondary analysis from the CAIRO3 study, a phase III randomized controlled trial of the Dutch Colorectal Cancer Group that investigated the effect of maintenance treatment with CAP-B versus observation in previously untreated mCRC patients who achieved stable disease or better (i.e. partial or complete response) after six cycles of initial treatment with capecitabine, oxaliplatin, and bevacizumab (CAPOX-B)²⁴. Main inclusion criteria were histological proof of colorectal cancer, unresectable metastatic disease, and World Health Organization performance status 0 or 1. On first progression of disease (defined as PD1), patients in both groups were to receive CAPOX-B reintroduction until second progression, which was the study’s primary endpoint. The CAIRO3 study was approved by the Committee on Human-Related Research Arnhem-Nijmegen and by the local institutional review boards. CAIRO3 is registered with ClinicalTrials.gov number NCT00442637. Written informed consent was obtained from all participants, and research was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Patients

Of the total 558 randomized CAIRO3 patients, 221 patients were analysed, of whom both HRQoL and SMM data were available at randomization and PD1 (Figure 1).

Figure 1.

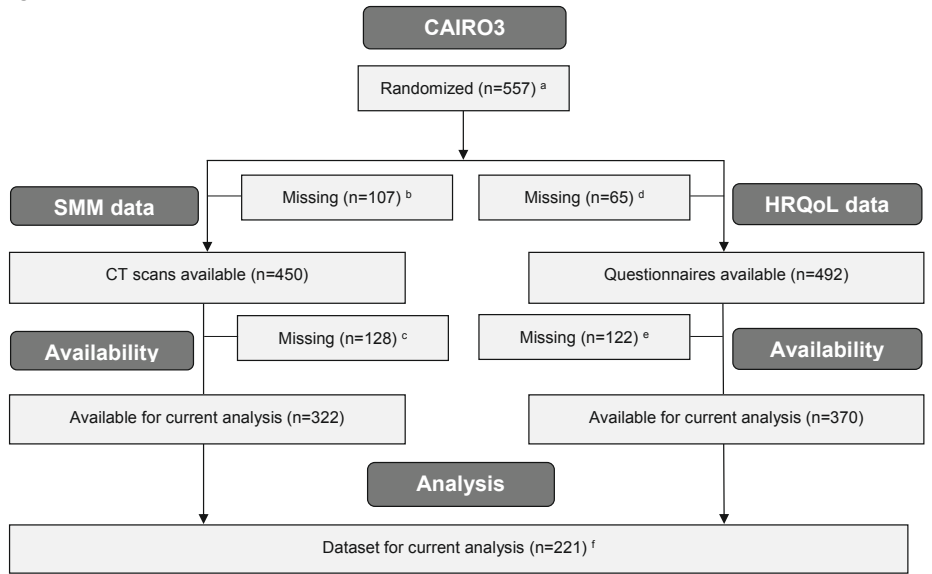


Fig. 1. Flow diagram of the selection of individuals for the current analyses. ^a One participating patient revoked informed consent. ^b No CT scans available from nine participating hospitals, due to logistic reasons. ^c No CT scan at randomization and/or PD1 {reasons: non-evaluable, i.e. incomplete depiction of skeletal muscle at L3, stoma through muscle layer at L3, scan of insufficient quality [n = 114 (89%)] or patient did not reach PD1 yet [n = 10 (8%)] or patient deceased before CT was made [n = 4 (3%)]}. ^d Reason: questionnaires not sufficiently completed. ^e Reasons for no data at PD1: no more questionnaires returned after baseline, patient did not reach PD1 yet, or unknown. ^f The final dataset is based on combined SMM and HRQoL data (n = 322 and n = 370, respectively) and contains data from 221 patients, as the available SMM and HRQoL data do not necessarily include the same patients. CT, computed tomography; HRQoL, health-related quality of life; L3, third lumbar vertebra; PD1, first progression of disease; SMM, skeletal muscle mass.

Measurements

Data were prospectively collected from patients at each medical visit either as part of their routine medical care or for study purposes. Data managers of The Netherlands Comprehensive Cancer Organisation (IKNL) extracted the data from medical records and also performed data monitoring.

Health-related quality of life

In CAIRO3, HRQoL was measured using the validated European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30, version 3.0)^{25,26} to assess differences over time, between, and within study groups. This questionnaire is used to evaluate patients’ global health, daily functioning, and

complaints of common symptoms. A detailed description of HRQoL scales from the EORTC QLQ-C30 can be found in Supporting Information, *Table S3*. Patients were asked to complete the questionnaire at randomization, and every 9 weeks post-randomization until PD1. For this analysis, we used 14 HRQoL scores from the EORTC QLQ-C30, including global health status (score composed of two items, both with a 7-point ordinal scale ranging from 'very poor' to 'excellent'). Five functional scales (physical, role, emotional, cognitive, and social functioning: five, two, four, two, and two items, respectively), three multi-item symptom scales (fatigue, nausea and vomiting, and pain: three, two, and two items, respectively), and five single-item symptom scales (dyspnoea, insomnia, appetite loss, constipation, and diarrhoea) all use a 4-point ordinal scale ranging from 'not at all' to 'very much'. Raw scores for multi-item scales were calculated by taking the average of the contributing items. Linear transformation was used to standardize the raw scores to scores ranging from 0 to 100, where a higher score represents a higher ('better') level of functioning or a higher ('worse') level of symptoms²⁷. Changes of 10 points or more are considered to be clinically relevant²⁸ and as such, perceptible to patients.

Skeletal muscle

Computed tomography scans were routinely made every 9 weeks (every three cycles) or at any time when disease progression was suspected based on clinical symptoms until the end of the study to evaluate disease progression according to RECIST criteria²⁹. Using CT images acquired during routine care is a precise approach to quantify specific tissues and to predict whole body composition³⁰. For the current analysis, we used CT scans at the time of CAIRO3 randomization and at the time of PD1 to quantify the change in muscle mass from start to end of maintenance and observation treatment. A single slice was selected to measure the skeletal muscle area (SMA; in cm²) by using the third lumbar vertebra (L3) as a landmark, because of its high correlation with whole body muscle mass^{30,31}. SMA at L3 consists of the entire cross-sectional area of skeletal muscle (i.e. musculus rectus abdominis, transversus, obliquus internus, obliquus externus, psoas major en minor, erector spinae, and quadratus lumborum) and was measured by a trained and blinded researcher (S.A.K.) using Slice-O-Matic software (version 5.0; Tomovision, Magog, Quebec, Canada). The second scan of each patient was aligned to the first scan using a rigid fusion method to reduce measurement error due to variation in positioning of patients during the consecutive CT scans, as described in detail elsewhere¹⁵. For tissue demarcation, predetermined thresholds of Hounsfield unit ranging from -29 to +150 HU for muscle tissue were applied^{32,33}. A random sample of 140 slices was analysed twice by the same researcher and another time by a second trained researcher (J.W.G.D.), during which both

analysts were blinded for patient study ID and the outcome of the first measurement. Mean coefficients of variation were 1.7% and 1.2% for inter-observer and intra-observer variation, respectively, which are consistent with published data³⁴. To estimate total body SMM, generally accepted regression equations were used³¹:

$$\begin{aligned}\text{Skeletal Muscle Volume (L)} &= 0.166 \text{ L/cm}^2 \times \text{Skeletal Muscle Area in cm}^2 + 2.142 \text{ L} \\ \text{Skeletal Muscle Mass (kg)} &= \text{Skeletal Muscle Volume (L)} \times 1.06 \text{ g/cm}^3\end{aligned}$$

Percentages of SMM change between randomization and PD1 were calculated. A measurement error of 2% was adopted based on previously reported accuracy of CT for SMM analysis³⁰. Therefore, changes in SMM were categorized into SMM loss (>2% loss), SMM stable (≤2% loss–≤2% gain), or SMM gain (>2% gain).

Statistical methods

Descriptive statistics (mean with standard deviation, or median and interquartile range, as appropriate) were used to describe patient characteristics. Paired samples *t*-tests were used to study the HRQoL and SMM changes. To test whether demographic and clinical patient characteristics were different between CAIRO3 patients included in the present analyses vs. those who were not included, we used the independent samples *t*-test, χ^2 test, or Kruskal–Wallis test, as appropriate. After checking the model assumptions, multivariable linear regression analyses were used to assess the association between categorized change in SMM [loss (>2%), stable (≤2% loss–≤2% gain), and gain (>2%)] and concomitant change in HRQoL scales. Multivariable regression analyses were adjusted for the potential confounders' age (years), sex (male vs. female), treatment arm (observation vs. CAP-B), World Health Organization performance status (0 vs. 1), time from randomization to PD1 (days), abnormal serum lactate dehydrogenase level at randomization (LDH; no vs. yes), previous adjuvant chemotherapy (no vs. yes), best response to initial treatment with CAPOX-B (partial or complete response vs. stable disease), and hospital (number). From these models, we report the beta coefficients of the SMM change and corresponding 95% confidence intervals (CIs) for each HRQoL scale.

To investigate whether the association between SMM and HRQoL differed between treatment arms, we tested the interaction terms 'SMM change category multiplied by treatment arm' for global health status and all 13 other HRQoL subscales. We performed and present analyses stratified according to treatment arm when the interaction term was statistically significant. Akaike's Information Criteria (AIC)³⁵ with small sample adjustment

(AICc)³⁶ was used to compare models in terms of their relative goodness of fit (using Occam’s razor principle)³⁷. All *P*-values were two-sided, and interpretation of the 95% CI was used to determine statistical significance (significance level 0.05). Statistical analyses were performed using SPSS (version 24.0; SPSS, Chicago, IL).

Results

Patient characteristics

From the CAIRO3 study (*n* = 557), a subgroup of 221 patients were included in the current analysis. Patients in this analysis did not differ from patients that were not included (i.e. no CT scan or HRQoL data available), in terms of demographic and clinical patient characteristics (*P* > 0.05). The flow diagram in *Figure 1* shows the number of participants reporting HRQoL at baseline and at PD1, as well as the availability of CT scans [reasons for no CT scan: non-evaluable (89%), patient did not reach PD1 yet (8%), and patient deceased before CT was made (3%)]. Demographic and clinical characteristics of the patients are summarized in *Table 1*. The mean age was 63.5 ± 8.4 years, 64% of the patients were men, and 47% received maintenance treatment (CAP-B). The median follow-up time (time from randomization to PD1) was 10.6 months (interquartile range: 4.2 to 17.0) in the maintenance group and 4.3 months (interquartile range: 3.1 to 6.5) in the observation group.

Descriptive statistics on skeletal muscle mass and health-related quality of life

In the total group, 24% of patients lost, 27% remained stable, and 49% gained SMM (*Table 1*). On average, patients in the maintenance and observation arm gained 0.4 kg (95% CI: 0.0 to 0.8 kg) and 0.5 kg (95% CI: 0.3 to 0.8 kg) SMM, respectively. Mean global health status at randomization was 73.5 ± 15.9 for patients in the maintenance arm and 75.1 ± 17.5 for patients in the observation arm (*P* = 0.48). Other mean HRQoL scores at randomization were also comparable between both arms (Supporting Information, *Table S1*), except for patients in the maintenance arm who reported slightly higher levels of appetite loss at randomization as compared with patients in the observation arm (17.2 ± 25.5 and 10.6 ± 20.4, respectively). We did not observe relevant differences in changes of HRQoL scores from randomization to PD1 between treatment arms (Supporting Information, *Table S1*).

Table 1. Demographic and clinical patient characteristics.

Characteristics	All analyzed patients <i>n</i> (%)	>2% loss SMM <i>n</i> (%)	Stable (≤2% loss - ≤2% gain) SMM <i>n</i> (%)	>2% gain SMM <i>n</i> (%)
Number of patients	221	53 (24)	60 (27)	108 (49)
Age, years				
Mean	63.5	64.7	62.8	63.3
SD	8.4	6.6	9.2	8.8
Sex				
Male	142 (64)	36 (68)	36 (60)	70 (65)
Female	79 (36)	17 (32)	24 (40)	38 (35)
WHO performance status				
0	132 (60)	33 (62)	38 (63)	61 (56)
1	89 (40)	20 (38)	22 (37)	47 (44)
Treatment arm				
Maintenance (CAP-B)	103 (47)	29 (55)	25 (42)	49 (45)
Observation	118 (53)	24 (45)	35 (58)	59 (55)
Time to PD1, months				
Maintenance				
Median	10.6	11.2	6.3	8.4
IQR	4.2-17.0	7.5-17.4	2.3-17.3	4.1-13.7
Observation				
Median	4.3	4.4	4.1	4.6
IQR	3.1-6.5	3.6-7.9	2.1-6.5	3.6-6.2
Prior adjuvant chemotherapy				
Yes	74 (33)	18 (34)	19 (32)	37 (34)
No	147 (67)	35 (66)	41 (68)	71 (66)
Response to induction treatment				
SD	73 (33)	19 (36)	15 (25)	39 (36)
PR/CR	148 (67)	34 (64)	45 (75)	69 (64)
Abnormal serum LDH				
Yes	117 (53)	29 (55)	29 (48)	59 (55)
No	104 (47)	24 (45)	31 (52)	49 (45)

CAP-B, capecitabine plus bevacizumab; CR, complete response; IQR, interquartile range; LDH, lactate dehydrogenase; PD1, first progression of disease; PR, partial response; SD, stable disease; SMM, skeletal muscle mass.

Figure 2.

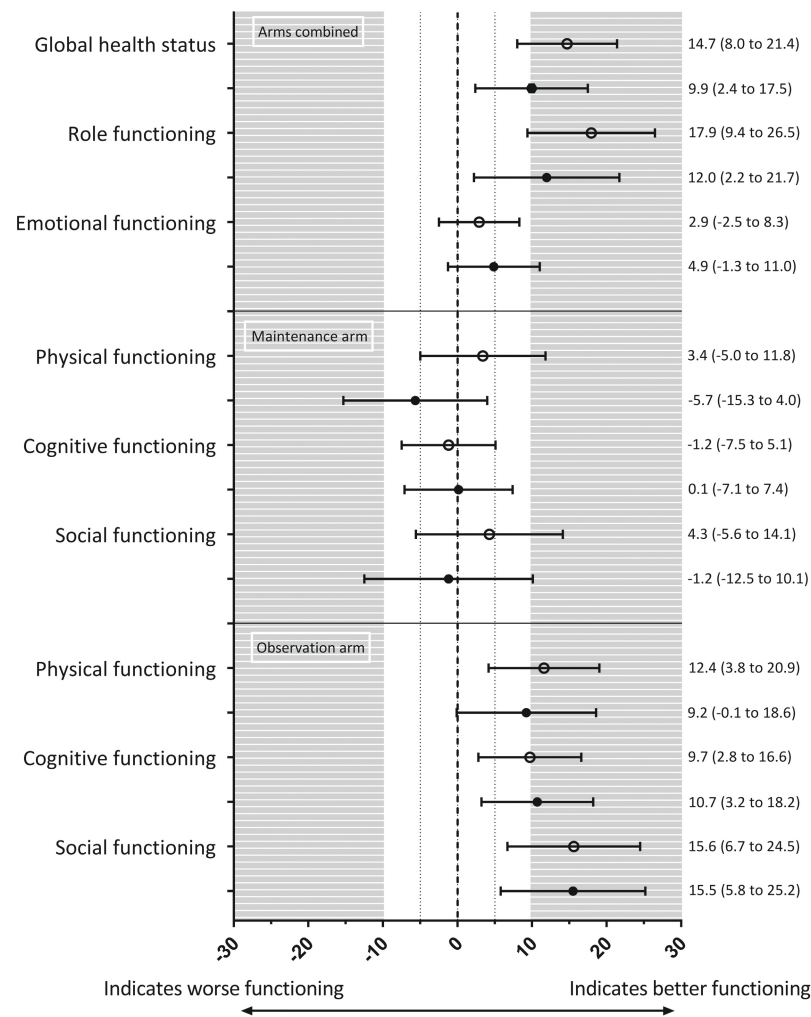


Fig. 2. Associations between stable (solid circles) or gain in SMM (open circles) vs. loss of SMM (reference) and change in global health status and functional subscales of HRQoL, for both CAIRO3 arms combined or stratified by treatment arm in case of a significant interaction ($n = 221$). Results from a multivariable linear regression analysis, which highlight the change in HRQoL scores for patients with stable SMM and patients who gained SMM. Grey zones show the cut-off for clinically relevant (i.e. ≥ 10 points) changes. Models were adjusted for age, sex, treatment arm, World Health Organization performance status, time to PD1, LDH at randomization, previous adjuvant chemotherapy, response to induction treatment, and hospital. Treatment arm was taken out of the model when stratified on treatment arm. This stratification is based on the relative goodness of fit (AICc) of the model with vs. without the interaction terms. Change scores are shown as means with 95% confidence interval. Confidence intervals not including 0 ($P < .05$) are considered statistically significant. HRQoL, health-related quality of life; LDH, lactate dehydrogenase; PD1, first progression of disease; SMM, skeletal muscle mass.

Figure 3.

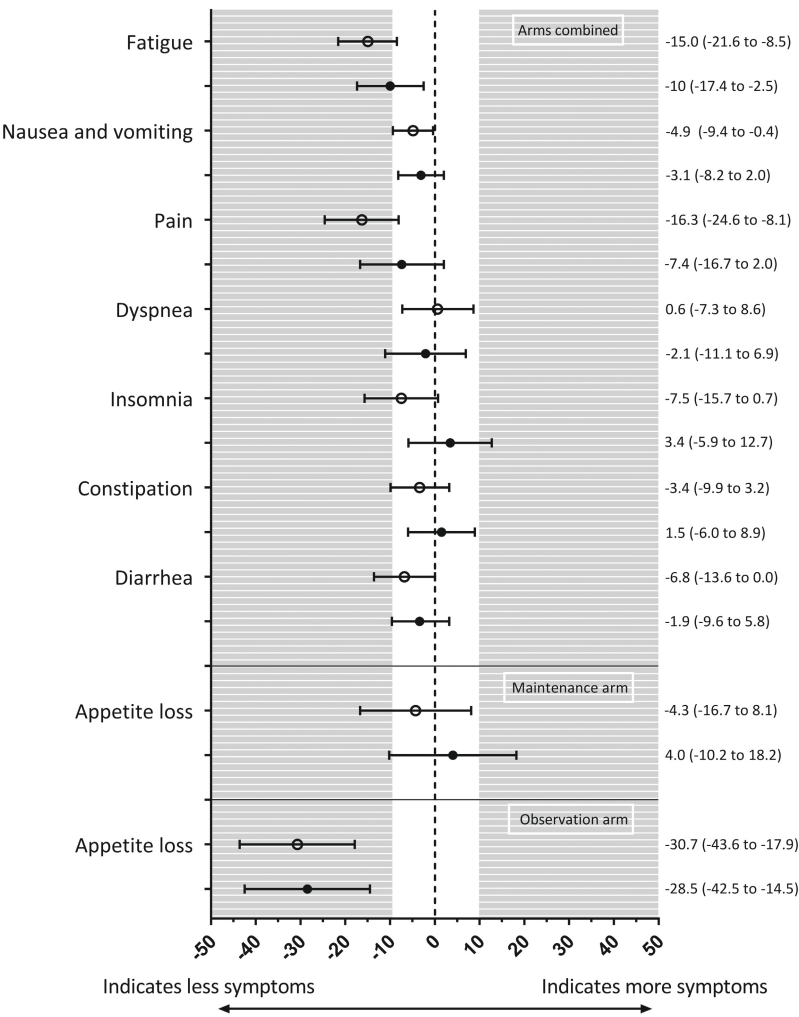


Fig. 3. Associations between stable (solid circles) or gain in SMM (open circles) vs. loss of SMM (reference) and change in symptomatic aspects of HRQoL, for both CAIRO3 arms combined or stratified by treatment arm in case of a significant interaction ($n = 221$). Results from a multivariable linear regression analysis, which highlight the change in HRQoL scores for patients with stable SMM and patients who gained SMM. Grey zones show the cut-off for clinically relevant (i.e. ≥ 10 points) changes. Models were adjusted for age, sex, treatment arm, World Health Organization performance status, time to PD1, LDH at randomization, previous adjuvant chemotherapy, response to induction treatment, and hospital. Treatment arm was taken out of the model when stratified on treatment arm. This stratification is based on the relative goodness of fit (AICc) of the model with vs. without the interaction terms. Change scores are shown as means with 95% confidence interval. Confidence intervals not including 0 ($P < .05$) are considered statistically significant. HRQoL, health-related quality of life; LDH, lactate dehydrogenase; PD1, first progression of disease; SMM, skeletal muscle mass.

Associations between change in skeletal muscle mass and change in health-related quality of life (Figures 2 and 3)

In terms of the subscale reflecting the patients' overall quality of life, a stable SMM was associated with an increase in global health of 9.9 points (95% CI: 2.4 to 17.5), compared with SMM loss. An increase in SMM was associated with a 14.7 point (95% CI: 8.0 to 21.4) increase in global health, compared with SMM loss. Both were statistically significant and clinically relevant. These associations did not differ between treatment arms. Interestingly, change in SMM was the only significant factor related to changes in overall quality of life (see Supporting Information, *Table S2* for the full model).

For 9 of the 13 remaining subscales, we also observed no significant differences between the two treatment arms. Of these subscales, role and emotional functioning, fatigue, nausea and vomiting, pain, and diarrhoea showed improvements when SMM remained stable or increased. Specifically, role functioning [12.0 points (95% CI: 2.2 to 21.7) for stable and 17.9 points (95% CI: 9.4 to 26.5) for gain in SMM], fatigue [−10.0 points (95% CI: −17.4 to −2.5) for stable and −15.0 points (95% CI: −21.6 to −8.5) for gain in SMM], and pain [−16.3 points (95% CI: −24.6 to −8.1) for gain in SMM] were observed to be statistically significant and clinically relevant.

For four subscales (physical, cognitive, and social function and appetite loss), we found significantly different associations between the two treatment arms ($P_{\text{interactions}} < 0.05$). In the observation arm, statistically significant and clinically relevant associations were found for improved physical functioning [12.4 points (95% CI: 3.8 to 20.9) for gain in SMM], cognitive functioning [10.7 points (95% CI: 3.2 to 18.2) for stable and 9.7 points (95% CI: 2.8 to 16.6) for gain in SMM], and social functioning [15.5 points (95% CI: 5.8 to 25.2) for stable and 15.6 points (95% CI: 6.7 to 24.5) for gain in SMM] and reduced appetite loss [−28.5 points (95% CI: −42.5 to −14.5) for stable and −30.7 points (95% CI: −43.6 to −17.9) for gain in SMM]. The association between stable SMM and improved physical functioning showed a trend towards significance [9.2 points (95% CI: −0.1 to 18.6)]. In patients receiving maintenance therapy, no statistically significant relations were observed.

Discussion

This is the first study that investigates the relationship between changes in SMM and associated changes in patient-reported HRQoL in patients with mCRC. We found that on average SMM increased in both the maintenance and observation arm. This increase may be influenced by the intensity of systemic regimens (i.e. after initial treatment patients switched to a lighter maintenance treatment without oxaliplatin or no treatment)¹⁵. Regarding patients' overall health and quality of life, we found that preserving muscle mass (i.e. stable or gain of SMM), compared with muscle loss during treatment with CAP-B and during observation as well, was associated with a significant and clinically relevant improvement in global health status. In addition, independent of treatment arm, we observed stable or gain of SMM to be significantly associated with a clinically relevant improvement of role function and decrease of fatigue and pain. Significant and clinically relevant associations of stable or gain of SMM with improvements in physical, cognitive, and social function and decrease of appetite loss were only observed in the observation arm and not in the maintenance arm. This may indicate that these factors are strongly related to treatment with CAP-B.

For several HRQoL subscales, we observed significantly different associations with SMM changes. Frequent side effects of CAP-B include gastrointestinal toxicities such as abdominal pain, diarrhoea, and stomatitis, as well as anorexia (appetite loss), fatigue, hand–foot syndrome, and neuropathy³⁸, which may have an impact on the relation between muscle mass and HRQoL. Indeed, for appetite loss, treatment arm was found to be an effect modifier. Patients in the observation arm with stable or gain in SMM reported a substantial reduction (approximately 30 points) in appetite loss compared with patients with SMM loss. In contrast, patients in the maintenance arm with stable or gain in SMM did not report a change in appetite loss in the period from randomization to PD1 compared with patient with SMM loss. Additionally, the relation between SMM change and several functional scales seems to be affected by concurrent treatment. Preservation of muscle mass was significantly associated with a clinically relevant improvement in physical, cognitive, and social functioning for patients in the observation arm but not for patients receiving maintenance therapy.

In previous studies in patients with advanced cancer, higher amounts of muscle mass at diagnosis^{18,19} or at start of chemotherapy²¹ were found to be associated with better physical functioning. In our study, however, stable or gain in SMM was not associated with improved physical functioning in patients who received maintenance treatment. Interestingly, for the symptoms, fatigue and pain, which are frequent side effects of CAP-B treatment, we did not

find a significant difference in the association of muscle mass changes and HRQoL scales between maintenance treatment and observation. This is of special interest, because both pain and fatigue are known to be independent predictors of survival in different cancer populations³⁹.

Our study differs in design and outcome with a previously published study in 28 stage IV mCRC patients²¹. In that study, a single CT scan was used to assess the relation between muscle mass and HRQoL at start of chemotherapy, but HRQoL assessment was performed using the same EORTC quality of life questionnaire as in our study. After adjusting for gender, they reported an association between low muscle mass and lower physical functioning but not with other HRQoL subscales. In our study, using two repeated measures of SMM and HRQoL in a larger sample size, we provide information about how changes in SMM are related to patients' HRQoL. However, given the observational design, we can only report associations and cannot disentangle the direction of the relationships.

This analysis contributed to the identification of a potentially modifiable factor related to patients' HRQoL, which is valuable input to future intervention studies aiming to improve clinical outcomes. Studying the effects of interventions, for example, physical exercise programmes and/or nutritional support (e.g. high-energy/high-protein/omega-3 polyunsaturated fatty acids containing oral nutritional supplement) prior to or during first-line treatment, will provide insight into the potential causality of associations between body composition parameters and HRQoL. A recent systematic review concluded that specific nutritional interventions (high-energy enriched with high-protein, n-3 polyunsaturated fatty acid-enriched) had a beneficial effect on muscle mass support and improved several aspects of HRQoL in cancer patients during chemotherapy treatment⁴⁰. In addition, several studies have already shown that individualized dietary counselling during treatment has beneficial effects on nutritional status and HRQoL in patients with head and neck squamous cell cancer⁴¹, as well as in patients with colorectal cancer^{42,43}. In terms of physical exercise interventions investigating HRQoL in patients with CRC, currently only patients treated with curative intent have been studied⁴⁴⁻⁴⁸. Research has shown inconclusive but mostly beneficial effects of physical exercise during and after treatment such as improved functional capacity and HRQoL^{44,45,49}. However, the current evidence remains sparse, which highlights the need for future research.

The main limitation of this analysis, which affects most HRQoL studies, is the concern that missing data may have potentially led to biased results^{50,51}. Nevertheless, approximately

75% of CAIRO3 patients who completed the HRQoL questionnaire at randomization also completed the questionnaire at PD1. Moreover, baseline characteristic of patients included in the analysis were comparable to baseline characteristics of the total CAIRO3 population. To note, this analysis was performed in mCRC patients with a good response (stable disease or better) to an intensive first-line induction treatment with CAPOX-B. This selection might restrict the generalizability to other mCRC patients. However, performing an analysis in a select group of patients can also be seen as a strength as it minimizes extraneous effects and thus, the amount of (residual) confounding.

A strength of this study is that data originated from a Dutch nationwide, clinical RCT with a homogeneous patient population²⁴. Regarding the assessment methods, using CT images is a well-acknowledged, accurate, and precise quantification method to measure body composition^{8,30}. Using questionnaires for the assessment of HRQoL provides the opportunity to study outcomes directly reported by the patient without interpretation by a clinician or anyone else. Additionally, it should be emphasized that the results were not just based on HRQoL changes that were statistically significant but, more importantly, on changes that were clinically meaningful. HRQoL assessment was performed using validated and widely used EORTC questionnaires²⁶, which is favourable when comparing results with other (future) studies.

To conclude, our data indicate that patients with a stable or gain in SMM reported to perceive significantly and clinically relevant improved global health status and multiple functional and symptomatic aspects of HRQoL. This suggests that interventions aiming for muscle mass preservation (e.g. exercise and nutritional interventions) during treatment may provide a window of opportunity to improve HRQoL. Further studies are warranted to confirm our findings and to investigate whether interventions targeting SMM in patients with mCRC lead to improved HRQoL, fewer symptoms, and better functioning.

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SUPPLEMENTARY
MATERIAL

Supplementary Table S1. Skeletal muscle mass and health-related quality of life scores at randomization, and changes from randomization to PD1, per treatment arm (n=221).

Variable	At randomization CAIRO3		Change from randomization to PD1	
	Maintenance arm (n=103)	Observation arm (n=118)	Maintenance arm (n=103)	Observation arm (n=118)
	Mean (±SD)	Mean (±SD)	Mean (95% CI)	Mean (95% CI)
Global health status	73.5 ± 15.9	75.1 ± 17.5	-0.3 (-4.0 to 3.4)	1.0 (-3.0 to 5.0)
Physical functioning	82.8 ± 16.2	83.6 ± 15.0	-1.6 (-4.9 to 1.8)	-1.9 (-5.2 to 1.4)
Role functioning	75.8 ± 22.8	75.4 ± 22.7	0.6 (-4.5 to 5.7)	2.3 (-2.8 to 7.3)
Emotional functioning	83.8 ± 17.3	86.2 ± 14.8	2.4 (-1.0 to 5.9)	-1.8 (-4.5 to 1.0)
Cognitive functioning	90.7 ± 16.8	87.0 ± 15.7	-1.9 (-4.3 to 0.6)	1.6 (-0.9 to 4.2)
Social functioning	87.5 ± 16.5	85.3 ± 16.0	-1.8 (-5.6 to 2.1)	1.1 (-2.4 to 4.5)
Fatigue	26.8 ± 17.6	27.6 ± 19.5	-1.9 (-5.5 to 1.8)	-2.5 (-6.6 to 1.5)
Nausea and vomiting	5.7 ± 13.5	5.2 ± 12.1	-4.1 (-6.4 to -1.8)	-1.8 (-4.6 to 0.9)
Pain	11.2 ± 19.2	10.7 ± 17.1	6.2 (1.6 to 10.8)	7.8 (2.9 to 12.8)
Dyspnea	14.6 ± 20.2	14.0 ± 21.5	-5.0 (-9.5 to -0.5)	-3.4 (-7.8 to 1.0)
Insomnia	9.4 ± 18.3	15.5 ± 24.4	2.9 (-1.2 to 7.0)	3.8 (-1.2 to 8.8)
Appetite loss	17.2 ± 25.5	10.6 ± 20.4	-9.4 (-14.4 to -4.4)	-3.0 (-8.0 to 2.1)
Constipation	5.2 ± 13.8	8.8 ± 17.8	-0.6 (-3.5 to 2.2)	0.6 (-3.7 to 4.8)
Diarrhea	11.0 ± 18.9	11.7 ± 18.7	-4.4 (-8.3 to -0.5)	-4.1(-8.0 to -0.2)
Skeletal Muscle Mass (kg)	26.9 ± 5.7	26.3 ± 5.2	0.4 (0.0 to 0.8) ^a	0.5 (0.3 to 0.8) ^a

^a Changes in muscle mass from randomization to PD1 in a subgroup of patients from the CAIRO3 study. The changes therefore differ from previously published data ¹⁵.

Supplementary Table S2. Full MLR model for the associations between stable or gain in SMM (vs. loss of SMM as reference) and change in global health status, for both CAIRO3 arms combined (n=221).

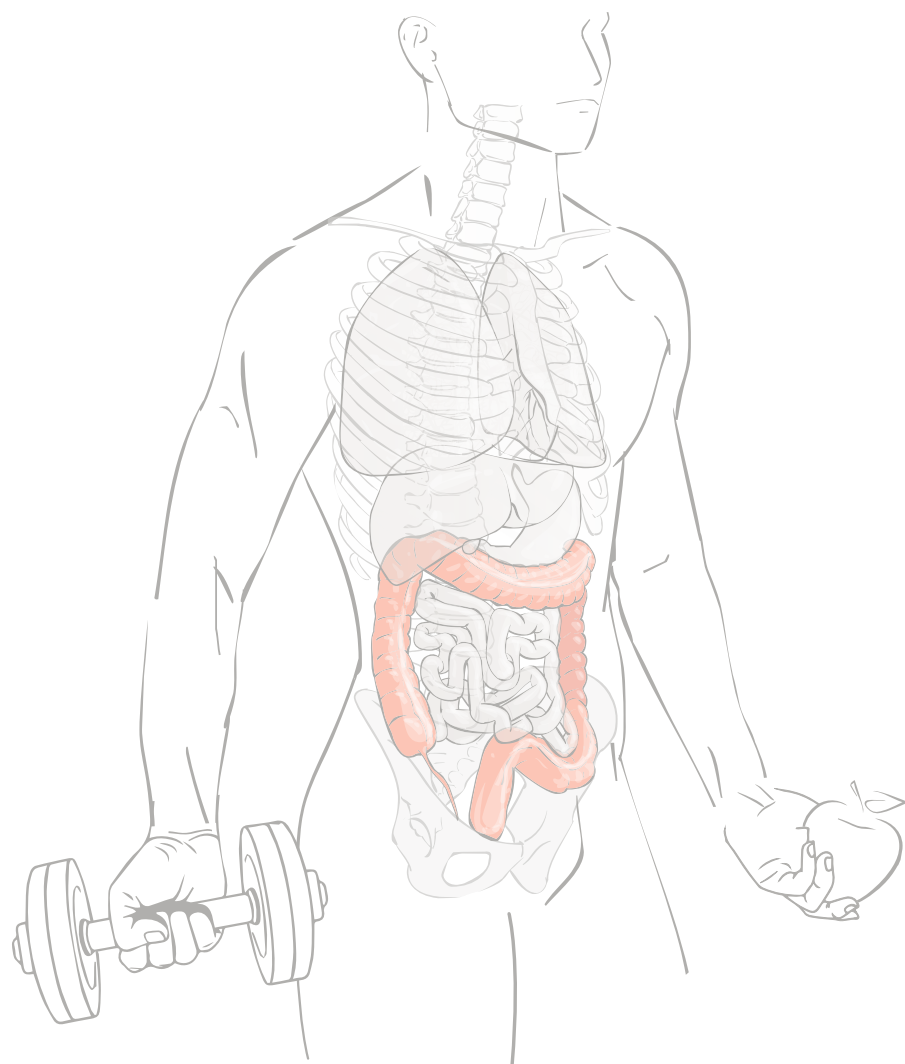
Model	Coefficient		95% CI for Beta	
	Beta	Std. Error	Lower bound	Upper bound
Intercept	-22.1	13.4	-48.6	4.3
Age (years)	0.2	0.2	-0.118	0.5
Sex (male vs. female)	1.6	2.8	-4.059	7.2
Treatment arm (observation vs. CAP-B)	-0.01	2.93	-5.78	5.76
WHO performance status (0 vs. 1)	1.8	2.8	-3.9	7.4
Hospital (number)	0.004	0.081	-0.157	0.164
Time from randomization to PD1 (days)	-0.002	0.006	-0.013	0.009
Previous adjuvant chemotherapy (no vs. yes)	-1.9	2.9	-7.6	3.8
Best response to initial treatment (partial or complete response vs. stable disease)	-3.6	2.9	-9.3	2.2
Abnormal serum lactate dehydrogenase level at randomization (no vs. yes)	4.3	2.7	-1.1	9.7
Stable SMM (≤2% loss - ≤2% gain)	9.9	3.8	2.4	17.5
Gain in SMM (>2% increase)	14.7	3.4	8.0	21.4

In bold: covariates that showed a statistically significant association with change in global health status.

Supplementary Table S3. Description of HRQoL scales from the EORTC QLQ-C30, v.3.0

HRQoL scale	Question #	Question description
Global health status / QoL		
Global health status / QoL	29	How would you rate your overall <u>health</u> during the past week?
	30	How would you rate your overall <u>quality of life</u> during the past week?
Functional scales		
Physical functioning	1	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?
	2	Do you have any trouble taking a <u>long</u> walk?
	3	Do you have any trouble taking a <u>short</u> walk outside of the house?
	4	Do you need to stay in bed or a chair during the day?
	5	Do you need help with eating, dressing, washing yourself or using the toilet?
Role functioning	6	Were you limited in doing either your work or other daily activities?
	7	Were you limited in pursuing your hobbies or other leisure time activities?
Emotional functioning	21	Did you feel tense?
	22	Did you worry?
	23	Did you feel irritable?
	24	Did you feel depressed?
Cognitive functioning	20	Have you had difficulty in concentrating on things, like reading a newspaper or watching television?
	25	Have you had difficulty remembering things?
Social functioning	26	Has your physical condition or medical treatment interfered with your <u>family</u> life?
	27	Has your physical condition or medical treatment interfered with your <u>social</u> activities?
Symptom scales / items		
Fatigue	10	Did you need to rest?
	12	Have you felt weak?
	18	Were you tired?
Nausea and vomiting	14	Have you felt nauseated?
	15	Have you vomited?
Pain	9	Have you had pain?
	19	Did pain interfere with your daily activities?
Dyspnea	8	Were you short of breath?
Insomnia	11	Have you had trouble sleeping?
Appetite loss	13	Have you lacked appetite?
Constipation	16	Have you been constipated?
Diarrhea	17	Have you had diarrhea?

The EORTC QLQ-C30 questionnaire v.3.0 consists of 30 questions. Question 28 refers to the item ‘financial difficulties’ which is not included in the current analysis. In CAIRO3, the Dutch translated version was used. Original EORTC manuals and guidelines can be found at: <https://qol.eortc.org/manuals>.



6

FACTORS CONTRIBUTING TO
CANCER-RELATED MUSCLE
WASTING DURING FIRST-LINE
SYSTEMIC TREATMENT FOR
METASTATIC COLORECTAL
CANCER

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Abstract

Background

Increasing evidence indicates that loss of muscle mass is associated with adverse outcomes in metastatic colorectal cancer. Here, we investigate which demographic, lifestyle- (smoking), tumor-, and treatment-related factors are associated with muscle loss in patients with metastatic colorectal cancer during first-line palliative systemic treatment.

Methods

Data from 300 patients with computed tomography scans both at start and after six initial cycles of capecitabine plus oxaliplatin and bevacizumab was used (CAIRO3). From computed tomography, muscle mass normalized for stature (skeletal muscle index [SMI]) was calculated. A priori-selected variables were tested using multivariable linear regression models (P values $\leq .05$). Two models were developed: Model 1 contained variables measured at start and Model 2 contained variables assessed after initial therapy.

Results

In Model 1, loss of SMI was statistically significantly associated with a higher initial SMI (-0.32% , 95% confidence interval [CI]: -0.45% to -0.19% per unit increase in initial SMI), smoking status (-2.74% , 95% CI: -5.29% to -0.19% for smokers), and interval of metastases (-3.02% , 95% CI: -5.50% to -0.53%) for metachronous vs synchronous metastases), and primary tumor resection was statistically significantly associated with a gain in SMI (2.17% , 95% CI: 0.13% to 4.21% for resection vs no resection). In Model 2, loss of SMI was statistically significantly associated with response to capecitabine plus oxaliplatin and bevacizumab (-2.48% , 95% CI: -4.33% to -0.62% for stable disease vs partial/complete response).

Conclusions

Our results highlight, given the association of sarcopenia and survival, that patients with higher SMI should not be ignored. In addition, smoking is a potentially modifiable factor associated with muscle loss. The association between smoking and muscle loss might relate to worse clinical outcomes in smokers with metastatic colorectal cancer.

Introduction

Skeletal muscle loss, one of the main characteristics of sarcopenia¹ and a diagnostic criterion for cancer cachexia², is a common, albeit occult, phenomenon in many cancer types, including colorectal cancer (CRC). A recent meta-analysis found that the overall prevalence of sarcopenia in patients with different primary tumors exceeded 40%, including CRC with prevalence varying from 19% to 71%³. Depletion of muscle mass has shown to be associated with poor clinical outcomes such as reduced responsiveness and tolerability to cancer treatment, quality of life, and survival³⁻⁸. Although several studies investigated the associations between skeletal muscle loss and disease outcomes³, only a few studies have investigated which characteristics are related to skeletal muscle loss in cancer patients.

We previously found that muscle loss is reversible, is more likely to occur during periods of systemic treatment, and may be influenced by the intensity of treatment regimens⁹. Other studies investigating which factors modulate muscle mass in patients with cancer described that skeletal muscle loss is more prevalent during periods of progressive disease⁷ and at the end of life^{7,10,11}. One study specifically focused on palliative patients during the last phase of life, and found that patients with male sex and increased systemic inflammation marker lost more muscle mass in the last 24 months of life compared with their counterparts¹². Recently, a study in non-small cell lung cancer patients found that a higher initial body mass index (BMI) and higher initial skeletal muscle mass (SMM) were factors related to more loss of muscle mass¹³. Lastly, one study that included CRC patients who underwent elective surgery reported that loss of SMM was statistically significantly associated with type of surgical approach (higher in open vs laparoscopic) and tumor stage (higher in stage III–IV vs. I–II)¹⁰. To date, no studies of a comparable nature have been conducted in patients with metastatic colorectal cancer (mCRC).

Despite the evidence on the reversibility of SMM loss in patients with mCRC⁹ and increasing knowledge on potential strategies to reverse sarcopenia³, recent data suggest that most patients with CRC, particularly those with advanced tumors, are not able to maintain SMM during systemic treatment^{7,9,11}. Understanding the determinants that are associated with SMM loss during treatment will help to better identify patients who are at risk of losing muscle mass and may contribute to the development of interventions that aim to avoid muscle mass loss. Therefore, the aim of our study was to investigate which

demographic, lifestyle-, tumor-, and treatment-related factors are associated with loss of muscle mass in mCRC patients during first-line palliative systemic treatment.

Methods

Patient Population

For the current analysis, we used data from the CAIRO3 study (ClinicalTrials.gov number NCT00442637)¹⁴. CAIRO3 is a randomized controlled phase III trial of the Dutch Colorectal Cancer Group on the effect of maintenance treatment with capecitabine plus bevacizumab vs observation in previously untreated mCRC patients who responded with stable disease or better (partial response [PR] or complete response [CR]) after six initial cycles with capecitabine plus oxaliplatin and bevacizumab (CAPOX-B). The main eligibility criteria for randomization in CAIRO3 were histological proof of CRC, unresectable metastatic disease, and World Health Organization performance status 0 or 1. For the current analyses, we used data from the first six cycles with CAPOX-B (later called “initial therapy”) to exclude the possible effect of disease progression on change in SMM. Patients with available computed tomography (CT) scans both at start and after six cycles of initial therapy were included. Primary approval for the CAIRO3 study was given by the Medical Ethical Committee Arnhem-Nijmegen and by local institutional review boards. Written informed consent was obtained from all participants, and research was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Skeletal Muscle Measurements

Skeletal muscle area was measured on abdominal CT scans that were routinely performed at the start and after six cycles of initial therapy. For the quantification of SMM, CT scans were acquired and analyzed by trained analysts using the software tool Slice-o-matic (version 5.0; Tomovision). Skeletal muscle area was measured on a single slice at the level of the third vertebra (L3), which is shown to highly correlate with total body SMM ($r^2 = 0.86$)¹⁵. Pre-specified thresholds in Hounsfield units (−29 to 150) were used to identify the different muscle compartments^{16,17}. To reduce measurement error due to variation in the positioning of patients between consecutive CT scans, each second scan was rotated and fused with a rigid fusion method and L3 of the first scan as a bony landmark. To calculate the skeletal muscle index (SMI), the generally accepted regression equation below was used^{15,18,19}:

$$\text{Skeletal Muscle Index} = (\text{Skeletal Muscle Area at L3 in cm}^2) / (\text{squared height in m}^2)$$

Data Collection

Data managers of The Netherlands Comprehensive Cancer Organisation collected sociodemographic and clinical data from medical records. To collect additional data from the initial treatment phase, medical records were reviewed to retrieve data on initial body weight and levels of leukocytes, thrombocytes, C-reactive protein (CRP), lactate dehydrogenase (LDH), and albumin. For this study, empirically selected variables collected at the start of initial therapy were sex, age, active smoking (yes vs no), primary tumor sidedness (left vs right), interval of metastases (metachronous vs synchronous), primary tumor resection (yes vs no), and prior adjuvant therapy (yes vs no). In addition, two variables that were assessed after initial therapy were selected, namely the occurrence of dose reductions during initial therapy (yes vs no) and the patient's response to initial therapy (stable disease vs CR or PR). The presence of sarcopenia was determined by previously suggested sex-specific cutoff points, which were SMI less than 43 cm²/m² for men with a BMI lower than 25 kg/m², SMI less than 53 cm²/m² for men with a BMI greater than 25 kg/m², and SMI less than 41 cm²/m² for women with any BMI¹⁹. For the interval of metastases, we distinguished between synchronous and metachronous, with synchronous metastases being defined as distant metastases occurring within 6 months after diagnosis of the primary tumor and metachronous metastases occurring later than 6 months after diagnosis of the primary tumor.

Statistical Analysis

All characteristics were described as mean (SD) or median with interquartile range. To meet model assumptions, logarithmic transformations were applied on the initial blood values of leukocytes, thrombocytes, CRP, and LDH. Missing data (varying between 0 and 15% per variable, except for laboratory measures because these were not measured for the study and retrieved retrospectively) were imputed using the R-package Multiple Imputation by Chained Equations²⁰ when appropriate, resulting in multiple ($n = 20$) imputed datasets. All empirically selected factors were tested on their univariate association with change in SMI (%) and subsequently analyzed using multivariable linear regression models. Models were fitted on each imputed dataset, and Rubin's rules were used to subsequently pool the estimates from each model into a single estimate²¹. Finally, to distinguish between associations at start and after initial therapy, two multivariable models were created. Model 1 contained only variables measured at the start of initial therapy and shows how they are related to changes in muscle mass during initial therapy, and Model 2 contained variables

measured after initial therapy and shows the cross-sectional associations with muscle mass changes at that time. Sex was included in both models given the increasing evidence on sex-specific differences in cancer-induced muscle wasting^{22,23}. The variable “initial presence of sarcopenia” was not included in the models because of multicollinearity, and “initial level of CRP” was not included because of the presence of selective missing values. All statistical tests were two sided, and significance of the results was interpreted based on confidence intervals ($P \leq .05$). All analyses were performed in R studio version 1.0.143.

Results

The flowchart of the selection of individuals for the current analyses is shown in Figure 1. In total, 557 patients from 64 participating hospitals in the Netherlands were originally included in the CAIRO3 study. Of the 450 patients for whom CT scans were available, 300 (66.7%) had evaluable CT scans both at start and after six cycles of initial therapy with CAPOX-B that were used for skeletal muscle measurements.

Figure 1.

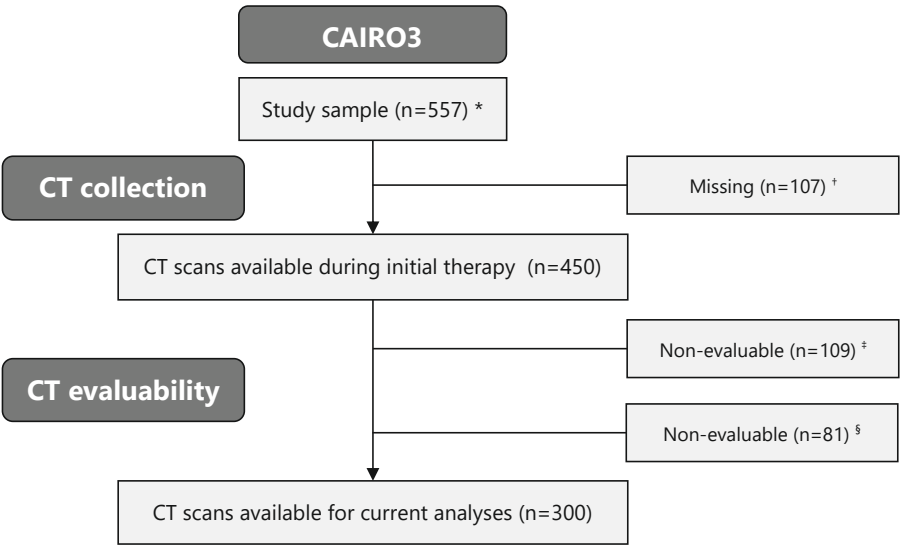


Fig. 1. Flowchart of the selection of patients for the current analyses. * One participating patient revoked informed consent. † No CT scans available from nine participating hospitals because of logistic reasons. ‡ CT scan at start of initial therapy non-evaluable. Reasons: no CT abdomen available, incomplete depiction of skeletal muscle at L3, stoma through muscle layer at L3, scan of insufficient quality. § CT scan at randomization non-evaluable. Reasons: no CT abdomen available, incomplete depiction of skeletal muscle at L3, stoma through muscle layer at L3, scan of insufficient quality. CAIRO3 was Maintenance Treatment Versus Observation After Induction in Advanced Colorectal Carcinoma; CT, computed tomography.

Table 1. Patient characteristics during initial therapy (n = 300)

	N	Missing	Descriptives †
Demographics			
Sex	300	0%	
Male			189 (63.0%)
Female			111 (37.0%)
Age (years)	300	0%	63.5 (±8.7)
Initial BMI (kg/m²)	287	4.3%	25.9 (±4.1)
Initial SMI (cm²/m²)	300	0%	
Total group			46.3 (±8.6)
Male			49.5 (±7.9)
Female			40.9 (±6.8)
Initial presence of sarcopenia ‡	294	2.0%	
Yes			149 (50.7%)
No			145 (49.3%)
Smoking status	256	14.7%	
Yes			43 (16.8%)
No			213 (83.2%)
Initial level of leukocytes (*10 ⁹ /L)	198	34.0%	8.4 [6.9 - 10.3]
Initial level of thrombocytes (*10 ³ /mm ³)	271	9.7%	339.0 [259.5 - 435.0]
Initial level of CRP (mg/L)	77	74.3%	17.0 [6.0 - 58.0]
Initial level of LDH (u/L)	212	29.3%	308.0 [197.8 - 487.0]
Initial level of albumin (g/L)	158	47.3%	39.6 [37.0 - 43.0]
Tumor characteristics			
Primary tumor sidedness	299	0.3%	
Left			224 (74.9%)
Right			75 (25.1%)
Interval of metastases	300	0%	
Metachronous			73 (24.3%)
Synchronous			227 (75.7%)
Treatment-related characteristics			
Primary tumor resection	300	0%	
Yes			178 (59.3%)
No			122 (40.7%)
Prior adjuvant therapy	300	0%	
Yes			102 (34.0%)
No			198 (66.0%)
Best response to initial therapy	300	0%	
Stable disease			99 (33.0%)
Complete or partial response			201 (67.0%)
Dose reduction during initial therapy	300	0%	
Yes			141 (47.0%)
No			159 (53.0%)

Descriptives are presented as count (percentage), mean (SD) or median [interquartile range]. BMI, body mass index; CRP, C-reactive protein; LDH, lactate dehydrogenase; SMI, skeletal muscle index. †. In case of missing data, the descriptive statistics of complete cases are presented. ‡. Sarcopenic status based on sex-specific cut-off points described by Martin *et al.*¹⁹.

Patient Population

Patient characteristics of our study population before and during initial therapy are shown in Table 1. A total of 63.0% were male and the mean age was 63.5 (8.7) years. Mean BMI at start of initial therapy was 25.9 (4.1) kg/m² and mean initial SMI was higher in male patients compared with female patients (49.5 [7.9] cm²/m² and 40.9 [6.8] cm²/m², respectively). On average, patients lost 1.17% SMI during initial therapy. Furthermore, 16.8% were active smokers, which is slightly lower than the Dutch general population at that time because the proportion of smokers older than 16 years in 2007–2012 decreased from 30% to 25%²⁴. Regarding tumor and treatment-related characteristics, 74.9% had a primary tumor located at the left side of the colon, and 24.3% had metachronous metastases. Primary tumor resection before inclusion in the study had been performed in 59.3% of the patients, 34.0% received prior adjuvant chemotherapy, 33.0% responded with stable disease, and 47.0% received dose reductions during initial therapy.

Characteristics Associated with SMI Change

In univariate linear regression analyses (Table 2), factors statistically significantly associated with SMI change were initial BMI, initial SMI, smoking status, initial level of thrombocytes, interval of metastases, and patients' response to initial therapy. Of these six variables, a higher (log-transformed) initial level of thrombocytes was statistically significantly associated with increased SMI, meaning that a 1% increase in initial thrombocyte levels was associated with a 0.09% (95% confidence interval [CI] = 0.03% to 0.15%) gain in SMI. For the other five statistically significantly associated variables, we found mean changes in SMI of –0.38% (95% CI = –0.60% to –0.17%) per unit increase in initial BMI, –0.32% (95% CI = –0.42% to –0.22%) per unit increase in initial SMI, –2.64% (95% CI = –5.17% to –0.12%) for active smokers, –3.61% (95% CI = –5.64% to –1.58%) for patients with metachronous metastases, and –2.56% (95% CI = –4.43% to –0.69%) for patients with stable disease during initial therapy.

In multivariable adjusted linear regression models with all factors measured at the start of initial therapy (Table 2, Model 1), we found that initial SMI, smoking status, and interval of metastases were still statistically significantly associated with SMI loss. The effect sizes remained comparable to univariate analyses because we found mean changes in SMI of –0.32% (95% CI = –0.45% to –0.19%) per unit increase in initial SMI, of –2.74% (95% CI = –5.29% to –0.19%) for active smokers, and –3.02% (95% CI = –5.50% to –0.53%) for patients with metachronous metastases. Primary tumor resection was statistically significantly associated with a 2.17% (95% CI = 0.13% to 4.21%) gain in SMI. In multivariable analysis, no statistically significant associations were found for initial level of thrombocytes and initial BMI.

Table 2. Factors associated with changes in SMI during initial therapy.

Variables	Univariable analysis			Multivariable Model 1			Multivariable Model 2		
Measured at start of initial therapy	β	95% CI		β	95% CI		β	95% CI	
Sex, female vs. male	1.67	-0.16 to 3.50		-1.52	-3.60 to 0.57		1.75	-0.06 to 3.57	
Age, years	-0.02	-0.12 to 0.08		-0.05	-0.15 to 0.06		-	-	
Initial BMI, kg/m ²	-0.38 *	-0.60 to -0.17		-0.05	-0.29 to 0.19		-	-	
Initial SMI, cm ² /m ²	-0.32 *	-0.42 to -0.22		-0.32 *	-0.45 to -0.19		-	-	
Smoking status, yes vs. no	-2.64 *	-5.17 to -0.12		-2.74 *	-5.29 to -0.19		-	-	
Initial level of leukocytes, *10 ⁹ /L †	0.06	-0.01 to 0.12		0.03	-0.05 to 0.11		-	-	
Initial level of thrombocytes, *10 ³ /mm ³ †	0.09 *	0.03 to 0.15		0.03	-0.05 to 0.11		-	-	
Initial level of LDH, u/L †	0.003	-0.03 to 0.04		-0.01	-0.05 to 0.02		-	-	
Initial level of albumin, g/L	0.01	-0.23 to 0.24		0.10	-0.19 to 0.40		-	-	
Primary tumor sidedness, left vs. right	0.34	-1.71 to 2.39		1.09	-0.93 to 3.11		-	-	
Interval of metastases, metachronous vs. synchronous	-3.61 *	-5.64 to -1.58		-3.02 *	-5.50 to -0.53		-	-	
Primary tumor resection, yes vs. no	0.23	-1.58 to 2.04		2.17 *	0.13 to 4.21		-	-	
Prior adjuvant therapy, yes vs. no	-0.43	-2.31 to 1.44		0.06	-1.79 to 1.91		-	-	
Measured after initial therapy									
Best response to initial therapy, SD vs. CR or PR	-2.56 *	-4.43 to -0.69		-	-		-2.48 *	-4.33 to -0.62	
Dose reduction during initial therapy, yes vs. no	-0.92	-2.69 to 0.86		-	-		-0.95	-2.71 to 0.81	

* Statistically significant association (P ≤ .05). Results are presented as regression coefficients (β), representing the average percentage change in SMI during initial treatment per unit (or per percentage for leukocytes, thrombocytes, and LDH) increase of the corresponding variable, including 95% confidence intervals (95% CI). Model 1 contains only variables measured at start of initial therapy, and model 2 contains variables measured after initial therapy. BMI, body mass index; CR, complete response; LDH, lactate dehydrogenase; PR, partial response; SMI, skeletal muscle index. † Analyzed as log-transformed variable.

When additional variables assessed after the course of initial therapy were studied in a multivariable model (Table 2, Model 2), we found that response to initial therapy was statistically significantly associated with SMI loss: Patients with a stable disease during initial therapy lost 2.48% (95% CI = -4.33% to -0.62%) more SMI compared with patients responding with a PR or CR.

Discussion

In this study, we investigated possible associations between demographic, lifestyle- (ie, smoking), tumor-, and treatment-related factors and changes in muscle mass during six cycles of first-line palliative systemic treatment in mCRC patients. Our main findings were that a higher initial SMI, active smoking at start of initial therapy, and metachronous metastases were factors independently associated with SMI loss, whereas having had a primary tumor resection before initial therapy was statistically significantly associated with a gain in SMI. The tumor's response to treatment also appeared to be a factor statistically significantly associated with SMI loss, because patients with a stable disease lost statistically significantly more SMI compared with patients responding with PR or CR.

The observed association between higher initial levels of SMI and SMI loss during first-line palliative systemic treatment is in line with a previous study conducted in patients with advanced non-small cell lung cancer¹³. This study aimed to identify (non-tumor-related) factors that modulate changes in body composition and found that SMM deterioration during anticancer treatment occurred in patients with a higher BMI and greater SMM. Interestingly, in our analysis we found that initial level of BMI, when adjusted for initial SMI, was not independently associated with SMI loss during treatment. The univariate association between initial BMI and SMI loss seems to be explained by initial SMI, because in Model 1 - including both initial BMI and SMI - only the initial level of SMI remains statistically significantly associated with SMI loss. Because higher SMI at start of initial therapy was associated with increased muscle loss, we emphasize that in clinical practice, attention should also be given to patients presenting with a higher SMI and interventions should not be offered only to sarcopenic patients.

Regarding tumor-related factors, we found that patients with metachronous metastases lost on average 3.0% more muscle mass during initial therapy compared with patients with synchronous metastases. This might be explained by prolonged exposure to tumor-induced metabolic changes that contribute to muscle wasting before start of

palliative systemic treatment²⁵. Moreover, we found that patients responding with a stable disease lost on average 2.5% more muscle mass compared with patients who achieved a PR or CR. This finding adds to a previous study in which progression of disease was associated with increased muscle wasting⁷ by showing that patients, next to a survival benefit, may also physically benefit from a good response to treatment. This consolidates the potential role of tumor load on cancer-related muscle wasting. However, causal inferences on treatment-related variables remain elusive because we cannot exclude the possibility of reversed causality in our analysis.

Although smoking has been established as a risk factor for the development of sarcopenia²⁶, previous studies did not include smoking status in their analyses, which is likely because of poor data collection on smoking behavior in clinical settings, including trials. In CAIRO3, smoking status was known for 85.3% of the patients, allowing us to include this factor in our models. Indeed, we found that active tobacco smokers lost on average 2.7% more SMI during initial therapy compared with nonsmokers. Potential molecular mechanisms involved in muscle wasting due to smoking are thought to be induced by particular free radicals and carcinogenic components of tobacco smoke (i.e. aldehydes, reactive oxygen species and reactive nitrogen species)^{26,27}. A recent meta-analysis including 62 278 CRC patients showed that smoking at the time of diagnosis and, to a lesser extent former smoking, is associated with a poorer survival compared with never smokers²⁸. In addition, it is known that smoking cessation has a positive impact on CRC prognosis²⁹. Here we show, for the first time to our knowledge, that smoking at the start of first-line systemic treatment is associated with increased SMI loss in mCRC patients, suggesting that SMI might be a mediator in the association between smoking and survival. Future research should investigate whether quitting smoking after diagnosis is positively associated with muscle mass. A recent perspective noted that, despite existing recommendations to offer effective evidence-based cessation treatment to all patients with cancer who smoke, clinicians often ignore these cessation treatments³⁰. To improve future cessation support for cancer patients, it should become an integrated component in cancer care, and resources to refer patients for such support as well as clinician education should be enhanced^{30,31}.

To maintain muscle mass in patients with higher initial SMI and to potentially improve muscle mass in patients with lower initial levels of SMI, various interventions have been described^{3,32}. It has been shown that physical activity interventions have the potential to reverse sarcopenia in cancer patients³³. Current interventions are mainly focused on

improving dietary intake and increasing physical activity to counteract muscle protein catabolism. Additionally, several pharmacologic approaches are being studied, of which orexigenic agents such as ghrelin and anamorelin hold the most evidence³⁴. However, it is suggested that a multimodal approach including both nutritional support (high energy, high protein, and omega-3 fatty acids) and exercise programs will synergistically contribute to preservation of muscle mass and possibly lead to improved outcomes^{3,35}.

This analysis also has a number of limitations. Because systemic inflammation is a process that plays a significant role in cancer cachexia^{36,37}, it is of interest when studying factors related to muscle wasting. In previous studies conducted in patients with CRC, elevated initial CRP levels and neutrophil to lymphocyte ratios were associated with skeletal muscle loss^{10,12,38}. Because CRP levels were determined only by clinical indication, we could not impute missing values and did not include this variable in our models. Unfortunately, other markers for inflammation, as well as data on nutritional intake, alcohol consumption, physical activity levels, corticosteroid use (e.g. dexamethasone), and comorbidities were not available at the start of initial therapy, and thus residual confounding cannot be ruled out.

This observational study was performed in a large homogenous group of mCRC patients with stable disease or a better response during initial therapy. The exclusion of patients with progression of disease removed the possible effect of disease progression on change in SMI from our analysis and allowed us to investigate which other factors play a role in muscle wasting. Another strength of this study was that the data originated from a Dutch nationwide randomized clinical trial in which high-quality data on patient-, tumor-, and treatment-related characteristics were available. Lastly, the use of abdominal CT scans is a well-acknowledged, accurate, and precise quantification method to measure body composition^{15,19}, which is favorable when comparing results to the current literature.

To conclude, our data indicate that SMI loss during first-line palliative systemic treatment for mCRC was associated with lifestyle-related as well as tumor- and treatment-related factors. We found that higher initial levels of SMI, active smoking, metachronous metastases, and treatment response with stable disease were associated with SMI loss, whereas the absence of the primary tumor is associated with a gain in SMI. We speculate that muscle mass might be a mediator in the association between active smoking and poor survival. Hence, our results further support efforts of oncologists and supportive

care nurses to facilitate in smoking cessation to improve outcomes including, but not limited to, muscle mass preservation.

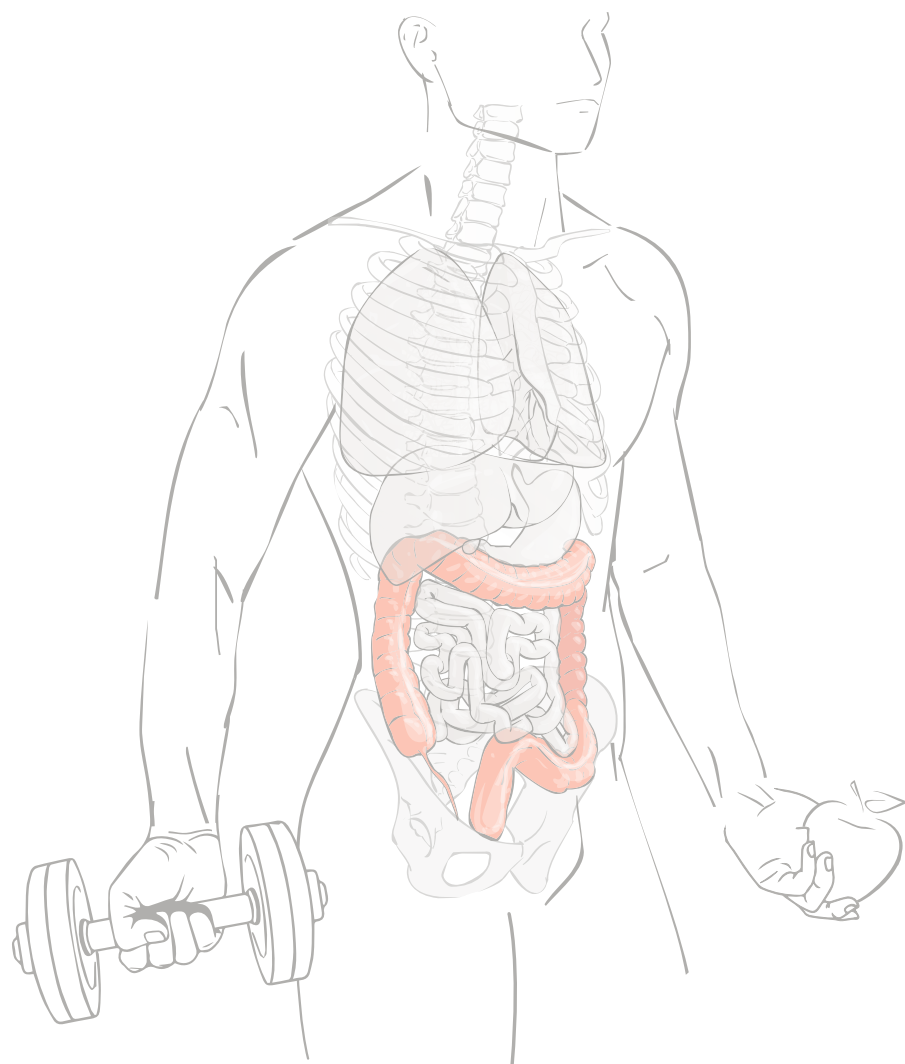
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7

PRACTICE PATTERNS AND BARRIERS TO SMOKING CESSATION AFTER A CANCER DIAGNOSIS IN THE SETTING OF CURATIVE VS. PALLIATIVE CANCER TREATMENT: A SURVEY OF EUROPEAN ONCOLOGISTS

REVISIONS
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* Collaborators are listed at the end of this chapter.

Abstract

Background

Significant advances in the past decade have clearly demonstrated that continued smoking after a cancer diagnosis causes adverse outcomes that can be improved with smoking cessation, but few contemporary studies report on cessation practice patterns by oncologists. No large surveys have focused on differences between the curative and palliative setting to date. The aim of this survey was to gain insight into the oncologist's perceptions on tobacco use, current practices, and barriers to providing smoking cessation support, while distinguishing between treatment with curative (C) and palliative (P) intent.

Methods

In 2019, an online 34-item survey was sent to approximately 6,235 oncologists from 16 European countries. Responses were analyzed and descriptively reported.

Results

Responses from 544 oncologists were included in the analysis. Overall, oncologists appeared to favor addressing tobacco in the curative setting more than in the palliative setting. The majority of oncologists believe that continued smoking impacts treatment outcomes (C:94%, P:74%) and that cessation support should be a standard part of cancer care (C:95%, P:63%). Only 23% reported to feel adequately trained to provide cessation interventions. Most respondents routinely assess tobacco use (C:93%, P:78%) and advise patients to stop using tobacco (C:88%, P:54%), but only 24-39% routinely discuss medication options, and only 18-31% provide cessation support. Hesitation to remove a pleasurable habit (C:13%, P:43%) and disbelief on smoking affecting outcomes (C:3%, P:14%) were disparate barriers between the curative and palliative setting, but dominant barriers of time, resources, education, and patient resistance were similar between settings.

Conclusion

Oncologists appear to favor addressing tobacco more in the curative than palliative setting, but little progress has been made in overall practice patterns reported by oncologists. To improve cancer care, all patients who report current smoking should have access to evidence-based smoking cessation support.

Introduction

Despite the great progress made in supportive care for people with cancer, smoking cessation treatments remain an often-neglected element of cancer care. Smoking by cancer patients and survivors causes adverse cancer treatment outcomes and poor quality of life with a median 50% increased risk of overall mortality and 60% increased risk of cancer-related mortality across cancer diagnoses and treatments ¹. The effects of continued smoking can result in significant additional cancer-related treatment costs ². Smoking cessation after a cancer diagnosis can improve survival ³, and improve outcomes for non-cancer related health effects that may have a more significant effect on mortality than cancer ⁴. Major organizations including the European Society for Medical Oncology (ESMO), American Society of Clinical Oncology (ASCO), American Association for Cancer Research (AACR), National Comprehensive Cancer Network (NCCN), International Association for the Study of Lung Cancer (IASLC), World Health Organization (WHO), and others advocate for smoking cessation as a standard part of cancer care ⁵⁻¹². However, approximately two-thirds of cancer patients who smoke at diagnosis continue to smoke in follow-up ¹³.

Evidence-based approaches to increase smoking cessation consists of providing counseling and medications ¹⁴. Prior to the landmark 2014 Surgeon General's Report concluding that smoking was a causal factor for poor cancer treatment outcomes ¹, large surveys of oncologists demonstrated that while most oncologists asked about tobacco use and advised patients to quit, few offered assistance with quitting ^{15,16}. There have been considerable efforts to raise awareness of the need to provide smoking cessation as a standard part of cancer care, but there have been few contemporary surveys of practice patterns to evaluate if improvement has occurred, and no large surveys that evaluate patterns in the curative vs. palliative setting. The purpose of this study is to evaluate practice patterns by oncologists to report their current perceptions on tobacco use after diagnosis, patterns of tobacco use assessment and cessation support, and identify current barriers to facilitating cessation support for patients with cancer, while distinguishing between the curative and the palliative setting.

Methods

Study population

Target respondents included clinical oncologists (i.e. medical oncologists and radiation oncologists) practicing in Europe. In total, 24 national societies for medical or clinical oncology - all partners of ESMO - were invited to participate in this international survey study (*Supplement S1*). Upon individual board approval, the societies distributed the survey among its members and most local coordinators sent two reminders after the initial invitation to complete the survey. The Medical Research Ethics Committee (MREC) of the University Medical Center Utrecht confirmed that the Medical Research Involving Human Subjects Act (WMO) does not apply, and MREC approval is not required under the WMO (reference WAG/mb/19/013713).

Survey

An online 34-item survey was developed based on the 2013 ASCO survey¹⁵ to assess European practice patterns in clinical oncology and perceptions regarding smoking cessation after a cancer diagnosis. The survey contained questions asking about respondent characteristics, the oncologist’s perceptions of tobacco use in patients with cancer, the oncologist’s interactions with cancer patients, and potential barriers to smoking cessation support (*Supplement S2*). Respondents were asked about practice patterns and perceptions in both the curative and palliative setting. Except for the respondent’s demographics, most questions could be answered on a five-level Likert scale ranging from always to never, or from strongly agree to strongly disagree. The survey was distributed between September 19, 2019, and December 20, 2019.

Data analysis

Responses to the survey are presented using descriptive statistics. Statistical analyses were performed using SPSS (version 25.0, IBM Corp, Armonk, NY). To determine the respondent’s smoking status, currently smoking every day or some days was classified as being a current smoker, currently no smoking but having smoked more than 100 in a lifetime was classified as being an ever smoker, and never smoking in a lifetime or no current smoking but having smoked less than 100 in a lifetime was classified as being a never smoker.

Results

A total of 6,235 members of participating medical or clinical oncology societies from Belgium, Denmark, Estonia, Finland, Germany, Greece, Ireland, Lithuania, Luxembourg, The Netherlands, Poland, Serbia, Spain, Sweden, Switzerland, and the United Kingdom were invited to participate. Of all invited members, 568 (~9.1%) completed the survey for this study. After excluding respondents with another profession (18 surgeons, 6 miscellaneous), a total of 544 respondents (~8.7%) were included in this analysis.

Respondent characteristics

Table 1 shows characteristics of the 544 survey respondents. Most respondents were older than 40 years of age (73%), and practicing as Medical Oncologist (90%). Further, 41% of respondents were male, 37% had an MD with a doctorate degree, and 50% reported to be working in a university or academic setting. Breast, gastrointestinal, and lung tumors were the three most frequently seen primary tumor types of respondents with respectively 49%, 46%, and 39%. The majority of respondents reported to spend more than half of their time on patientcare (90%). Regarding smoking behavior, 5% of the clinical oncologists reported currently smoke, and 17% were classified as ever smoker.

Perceptions on tobacco and cancer

Responses on questions regarding perceptions towards tobacco use in patients with cancer are shown in Table 2. Oncologists strongly believe that tobacco use impacts treatment outcomes, both in the curative (94%) and in the palliative setting (74%). Subsequently, 95% of the respondents agreed that smoking cessation should be a standard part of curative cancer treatment, and 63% agreed that it should be standard in the palliative setting as well. Interestingly, 52% reported to not have adequate training in smoking cessation interventions, and 73% indicated that more training in tobacco assessment and cessation interventions is needed. This is especially relevant as 42% found that the treating oncologist would be an appropriate provider of cessation support. The two other most frequently suggested providers were primary care physicians (58%) and clinical support staff such as nurses (56%). A stratification by country showed that primary care physicians were less often (<50%) suggested in Germany, Greece, Luxemburg, Serbia and Sweden, and more often (>75%) in Spain, Switzerland, and the UK. The most commonly reported methods in the respondents’ hospital to support patients in tobacco cessation are face-to-face counseling (37%), and the provision of information materials such as pamphlets (29%), but 23% of the respondents reported no knowledge of a dedicated smoking cessation program available in their center.

Table 1. Respondent Characteristics (n = 544)

Characteristic	No.	%
Age (n = 452 [†])		
<40	121	27
40-49	149	33
≥50	182	40
Sex (n = 453 [†])		
Male	185	41
Female	268	59
Degree (n = 453 [†])		
MD	283	63
MD, PhD	168	37
Other	2	1
Primary area of clinical practice (n = 449 [†])		
Medical oncology	406	90
Radiation oncology	29	7
Clinical oncology	11	2
Thoracic oncology	3	1
Work-setting (n = 453 [†])		
University, academic	227	50
Hospital-based, non-academic	199	44
Other	27	6
Most frequently seen primary tumor types (1-3 sites)		
Breast	265	49
Gastrointestinal	252	46
Lung	213	39
Genitourinary	124	23
Lymphoma	69	13
Gynecologic	72	13
Head and neck	47	9
Skin	49	9
Hepatobiliary	34	6
Brain	32	6
Leukemia	15	3
Other	35	6
Years since completion final degree (n = 451 [†])		
0-4	70	16
5-9	83	18
10-19	128	28
≥20	170	38
Percentage of time devoted to patient care (n = 453 [†])		
0-24	15	3
25-49	32	7
50-74	127	28
75-100	279	62
Respondent's tobacco use history (n = 453 [†])		
Current smoker	22	5
Ever smoker	79	17
Never smoker	352	78

† = 17% missing, and descriptive statistics of complete cases are presented.

Table 2. Oncologist's perceptions of tobacco use in patients with cancer

Setting	Strongly agree	Agree	No opinion or neutral	Disagree	Strongly disagree	
Question (n = 479)						
Current smoking or tobacco use impacts treatment outcomes in cancer patients	C	286 (60%)	164 (34%)	23 (5%)	4 (1%)	2 (<1%)
	P	135 (28%)	220 (46%)	96 (20%)	25 (5%)	3 (1%)
Smoking/tobacco cessation should be a standard part of cancer treatment interventions	C	308 (64%)	147 (31%)	18 (4%)	5 (1%)	1 (<1%)
	P	123 (26%)	179 (37%)	112 (23%)	62 (13%)	3 (1%)
I have had adequate training in smoking/tobacco cessation interventions	-	19 (4%)	90 (19%)	119 (25%)	209 (44%)	42 (9%)
Clinicians need more training in smoking/tobacco assessment and cessation interventions	-	120 (25%)	231 (48%)	94 (20%)	32 (7%)	2 (<1%)
Selected						
Question	No. (%)					
Which of the following providers do you think is appropriate to provide cessation support for cancer patients on a regular basis (more answers were possible):						
A. Primary care physician	315 (58%)					
B. MD level provider, other than primary care physician	75 (14%)					
C. Mid-level clinician such as a nurse practitioner or physician assistant	202 (37%)					
D. Clinical support staff within the clinic such as a nurse, psychologist, or social worker	306 (56%)					
E. The treating oncologist	227 (42%)					
F. I would not use any of the above resources	9 (2%)					
G. Other	29 (5%)					
What type of dedicated smoking/tobacco cessation program does your Cancer Center or Clinic have available for your cancer patients (more answers were possible):						
A. A tobacco cessation clinic/specialist that provides face-to-face counseling	199 (37%)					
B. A tobacco cessation specialist who provides telephone based counseling	47 (9%)					
C. A tobacco cessation clinic/specialist that provides pharmacotherapy	92 (17%)					
D. Provision of tobacco cessation materials, such as pamphlets or a DVD	159 (29%)					
E. None to my knowledge	124 (23%)					
F. I don't know	55 (10%)					
G. Other	20 (4%)					

C, curative, P, palliative. † = 12% missing, and descriptive statistics of complete cases are presented.

Interactions with the patient

Table 3 shows the oncologists’ practices and communication with the patient. The vast majority of respondents reported to always or most of the time ask patients if they smoke tobacco products, both in the curative (93%) and the palliative (78%) setting. Asking about using alternative tobacco products was less frequently reported as 57% of oncologists indicated to ask for cigar, pipe, snuff use in in the curative and 48% in the palliative setting, while the use of electronic cigarettes or devices was reported to be asked always or most of the time by 39% of the oncologists in the curative setting and by 33% in the palliative setting. When asking patients about tobacco use, most oncologists do not use a structured method for the assessment (rarely or never by 69% in the curative and 71% in the palliative setting). Although oncologists indicated that they do ask smokers if they want to quit smoking (always or most of the time by 75% in the curative and 50% in the palliative setting) and also advise smokers to quit (88% in the curative and 54% in the palliative setting), only 39% reported to discuss medication options always or most of the time with curative patients, and 24% with palliative patients. Overall, 69% of the respondents reported to discuss tobacco use and cessation options equally in patients with tobacco-related and non-tobacco-related cancers in the curative setting, and 58% in the palliative setting.

Barriers for interventions

Oncologists agreed or strongly agreed that the perceived inability to get patients to quit (69% in the curative and 61% in the palliative setting), the patient’s resistance (69% in the curative and 70% in the palliative setting), the lack of time for counseling (59% in the curative and 54% in the palliative setting), and a lack of training in cessation interventions (65% in the curative and 61% in the palliative setting) are barriers to facilitate smoking cessation interventions (Table 4). In contrast, very few respondents agreed or strongly disagreed that smoking cessation after diagnosis is a waste of time (3% in the curative and 14% in the palliative setting). The oncologist’s own hesitation and “not feeling comfortable taking something away patients might enjoy doing” are more present in the palliative setting since 43% agreed or strongly agreed to this statement, as compared to 13% in the curative setting.

Table 3. Oncologist's interactions with cancer patients

Setting		Always	Most of the time	Some of the time	Rarely	Never	N/A	
Question (n = 496 ¹)		No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	
ask patients if they smoke or use tobacco products	C	361 (73%)	100 (20%)	22 (4%)	8 (2%)	2 (<1%)	3 (1%)	
	P	260 (51%)	136 (27%)	48 (10%)	41 (9%)	11 (2%)	0 (0%)	
ask patients if they use other tobacco products such as cigars, pipes, snuff, hookah/shisha, IQOS, etc.	C	183 (37%)	97 (20%)	84 (17%)	93 (19%)	35 (7%)	4 (1%)	
	P	136 (27%)	102 (21%)	83 (17%)	117 (24%)	55 (11%)	3 (1%)	
ask patients if they use electronic cigarettes or other electronic nicotine delivery devices	C	132 (27%)	63 (13%)	65 (13%)	121 (24%)	108 (22%)	7 (1%)	
	P	100 (20%)	64 (13%)	70 (14%)	127 (26%)	130 (26%)	5 (1%)	
When asking about tobacco use, I use a structured questionnaire or other structured method for asking questions	C	69 (14%)	43 (9%)	27 (5%)	61 (12%)	279 (56%)	17 (3%)	
	P	59 (12%)	38 (8%)	30 (6%)	61 (12%)	293 (59%)	15 (3%)	
ask patients who smoke or use tobacco if they want to quit smoking	C	231 (47%)	139 (28%)	69 (14%)	32 (7%)	22 (4%)	3 (1%)	
	P	134 (27%)	113 (23%)	117 (24%)	84 (17%)	48 (10%)	0 (0%)	
advise patients who smoke or use tobacco products to stop smoking	C	313 (63%)	123 (25%)	37 (8%)	14 (3%)	6 (1%)	3 (1%)	
	P	134 (27%)	135 (27%)	117 (24%)	75 (15%)	35 (7%)	0 (0%)	
discuss medication options such as nicotine replacement, bupropion, varenicline, etc.	C	71 (14%)	122 (25%)	146 (29%)	102 (21%)	49 (10%)	6 (1%)	
	P	35 (7%)	84 (17%)	138 (28%)	149 (30%)	83 (17%)	7 (1%)	
actively treat or refer patients for a smoking/tobacco cessation intervention	C	62 (13%)	93 (19%)	145 (29%)	121 (24%)	64 (13%)	11 (2%)	
	P	30 (6%)	60 (12%)	113 (23%)	160 (32%)	123 (25%)	10 (2%)	
During follow-up appointments, I continue to assess smoking behavior in active smokers, and ask patients that have quit whether they might have relapsed back into tobacco use	C	118 (24%)	135 (27%)	113 (23%)	84 (17%)	33 (7%)	13 (3%)	
	P	50 (10%)	79 (16%)	139 (28%)	141 (28%)	78 (16%)	9 (2%)	
		No, I discuss this equally in patients with tobacco-related and non-tobacco related cancers		Yes, I mostly discuss this with patients with tobacco-related cancers		Yes, I mostly discuss this with patients with non-tobacco-related cancers		N/A
Question (n = 496 ¹)		No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	
My interactions with patients regarding smoking/tobacco use (above questions), differ between tobacco-related vs. non-tobacco-related cancers	C	343 (69%)	113 (23%)	8 (2%)			32 (7%)	
	P	288 (58%)	126 (25%)	18 (4%)			64 (13%)	

C, curative; P, palliative. + = 9% missing, and descriptive statistics of complete cases are presented.

Table 4. Potential barriers to smoking/tobacco cessation support

Question (n = 466 [†])	Setting	Strongly agree		Agree		No opinion or neutral		Disagree		Strongly disagree	
		No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
The inability to get patients to quit smoking/tobacco use	C	80 (17%)	243 (52%)	83 (18%)	53 (11%)	7 (2%)					
	P	77 (17%)	205 (44%)	131 (28%)	47 (10%)	6 (1%)					
My own hesitation; it feels like bothering the patient, and I do not feel comfortable taking something away they might enjoy doing	C	5 (1%)	57 (12%)	45 (10%)	238 (51%)	121 (26%)					
	P	35 (8%)	163 (35%)	88 (19%)	130 (28%)	50 (11%)					
Waste of time; cessation after diagnosis does not affect outcomes in cancer patients	C	2 (<1%)	12 (3%)	35 (8%)	236 (51%)	181 (39%)					
	P	8 (2%)	55 (12%)	103 (22%)	207 (44%)	93 (20%)					
Lack of time for counseling or to set up a referral	C	68 (15%)	208 (45%)	70 (15%)	89 (19%)	31 (7%)					
	P	68 (15%)	183 (39%)	111 (24%)	82 (18%)	22 (5%)					
No or limited reimbursement (financial reasons)	C	26 (6%)	74 (16%)	170 (37%)	129 (28%)	67 (14%)					
	P	28 (6%)	69 (15%)	174 (37%)	129 (28%)	66 (14%)					
Patient's resistance to a cessation treatment	C	68 (15%)	255 (55%)	69 (15%)	62 (13%)	12 (3%)					
	P	75 (16%)	252 (54%)	83 (18%)	49 (11%)	7 (2%)					
Lack of training or experience in cessation interventions	C	57 (12%)	246 (53%)	89 (19%)	66 (14%)	8 (2%)					
	P	52 (11%)	234 (50%)	103 (22%)	69 (15%)	8 (2%)					
Lack of available resources or referrals for cessation interventions	C	73 (16%)	184 (40%)	85 (18%)	109 (23%)	15 (3%)					
	P	68 (15%)	173 (37%)	103 (22%)	107 (23%)	15 (3%)					

C, curative, P, palliative. † = 14% missing, and descriptive statistics of complete cases are presented.

Discussion

Among European oncologists who responded to the online survey on smoking cessation in patients with cancer, most oncologists reported to believe that tobacco use impacts treatment outcomes, and that smoking cessation interventions should be a part of the multidisciplinary treatment. Most oncologists ask patients for tobacco use and advise those who use tobacco to quit – both in the curative and the palliative setting, and with similar frequency for both patients with tobacco-related and non-tobacco related cancers. Use of other tobacco products or electronic cigarettes is less frequently interrogated. Barriers to provide cessation support were conceived rather equally between the curative and the palliative setting, with a lack in training, the perception of inability to get patients to quit, patient resistance, and a lack of time being the most frequently reported. Oncologists appeared to report higher rates of addressing tobacco in the curative as compared to the palliative setting, but except for the oncologist’s own hesitations to take away a pleasurable habit and disbelief in an effect on outcomes, barriers were remarkably similar between the curative and palliative setting. To our knowledge, this is the first large survey to report the effects of cancer treatment setting on tobacco assessment and barriers to support.

In curative setting patients, results are consistent with the 2013 ASCO¹⁵ and IASLC¹⁶ surveys demonstrating that about 90% of oncologists regularly ask about tobacco use, 80-90% regularly advise patients to quit smoking, and 30-40% regularly provide assistant to quit through medications or counseling. In contrast, patients in the palliative setting received consistently lower support with 54% advised to quit and 18-24% provided medications or counseling. This unique finding suggests that oncologists perceive tobacco cessation as less important in the palliative setting, particularly due to the reported hesitations from not feeling comfortable taking something away patients might enjoy doing, and less belief in an effect on outcomes. Nevertheless, still 64% of oncologists disagreed that cessation is a waste of time because of no impact on outcomes.

In contrast to assessing and addressing tobacco use, barriers to support appeared more consistent between the curative and palliative setting. Analysis of the IASLC survey demonstrated that significant predictive barriers to providing medications or counseling were a lack of time for counseling or referral, lack of available resources, and lack of training or experience¹⁷. Our results show that these predictive barriers were remarkably consistent according to cancer treatment intent with 60% vs. 55% for lack of time, 56% vs.

53% for lack of resources, and 65% vs. 61% for lack of training or experience for curative vs. palliative setting, respectively.

Further comparison between the current survey and the 2013 surveys ^{15, 16} shows that a lack of time and adequate training were more frequently reported compared to 2013, whereas no reimbursement and financial reasons were less frequently reported. The latter might be caused by the nationality of the respondents where financial healthcare policies could be different as compared to most European countries. Our results show a high percentage of oncologists reporting inadequate training and that more training is needed to better support patients, which suggests that oncologists are receptive to additional training regarding the impact of cessation after diagnosis and possibilities of effective interventions.

Clinicians might feel that smoking cessation should mainly be emphasized in patients with either early stage or curable disease. However, a large review of the literature showed that smoking increases mortality in patients with both early and advanced or metastatic cancer ¹. Moreover, the 2020 Surgeon General's Report demonstrated that smoking cessation after a cancer diagnosis was associated with improved overall survival ³. Smoking cessation after a cancer diagnosis has further shown to improve cancer-related survival, risk of second primary cancer, and quality of life ¹⁸⁻²⁷. Although limited evidence suggests that for immunotherapy there seems to be an association between current or ever smoking and a better treatment response ²⁸, one study (KEYNOTE-024) has revealed better treatment outcomes for former smokers compared to current smokers, suggesting that smoking cessation before and during immunotherapy could be beneficial ²⁹. Much work remains to clarify the relationship between smoking and targeted cancer therapeutics.

An enhanced focus on smoking cessation at the time of a cancer diagnosis may increase patients' action to quit. It has been shown that patients with cancer have a higher quit rate, compared to people without cancer ³⁰. Hence, this highly opportune situation - often referred to as the "teachable moment" - should be utilized by health care professionals to introduce cessation support ³¹. In our survey, oncologists indicated that next to the treating oncologist, the primary care physician and clinical support staff were the three most suitable to provide cessation support. We would like to argue that there is a role for the treating oncologist to identify tobacco use, advise patients to quit, and either provide support to help patients quit or provide referral to evidence-based tobacco treatment resources. Depending on the clinical situation and resources, the treating oncologist may refer the patient to the primary care physician, a dedicated tobacco treatment clinician, a

phone based tobacco treatment program such as a quitline, or clinical support staff who have been trained to deliver evidence-based tobacco treatment.

It has recently been shown that providing comprehensive tobacco treatments including intensive counseling and proactive pharmacologic management in the oncologic setting can lead to sustained cessation in almost half of patients with cancer who smoke ³². In response to these study results, Fiore and colleagues ³³ stated that an effective cessation treatment for patients with cancer who smoke should become the fourth pillar - and an integral and essential component - of comprehensive cancer care, and describe in detail which steps are needed to promote smoking cessation treatment implementation in cancer care. This approach fits well in the current era in which there is an increased focus on delivering the best oncologic care at the lowest cost to assure an appropriate allocation of resources in health care systems ³⁴. When new antineoplastic agents are introduced, the efficacy, safety and costs of treatment are currently the main considerations ³⁵. Continued smoking is a factor that contributes to potential failure of first-line treatment and leads to significant incremental costs to the healthcare system ². Hence, smoking behavior should be given more consideration, especially given its potentially modifiable nature.

The inevitable limitation of the current survey study is the presence of selective response. Since respondents are likely to be oncologists with a higher interest in the role of lifestyle factors, such as smoking, the results may be an optimistic representation of "true" daily practices and perceptions towards tobacco use and cessation support. Although generalizability might be affected by the low response rate (~9.1%), the obtained response rate is in line with other international lifestyle-related surveys in the oncology setting ^{15, 36} and results are highly congruent with prior published surveys using similar or identical questions ^{15, 16}. In general, true practice patterns of oncologists are likely to be worse than our results show, which only strengthens our recommendations of implementing routine smoking behavior assessments in every patient with cancer and including evidence-based smoking cessation support in the oncologic care path. Strengths of this study include the large sample of oncologists and participation of 16 European countries, which underpins the broad support for the obtained results. Lastly, the specific distinction between the curative and the palliative setting allowed to study the current views towards cessation support in the palliative trajectory.

To conclude, this study demonstrates that oncologists appear to address tobacco use more frequently in the curative setting than in the palliative setting. Unfortunately, this study

further suggests that practice patterns remain relatively unchanged despite significant advances in the evidence base that smoking affects cancer treatment outcomes. The dominant barriers of lack of time, resources, and education suggest that addressing these issues may improve tobacco treatment in both the curative and palliative setting. We recommend that all cancer patients should be screened for smoking status at diagnosis, and active smokers should have access to evidence-based smoking cessation support to improve cancer treatment outcomes as well as improve outcomes for non-cancer related health conditions known to be improved with smoking cessation.

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SUPPLEMENTARY
MATERIAL

Supplementary S1. List of participating countries (organizations)

- Belgium** (Belgian Society of Medical Oncology [BSMO], in Belgian: Belgische Vereniging voor Medische Oncologie - Société belge d'Oncologie médicale)
- Denmark** (Danish Society for Medical Oncology, In Danish: Dansk Selskab Klinisk Onkologi [DSKO])
- Estonia** (Estonian Society of Medical Oncology, in Estonian: Eesti Onkoterapia Ühing [EOU])
- Finland** (Finnish Society for Oncology, in Finnish: Suomen Onkologiayhdistys)
- Germany** (Medical Oncology Association as part of the German Cancer Society, in German: Arbeitsge-meinschaft Internistische Onkologie (AIO))
- Greece** (Hellenic Society of Medical Oncology [HeSMO])
- Ireland** (Irish Society of Medical Oncology [ISMO])
- Lithuania** (Lithuanian Society for Medical Oncology [LSMO], in Lithuanian: Lietuvos onkologų chemo-terapeutų draugija)
- Luxembourg**, (Luxembourg Society of Oncology [SLO], in Luxembourg: Société Luxembourgeoise d'Oncologie)
- The Netherlands** (Dutch Colorectal Cancer Group [DCCG], Dutch Upper GI Cancer Group [DUCG], and the Dutch Neuro-Oncology Society [DNOS])
- Poland** (Polish Society of Clinical Oncology, in Polish: Polskie Towarzystwo Onkologii Klinicznej [PTOK])
- Serbia** (Serbian Society of Medical Oncology, in Serbian: Udruženje Medikalnih Onkologa Srbije [UMOS])
- Spain** (Spanish Society of Medical Oncology, in Spanish: Sociedad Española de Oncología Médica [SEOM])
- Sweden** (Swedish Society of Oncology, in Swedish: Svensk Onkologisk Förening [SOF])
- Switzerland** (Swiss Society of Medical Oncology, in Swiss: Schweizerische Gesellschaft für Medizinische Onkologie [SGMO])
- United Kingdom** (Association of Cancer Physicians [ACP])

Supplementary S2. Survey on smoking in patients with cancer.

1/5. Respondent's practice:

1. Which primary tumor types do you see most often? (max of 3 answers)

Breast	Check
Lung	Check
Gastrointestinal	Check
Lymphoma	Check
Genitourinary	Check
Head and neck	Check
Gynecologic	Check
Leukemia	Check
Skin	Check
Brain	Check
Other, [open text field]	Check

2/5. Physician's interactions with patients

2. I ask patients if they smoke or use tobacco products

	Always	Most of the time	Some of the time	Rarely	Never	N/A
In the curative setting						
In the palliative setting						

3. I ask patients if they use other tobacco products such as cigars, pipes, snuff, hookah/shisha, IQOS, etc.

	Always	Most of the time	Some of the time	Rarely	Never	N/A
In the curative setting						
In the palliative setting						

4. I ask patients if they use electronic cigarettes or other electronic nicotine delivery devices

	Always	Most of the time	Some of the time	Rarely	Never	N/A
In the curative setting						
In the palliative setting						

5. When asking about tobacco use, I use a structured questionnaire or other structured method for asking questions

	Always	Most of the time	Some of the time	Rarely	Never	N/A
In the curative setting						
In the palliative setting						

6. I ask patients who smoke or use tobacco if they want to quit smoking

	Always	Most of the time	Some of the time	Rarely	Never	N/A
In the curative setting						
In the palliative setting						

7. I advise patients who smoke or use tobacco products to stop smoking

	Always	Most of the time	Some of the time	Rarely	Never	N/A
In the curative setting						
In the palliative setting						

8. I discuss medication options such as nicotine replacement, bupropion, varenicline, etc.

	Always	Most of the time	Some of the time	Rarely	Never	N/A
In the curative setting						
In the palliative setting						

9. I actively treat or refer patients for a smoking/tobacco cessation intervention

	Always	Most of the time	Some of the time	Rarely	Never	N/A
In the curative setting						
In the palliative setting						

10. During follow-up appointments, I continue to assess smoking behavior in active smokers and ask patients that have quit whether they might have relapsed back into tobacco use

	Always	Most of the time	Some of the time	Rarely	Never	N/A
In the curative setting						
In the palliative setting						

11. My interactions with patients regarding smoking/tobacco use (question 1-10) differ between tobacco-related vs. non tobacco-related cancers

	No, I discuss this equally in patients with tobacco-related and non tobacco-related cancers	Yes, I mostly discuss this with patients with tobacco-related cancers	Yes, I mostly discuss this with patients with non tobacco-related cancers	N/A
In the curative setting				
In the palliative setting				

3/5. Physician's perceptions of tobacco use in patients with cancer:

12. Current smoking or tobacco use impacts treatment outcomes in cancer patients

	Strongly agree	Agree	No opinion or neutral	Disagree	Strongly disagree
In the curative setting					
In the palliative setting					

13. Smoking/tobacco cessation should be a standard part of cancer treatment interventions

	Strongly agree	Agree	No opinion or neutral	Disagree	Strongly disagree
In the curative setting					
In the palliative setting					

14. I have had adequate training in smoking/tobacco cessation interventions

Strongly agree	Agree	No opinion or neutral	Disagree	Strongly disagree

15. Clinicians need more training in smoking/tobacco assessment and cessation interventions

Strongly agree	Agree	No opinion or neutral	Disagree	Strongly disagree

16. Which of the following providers do you think is appropriate to provide cessation support for cancer patients on a regular basis? (check at least one)

A. Primary care physician	Check
B. MD level provider (other than primary care physician)	Check
C. Mid-level clinician such as a nurse practitioner or physician assistant	Check
D. Clinical support staff within the clinic such as a nurse, psychologist, or social worker	Check
E. The treating oncologist	Check
F. I would not use any of the above resources	Check

17. What type of dedicated smoking/tobacco cessation program does your Cancer Center or Clinic have available for your cancer patients (check at least one)

A. A tobacco cessation clinic/specialist that provides face-to-face counseling	Check
B. A tobacco cessation specialist who provides telephone based counseling	Check
C. A tobacco cessation clinic/specialist that provides pharmacotherapy	Check
D. Provision of tobacco cessation materials (such as pamphlets or a DVD)	Check
E. I don't know	Check
F. None to my knowledge	Check
G. Other	Specify, [open text field]

4/5. What do you think are potential barriers to smoking/tobacco cessation interventions:

18. The inability to get patients to quit smoking/tobacco use

	Strongly agree	Agree	No opinion or neutral	Disagree	Strongly disagree
In the curative setting					
In the palliative setting					

19. My own hesitation; it feels like bothering the patient, and I do not feel comfortable taking something away they might enjoy doing

	Strongly agree	Agree	No opinion or neutral	Disagree	Strongly disagree
In the curative setting					
In the palliative setting					

20. Waste of time; cessation after diagnosis does not affect outcomes in cancer patients

	Strongly agree	Agree	No opinion or neutral	Disagree	Strongly disagree
In the curative setting					
In the palliative setting					

21. Lack of time for counseling or to set up a referral

	Strongly agree	Agree	No opinion or neutral	Disagree	Strongly disagree
In the curative setting					
In the palliative setting					

22. No or limited provider reimbursement (financial reasons)

	Strongly agree	Agree	No opinion or neutral	Disagree	Strongly disagree
In the curative setting					
In the palliative setting					

23. Patient's resistance to a cessation treatment

	Strongly agree	Agree	No opinion or neutral	Disagree	Strongly disagree
In the curative setting					
In the palliative setting					

24. Lack of training or experience in cessation interventions

	Strongly agree	Agree	No opinion or neutral	Disagree	Strongly disagree
In the curative setting					
In the palliative setting					

25. Lack of available resources or referrals for cessation interventions

	Strongly agree	Agree	No opinion or neutral	Disagree	Strongly disagree
In the curative setting					
In the palliative setting					

5/5. Respondent's characteristics:

26. What is your age?

Open answer:

27. What is your sex?

Male	Female
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28. What is your degree?

Medical Doctor (MD)	MD, PhD	College (e.g. nurse)	Other [open text]
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29. What is your primary area of clinical practice?

Medical oncology	Surgical oncology	Radiation oncology	Other [open text]
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30. What is your work setting?

University or academic	Hospital based non-academic	Stand alone	Other [open text]
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31. How many years has it been since you completed your final degree?

Open answer:

32. What percentage of your time do you devote to patient care?

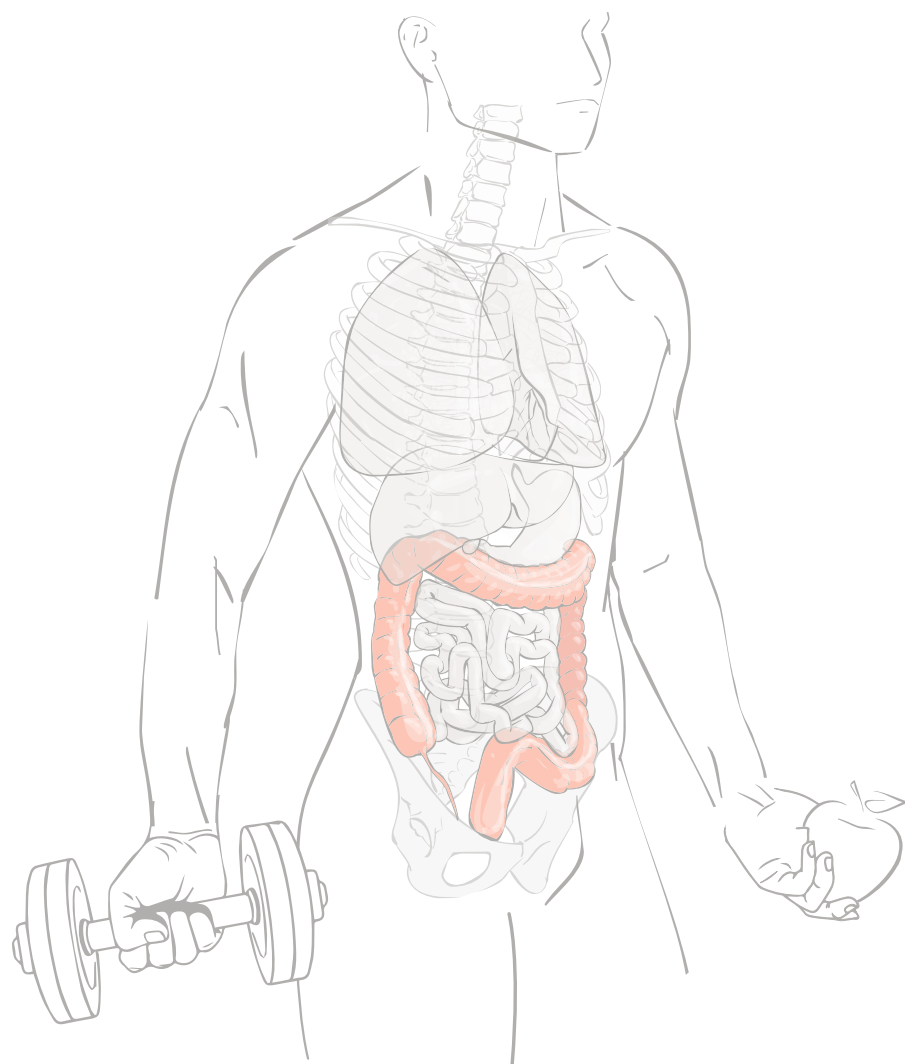
Open answer:

33. Do you currently smoke cigarettes/tobacco?

No, not at all	Yes, some days	Yes, every day	Other [open text]
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34. Have you ever smoked cigarettes/tobacco in your life?

No, never	Yes, but less than 100	Yes, more than 100	Other [open text]
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8

GENERAL DISCUSSION
AND FUTURE PERSPECTIVES

In this thesis we aimed to describe research methods to improve clinical research in the field of cancer survivorship, and to contribute to evidence on the role of lifestyle-related factors in CRC. We focused on body composition measures, more specifically skeletal muscle mass (SMM), which is considered potentially modifiable by means of diet and physical exercise. Within the oncological community there is increasing interest in understanding how body composition measures can be used to optimize cancer treatment and survivorship care ¹. Among other methods, computed tomography (CT) can be used to distinguish muscle from subcutaneous and visceral adipose tissue, and muscle mass has been shown to be a more sensitive prognostic factor compared to body mass index (BMI) ². Previous research from our department in patients with metastatic colorectal cancer (mCRC), treated with first-line palliative systemic therapy in the CAIRO3 study, showed that muscle loss during initial treatment is reversible and may be influenced by the type and intensity of subsequent regimens ³. Additionally, muscle loss was associated with 1) an increased risk of dose-limiting toxicities ⁴, 2) earlier disease progression ⁵, and 3) reduced survival ⁶. This thesis adds further evidence to the detrimental outcomes related to muscle wasting and shows that independent of treatment, preserving SMM relates to improved overall quality of life and role functioning, as well as a decrease in fatigue and pain, all of which are considered to be clinically relevant improvements ⁷. Factors that we found to be related to muscle wasting during first-line systemic treatment for mCRC were a higher initial muscle mass, smoking, and having metachronous metastases, while primary tumor resection was associated with muscle gain ⁸.

Moreover, these observations from the metastatic setting are further supported by a meta-analysis of 12 studies including 5337 non-metastatic CRC patients, in which sarcopenia at diagnosis - defined as low muscle mass - was shown to be associated with decreased overall survival [HR: 1.63, 95% CI: 1.24–2.14] ⁹. In addition, losing SMM during one year post-diagnosis, independent of change in body mass, is also negatively associated with survival in patients with stage I–III CRC as Brown and colleagues showed that losing ≥11% of SMM since diagnosis was associated with decreased overall survival [HR: 2.15, 95% CI: 1.59–2.92] ¹⁰. The patient's muscle mass can also be used as a prognostic biomarker to identify patients at risk of chemotherapy-related toxicity. For example, low SMM at the time of diagnosis was shown to be associated with an increased risk of neutropenia or thrombocytopenia and poor adherence to adjuvant chemotherapy [OR: 2.34, 95% CI: 1.04–5.24] in patients with non-metastatic colon cancer ¹¹.

Body composition analysis using repeated measures have mainly been performed using data from metastatic cancer patients, since CT scans are routinely available in these patients and can easily be used for research purposes. To date, it has not been studied whether a loss of SMM is associated with treatment-related toxicities from adjuvant chemotherapy in stage II - III colon cancer patients. For this reason, we initiated the PLCRC-PROTECT-Plus study in 2016 to investigate the association between change in body composition and toxicities from adjuvant chemotherapy. In 150 patients, the evolution of body composition will be measured based on repeated routine and additional research-specific CT scans. Furthermore, the occurrence and severity of treatment-related toxicities are collected, both patient-reported and clinically reported by the treating oncologist. This study will provide insight into the evolution of body composition during and after adjuvant chemotherapy, which factors are related to the deterioration of body composition, and how this is associated with the occurrence and severity of treatment-related toxicities. In anticipation, and based on the publication of Cespedes and colleagues ¹¹, various groups globally have started intervention trials that personalize chemotherapy dosing. For example, Sawyer and colleagues are currently performing a phase-II double-blind randomized trial in which patients with advanced lung cancer are randomized between conventional dosing based on body surface area vs. dosing based on lean body mass (ClinicalTrials.gov Identifier: NCT01624051), with the aim to reduce dose-limiting toxicity rates and optimize the number of cycles completed ^{12, 13}.

Other approaches that are based on the same hypothesis to minimize dose-limiting toxicities are interventions that target muscle mass to prevent cancer-related muscle wasting, including physical exercise and nutritional supplementation. Within our regional "specialized nutrition to improve clinical outcomes in colorectal cancer patients (SCOPE)" consortium, several clinical as well as preclinical projects are ongoing to further investigate the role of muscle mass on clinical colorectal cancer outcomes. These studies will contribute to scientific evidence on the potential of a specific medical nutrition supplement developed to limit the loss of muscle mass observed during chemotherapy. Mechanisms by which muscle mass is supported include the stimulation of muscle protein synthesis while limiting inflammation-related protein degradation. Currently, the compliance to the recommended daily intake during the first three cycles of palliative treatment is studied, after which a larger phase 3 trial may provide evidence on the impact of oral nutritional supplementation on clinical outcomes.

Until more definitive clinical trial results become available, observational studies so far have shown that body composition measures can be used as guidance for clinicians to identify patients who may benefit from preventive interventions. In patients with low SMM, several interventions can be considered, including the administration of pegfilgrastim as prophylaxis to prevent febrile neutropenia ¹⁴, providing smoking cessation support in current smokers to limit further muscle wasting and improve clinical outcomes ^{8,15}, referral to an (oncology-)dietician for advice to meet energy and macronutrient requirements ¹⁶, and referral to an (oncology-)physiotherapist or specialized fitness center to engage in physical exercise, which has been shown to be safe and feasible in patients with early stage ¹⁷ and advanced cancer ^{18,19}, and has proven to increase SMM ²⁰.

In order to have body composition assessment and utilization implemented into large-scale oncologic workflows, several barriers need to be addressed. First, it remains uncertain whether changes in body composition are causally related to clinical outcomes. Therefore, more trial-based evidence is needed to prove causality, and even more important, reversibility and subsequent improvements of clinical outcomes through interventions. Second, body composition is currently quantified by hand using software designed for research purposes. Automated and cost-efficient methods to assess body composition in clinically acquired images are needed to facilitate the utilization by clinicians.

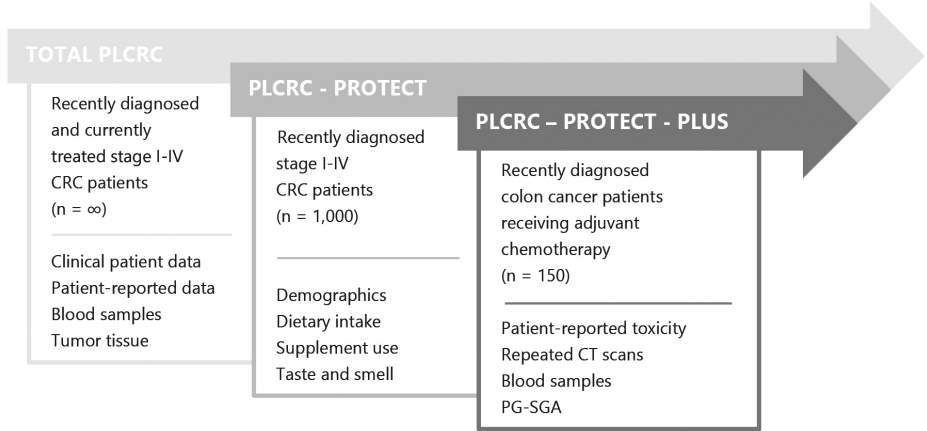


Figure 1. Flowchart of the interconnectedness of PLCRC and the two PROTECT studies.

The above described PROTECT-Plus study is embedded in the PLCRC-PROTECT study which was initiated in 2016 aiming to recruit 1,000 patients with stage I-IV CRC to collect repeated patient-reported measures on dietary intake for a period of 24 months post-

diagnosis (Figure 1). This will provide additional data on (changes in) dietary patterns that can be used in our analyses on body composition. The PROTECT study was initiated to collect comprehensive data on general demographics, the occurrence of taste and smell alterations (as a common side effect of chemotherapeutics), dietary intake, as well as dietary supplement use, to study associations between dietary factors and CRC outcomes. To date, over 700 patients have been recruited from 19 hospitals, more than 180 participants have attained the last follow-up time point at 24 months post-inclusion (T24), and questionnaire completion rates range from 82% at baseline to 50% at T24. Both PROTECT studies are incorporated in the Prospective Dutch Colorectal cancer (PLCRC) cohort, which was initiated in 2013 to become a nationwide infrastructure for a wide variety of research projects ²¹. PLCRC is linked with the Netherlands Cancer Registry to ascertain clinical follow-up data that covers the complete treatment trajectory. Besides informed consent for linkage and use of longitudinal clinical patient data, informed consent can also be provided for biobanking of blood samples and (tumor) tissue, being informed about future studies including trials embedded in the cohort (TwiCs), and for receiving repeated questionnaires to provide patient-reported outcome data including health-related and stoma-related quality of life, ability to work, comorbidities, physical activity, and side effects such as fatigue, anxiety and depression, and peripheral neuropathy. With this infrastructure, PLCRC aims to facilitate a wide range of research in a nationwide cohort of increasing “real-world” nature.

Future perspectives

The majority of evidence on the role of lifestyle factors such as diet, physical activity, and smoking behavior and their association with cancer outcomes originates from cohort studies that largely rely on self-reported measures. Even though novel technologies for measuring lifestyle factors have been introduced, most are still in their infancy, and research strategies in the next decade will continue to focus on cohort studies with repeated measures, which are feasible to obtain on a large scale. Nevertheless, nutritional epidemiology studies should evolve as a result of our increased understanding of CRC biology. Generally, there are different (epi)genetic pathways involved in CRC carcinogenesis and tumors resulting from each pathway have specific molecular characteristics that are often associated with different clinical outcomes ^{22,23}. A recent significant advancement in CRC research was the development of a classification system called the Consensus Molecular Subtypes (CMS) to facilitate CRC stratification into four robust subtypes based on molecular differences ²⁴. Given these differences and the heterogeneity of CRC,

traditional epidemiological analyses may conceal or underestimate true associations between diet, lifestyle and disease outcomes ²⁵.

The emerging field of molecular pathological epidemiology (MPE) has been adopted in clinical medicine to enhance insights into pathogenic processes and better elucidate diet and lifestyle-related mechanisms of action in disease evolution ^{26,27}. Using this MPE approach it has been shown for example that a beneficial association exists between higher omega-3 polyunsaturated fatty acid intake and improved survival among patients with stage III colon cancer, specifically in case of wild-type *KRAS* and deficient MMR ²⁸. We speculate that MPE may also advance our understanding of the role of smoking in anti-cancer treatment. Active smoking during targeted therapy might mediate drug resistance given the nicotine-mediated activation of the *RAS-RAF* signaling pathway in colon cancer cells ^{29,30}. Hence, it may well be that quitting smoking, in addition to its general benefits in cancer patients who smoke, has even more benefits in certain subgroups. Future studies on this topic will further contribute to integrative oncology in which multiple factors are considered alongside conventional therapies. Lastly, an inherent limitation of MPE is that analyses are, by definition, performed in subsets of tumor subtypes, which typically limits sample sizes. Therefore, to obtain adequate statistical power, pooling data with other (inter-)national nutritional epidemiology studies will be beneficial. Besides PROTECT, two other large ongoing Dutch cohort studies in colorectal cancer are COLON ³¹ and EnCoRe ³², and future pooling initiatives could allow for robust analyses on CRC outcomes.

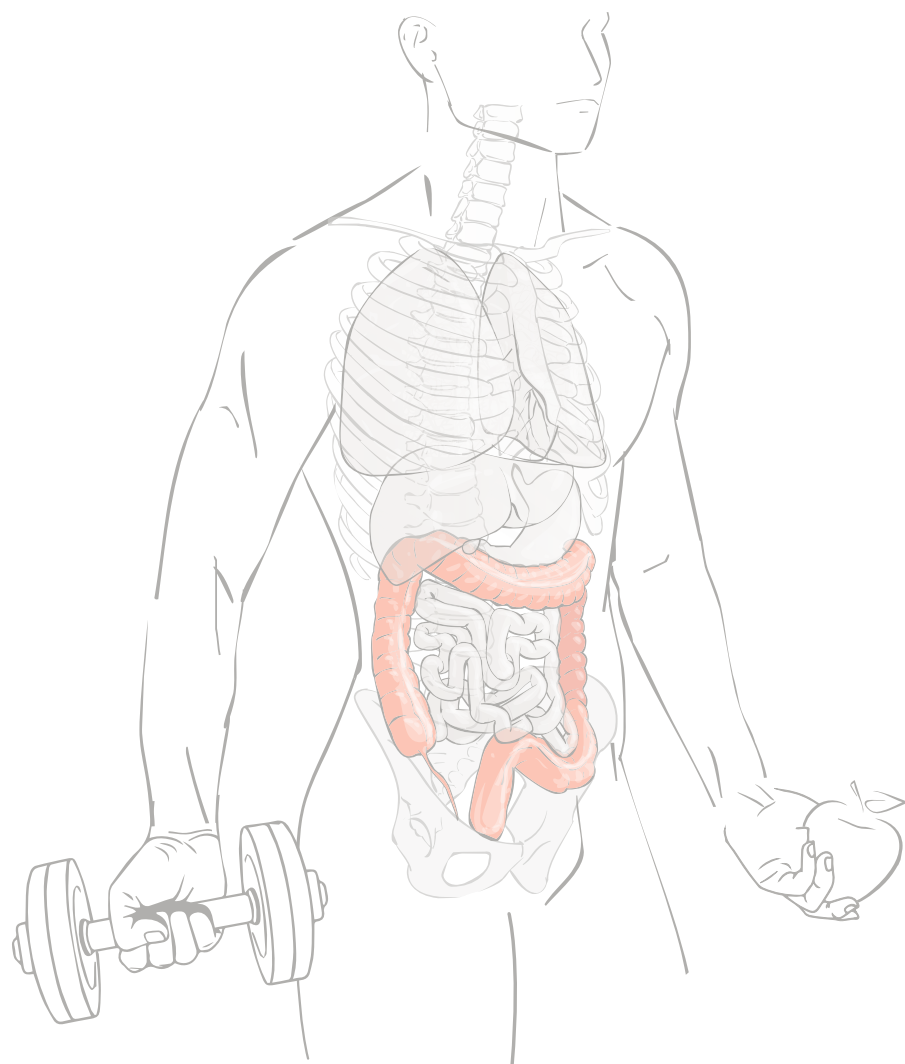
Conclusion

Despite the relatively parallel progresses made in the fields of medical nutrition and medical oncology, paths have recently started to cross. The current recognition of the role of a poor nutritional status including deteriorated muscle mass in affecting both the adherence and response to oncological treatments is a big step forward in the multimodal treatment of cancer. The increasing evidence on nutritional and physical exercise interventions, is the basis for future trials that aim to investigate the combined effectiveness on reversing cancer-related muscle wasting and improving clinical outcomes in patients capable of undergoing these interventions. Initiatives that translate and apply results from exercise-oncology trials are essential to make physical exercise programs more accessible to a larger patient population.

Surgeons and oncologists should not only coordinate the priority and the sequence of the therapeutic approaches, but also include specialists from fields including but not limited to medical nutrition, physical therapy, tobacco cessation treatment, supportive care, and palliative care. In the near future, we need a paradigm shift of all stakeholders involved in cancer care to further intertwine research and clinical practice. Receiving treatments means participation in research while providing clinical care means contributing to research. The development of “real-world” data sources that contain meaningful and high-quality clinical data will facilitate a learning healthcare system that continuously evaluates innovations in clinical practice. In conclusion, professionals from multiple areas including clinicians, epidemiologists, physical therapists, and nutritionists should continue to closely collaborate in order to further advance cancer research and improve colorectal cancer outcomes. This multidisciplinary approach will ultimately lead to an integrative oncology program in which oncologic treatments and supportive care strategies are tailored to the individual patient.

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APPENDICES

SUMMARY (IN ENGLISH AND IN DUTCH)

AUTHORS AND AFFILIATIONS

REVIEW COMMITTEE

LIST OF PUBLICATIONS

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SUMMARY

In the Netherlands, 1 in 20 individuals develop colorectal cancer (CRC) in their lifetime. Survival rates have improved with the advances in early detection and anticancer treatments. In the last decade, a large number of CRC subgroups have been identified, which are defined by clinical characteristics in combination with different molecular markers. Nonetheless, the increased understanding of the biology of disease is both an advancement as well as a challenge in cancer research. "Real-world" data sources can be used to facilitate the evaluation of (innovations in) clinical practice, but also offer a solution when study populations of interest include small subgroups. In the near future, the number of patients living with and beyond cancer will increase, and therefore advancements in supportive care are needed in order to better maintain a patient's physical functioning and health-related quality of life (HRQoL) after diagnosis. The aim of this thesis was to add further evidence to the integrative oncology program in which additional, patient-specific factors are considered to improve CRC outcomes, and to evaluate research methods to enhance future research including lifestyle-related studies and CRC survivorship.

Part I: Research methodologies in oncology

Chapter 2

Novel study designs and (inter)national collaborations collecting data from a large number of patients will allow to perform a range of basic, translational, and clinical studies to support research to improve CRC treatment, tailored to the individual patient. With this patient-centered cancer care the aim is to improve clinical outcomes such as treatment-related side effects, HRQoL and survival. In the Netherlands, the Prospective Dutch Colorectal cancer (PLCRC) cohort was initiated to collect extensive longitudinal clinical patient data, together with blood, (tumor) tissue, and repeated patient-reported outcomes in patients with stage I - IV CRC. PLCRC aims to centralize national CRC research initiatives as much as possible to maximize its potential and lower research burden of individual patients. The increasing number of recruiting hospitals in the PLCRC cohort contributes to the aim of enrolling all newly diagnosed CRC patients in the Netherlands. In Chapter 2 we described the developments of PLCRC and evaluated its representativeness as compared to the general Dutch CRC population. Although our results showed an overall shift towards the general population for participants enrolled between 2017 and 2019, PLCRC participants were still younger and more often diagnosed with stage III disease. However, the observed age disparity is substantially lower than the difference observed in trial populations. Emphasis was put on the importance of the integration of research into daily clinical practice to increase completeness of clinical data, which currently mainly

depends on how well clinicians document clinical data in electronic health records (EHRs). We think that nationwide harmonization and standardization of clinical data entry in EHRs will significantly enhance the completeness and quality of clinical data. For this we need the engagement of the clinical and research community, together with logistics that facilitate optimal entry and data extraction, including a standardized set of clinical data to be registered and a user-friendly data entry interface in EHRs. Since data from PLCRC can be shared with other (inter)national research groups, it will contribute to the need for large collaborations and comprehensive analysis to improve CRC outcomes.

Chapter 3

In a recent review paper, Booth and colleagues provided a comprehensive overview of the challenges and future perspectives related to using real-world data (RWD) in oncology. In response to the authors' appeal for increasing focus to be placed in the implementation of randomized clinical trials (RCTs) in real-world settings, we described how alternative trial designs can be utilized to enhance the "real-world" nature of the data obtained from RCTs in Chapter 3. First of all, registry-based RCTs can - although often methodologically relatively limited - efficiently address research questions about comparative effectiveness in real-world settings. An innovative trial design of interest in RCTs is the "Trials within Cohorts" (TwICs) design. The use of the TwICs design has been incorporated in the PLCRC cohort, by means of a two-stage informed consent procedure. At cohort entry, patients are asked to give informed consent for participation in future research including TwICs studies, and once eligible for a trial only the patients randomized into the intervention group are asked to give a second consent. This approach has methodological advantages, such as avoiding disappointment bias, high recruitment rates, and improved generalizability of trial results. Since the first TwICs studies have only recently been completed, further methodologic research on trial development, execution and statistical analysis is ongoing.

Part II: Lifestyle factors, body composition and quality of life

Chapter 4

Given the increasing proportion of patients surviving longer than 5 years after primary diagnosis, there is an increasing number of studies focusing on improving long term HRQoL and survivorship. In Chapter 4, we described current and novel methodologies for ambulant large-scale monitoring of potentially modifiable lifestyle-related factors, including dietary intake, body composition, alcohol consumption, smoking behavior and physical activity, in cancer survivors from the moment of diagnosis onwards. Despite the

presence of many tools that allow (objective) ambulant measurements of the discussed lifestyle factors, improvements are needed to ascertain their applicability on a large scale. While new tools are currently under development, we highlight the importance of harmonizing data collection in order to allow between-study comparisons or (inter) national pooling projects.

Chapter 5

Owing to the widespread adoption of CT assessments to measure body composition, more than 950 publications in the last decade have shown that sarcopenia (severe muscle depletion) and a catabolic loss of muscle over time are both associated with poor clinical outcomes including complications of cancer surgery, increased treatment-related toxicities and mortality in different populations of cancer patients. However, only a few studies have investigated the association of muscle mass and HRQoL. More evidence on this potential association will justify further research into strategies that may improve HRQoL. In Chapter 5, we showed the results of our analysis on changes in muscle mass and subsequent changes in disease-specific symptoms, daily functioning and overall HRQoL in 221 patients treated in the CAIRO3 study. Independent of treatment arm, patients who preserved, i.e. stabilized or increased, muscle mass reported to perceive a significant and clinically relevant increase in overall quality of life and role functioning, as well as a decrease in fatigue and pain. The reductions in fatigue and pain, which are frequent side effects of treatment with capecitabine and bevacizumab (CAP-B), are of special interest since both are known to be independent predictors of survival in different cancer populations. This study contributed to the identification of muscle mass as a potentially modifiable factor that relates to patients' HRQoL. This finding is valuable input for future intervention studies.

Chapter 6

In order to investigate which patients might be at increased risk of muscle loss, we investigated in Chapter 6 which demographic, lifestyle- (smoking), tumor-, and treatment-related factors were associated with muscle loss in metastatic CRC patients during first-line systemic treatment. In this study, we excluded the possible effects of disease progression on change in muscle mass, as all patients responded with stable disease or (partial or complete) response to the six initial cycles of capecitabine, oxaliplatin, and bevacizumab (CAPOX-B) combination therapy. We found that a higher muscle mass at the start of systemic treatment, having metachronous metastases, and active smoking at the start of therapy were factors independently associated with muscle loss, whereas local resection of the primary tumor before systemic therapy was significantly associated with muscle gain.

Additionally, patients with stable disease lost significantly more muscle mass as compared to patients who responded with a partial or complete response.

We hypothesized that muscle mass might play a role in the association between active smoking and poor survival in patients with cancer. Hence, our results support the added value of discussing smoking behavior and facilitating cessation support after a CRC diagnosis to enhance patient-centered cancer care and possibly improve clinical outcomes.

Chapter 7

Continued smoking after a cancer diagnosis is associated with a poor prognosis, which can be attributed to multiple factors including but not limited to increased prevalence of tobacco-related comorbidities, increased second primary tumors, smoking-induced skeletal muscle wasting, and biological interactions of tobacco-related carcinogens in malignant processes. As a result of the growing evidence for improved outcomes in patients who quit smoking at the time of diagnosis, we were interested in the opinion of oncologists towards the influence of smoking cessation after diagnosis, current practice patterns in terms of providing cessation support, and the identification of possible barriers to providing support, while distinguishing between the curative and palliative setting. In Chapter 7, we provided the results of a survey study on these topics among European oncologists. Our results showed that most oncologists believe that tobacco use impacts treatment outcomes, and that cessation interventions should be a part of the multidisciplinary treatment. Although oncologists indicated that they ask about the patient's intentions to quit smoking and advise smokers to quit, only 23% reported to feel adequately trained to provide cessation interventions. Moreover, only few routinely discuss medication options, and provide cessation support. Hesitation to remove a pleasurable habit and disbelief on smoking affecting outcomes were disparate barriers between the curative and palliative setting, but dominant barriers of time, resources, education, and patient resistance were similar between settings. As part of the developments towards integrative oncology and possible optimization of treatment outcomes, more research on the role of smoking during treatment is required. In anticipation, we believe that routine assessment of smoking behavior should become standard of practice in all cancer patients, and when indicated followed by individualized cessation interventions that are provided by experts, preferably shortly after diagnosis and before start of treatment.

SUMMARY IN DUTCH

In Nederland ontwikkelt 1 op de 20 mensen dikkedarmkanker. De kans op (langdurige) overleving is toegenomen doordat darmtumoren vaker in een vroeger stadium worden ontdekt en doordat zowel de initiële als de latere behandeling is verbeterd. In het afgelopen decennium is een groot aantal subgroepen binnen het colorectaal carcinoom (CRC) geïdentificeerd, die van elkaar onderscheiden kunnen worden door klinische kenmerken in combinatie met verschillende moleculaire markers. Deze toename van subgroepen en kennis van onderliggende biologische mechanismen is zowel een vooruitgang als een uitdaging voor het oncologisch onderzoek en de behandeling van dikkedarmkanker. Bovendien neemt het aantal patiënten dat leeft met en na kanker voortdurend toe. Ook aan deze groeiende groep mensen moet optimale 'evidence-based' ondersteunende zorg geboden worden waardoor hun fysieke functioneren en kwaliteit van leven zo goed mogelijk kan worden behouden.

Gegevens die representatief zijn voor de gehele patiëntenpopulatie, zogenoemde "real-world data", kunnen worden gebruikt om de evaluatie van (innovaties in) de klinische praktijk te vergemakkelijken. Tevens bieden real-world data de mogelijkheid om onderzoek te doen naar kleine subgroepen, wat door de kleine aantallen vaak niet goed mogelijk is in klinische trials.

Het doel van dit proefschrift is om aanvullend bewijs te leveren dat een integrale oncologische behandeling ondersteunt; een behandeling waarin patiënt-specifieke factoren worden meegewogen om behandeluitkomsten te verbeteren. Daarnaast worden onderzoeksmethoden beschreven en geëvalueerd die kunnen bijdragen aan toekomstig onderzoek ter verbetering van klinische uitkomsten van dikkedarmkanker, waaronder onderzoek naar leefstijlfactoren.

Deel I: Onderzoeksmethodologie in de oncologie

Hoofdstuk 2

Nieuwe onderzoeksopzetten en (inter)nationale samenwerkingen waarmee gegevens kunnen worden verzameld van een groot aantal patiënten kan een breed scala aan basale-, translationele en klinische studies mogelijk maken. Daarnaast kan hiermee onderzoek worden gefaciliteerd dat gericht is op het vooruitgaan van de behandeling van darmkanker, afgestemd op de individuele patiënt. Het doel van deze patiëntgerichte oncologische zorg is het verbeteren van klinische uitkomsten, zoals het verminderen van bijwerkingen van behandelingen, het verbeteren van kwaliteit van leven en het verhogen van de kans op overleving. In Nederland is het "Prospectief Landelijk

ColoRectaal carcinoom Cohort" (PLCRC) opgezet om uitgebreide longitudinale klinische patiëntgegevens, bloed, (tumor)weefsel en herhaaldelijke patiënt-gerapporteerde uitkomsten te verzamelen van patiënten met darmkanker. PLCRC streeft ernaar om nationale onderzoeksinitiatieven op het gebied van dikkedarmkanker bij elkaar te brengen en multidisciplinair onderzoek te faciliteren. Op deze manier kan er optimaal gebruik gemaakt worden van dit platform en de belasting van onderzoeksactiviteiten op individuele patiënten worden geminimaliseerd. De doelstelling van PLCRC is om uiteindelijk iedere patiënt met dikkedarmkanker de kans te geven om deel te nemen. Het gestaag toenemend aantal ziekenhuizen waar patiënten kunnen worden geïncludeerd is een grote stap richting dit doel. In Hoofdstuk 2 hebben we de ontwikkelingen van PLCRC beschreven en onderzoek gedaan naar de representativiteit van PLCRC-deelnemers ten opzichte van de algemene Nederlandse populatie met dikkedarmkanker. Hoewel de resultaten een kleine verschuiving naar de algemene populatie lieten zien voor patiënten die tussen 2017 en 2019 zijn geïncludeerd, waren PLCRC-deelnemers jonger en hadden vaker een stadium III tumor. Het waargenomen leeftijdsverschil is echter aanzienlijk kleiner dan het verschil dat werd waargenomen in vergelijking met studie (trial) populaties. In hoofdstuk 2 werd tevens de nadruk gelegd op het belang van integratie van onderzoek in de dagelijkse klinische praktijk om de volledigheid van beschikbare klinische gegevens te vergroten. Op dit moment hangt de beschikbaarheid van klinische gegevens voor onderzoek voornamelijk af van de mate van consistentie en uniformiteit van documenteren van gegevens in de elektronische patiëntendossiers (EPD's). We zijn van mening dat landelijke harmonisatie en standaardisatie van klinische gegevensinvoer in EPD's de volledigheid en kwaliteit van klinische gegevens voor wetenschappelijk onderzoek aanzienlijk zal verbeteren. Hiervoor is de betrokkenheid nodig van zowel clinici als onderzoekers. Daarnaast dient het logistieke proces rondom de invoer en extractie van klinische gegevens uit EPD's te worden geoptimaliseerd. Een gestandaardiseerde set van klinische gegevens en een gebruikersvriendelijke interface voor de invoer van deze gegevens in EPD's zou dit proces kunnen verbeteren. Omdat PLCRC-data ook kunnen worden gedeeld met andere (inter)nationale onderzoeksgroepen, wordt tevens bijgedragen aan de behoefte aan grote samenwerkingen en uitgebreide analyses om de behandeling en uitkomsten van dikkedarmkanker te verbeteren.

Hoofdstuk 3

In een recent overzichtartikel gaven Booth en collega's een uitgebreid overzicht van de uitdagingen en toekomstperspectieven met betrekking tot het gebruik van real-world data in de oncologie. In reactie op de oproep van de auteurs om meer aandacht

te besteden aan de implementatie van gerandomiseerde klinische studies (RCT's) in een real-world setting, hebben we in hoofdstuk 3 beschreven hoe alternatieve studie ontwerpen kunnen worden gebruikt om het "echte" karakter van de gegevens verkregen uit RCT's te verbeteren. Allereerst kunnen RCT's die gebaseerd zijn op en voortkomen uit registers - hoewel methodologisch vaak gelimiteerd - worden gebruikt voor een directe vergelijking van bestaande zorginterventies om te bepalen welke het beste werken voor welke patiënten in een real-world situatie. Een innovatief en nieuw soort RCT is het "Trials within Cohorts" (TwICs) studie ontwerp. Het gebruik van de TwICs onderzoeksopzet is opgenomen in PLCRC en kent een twee-staps procedure voor het verkrijgen van toestemming van de patiënt. Allereerst worden patiënten bij inclusie in PLCRC gevraagd om toestemming te geven voor deelname aan toekomstig onderzoek, inclusief TwICs studies. Als patiënten vervolgens in aanmerking komen voor deelname aan een studie, worden alleen de patiënten die gerandomiseerd zijn naar de interventiegroep gevraagd om een tweede toestemming te geven om de interventie te volgen. Deze aanpak heeft methodologische voordelen, zoals het voorkomen van teleurstelling in de controlegroep wat kan leiden tot vertekening van de resultaten, hogere wervingspercentages en verbeterde generaliseerbaarheid van studieresultaten. Internationaal zijn de eerste TwICs studies recent afgerond en momenteel wordt er aanvullend methodologisch onderzoek gedaan naar het optimaliseren van de opzet, uitvoer en analyse van TwICs.

Deel II: Leefstijlfactoren, lichaamssamenstelling en kwaliteit van leven

Hoofdstuk 4

Gezien het toenemende aantal patiënten dat meer dan 5 jaar na de diagnose darmkanker nog leeft, neemt het aantal onderzoeken gericht op het verbeteren van de (lange termijn) kwaliteit van leven en prognose toe. In hoofdstuk 4 hebben we methoden beschreven die gebruikt kunnen worden voor grootschalige ambulante monitoring van potentieel aanpasbare leefstijl-gerelateerde factoren. Hierbij is specifiek gekeken naar voedingsinname, lichaamssamenstelling, alcoholgebruik, rookgedrag en fysieke activiteit na de diagnose kanker. Ondanks de aanwezigheid van instrumenten die (objectieve) ambulante metingen van de bovengenoemde leefstijlfactoren mogelijk maken, zijn er verbeteringen nodig om de toepasbaarheid ervan op grote schaal vast te stellen. Hoewel zelfrapportage een veelgebruikte en haalbare meetmethode zal blijven, verwachten we dat ambulante monitoring met behulp van sensoren en draadloze hulpmiddelen in toenemende mate gebruikt zal gaan worden aangezien dit de patiëntlast kan verlagen en objectieve informatie oplevert. Echter benadrukken we het belang van het harmoniseren

van gegevensverzameling, zodat resultaten van studies kunnen worden vergeleken en bij (inter)nationale samenwerkingen de onderzoeksgegevens kunnen worden samengevoegd.

Hoofdstuk 5

Meer dan 950 publicaties in het afgelopen decennium hebben laten zien dat sarcopenie (ernstige lage spiermassa) en verlies van spiermassa zijn geassocieerd met slechte klinische uitkomsten, waaronder post-chirurgische complicaties, behandel-gerelateerde toxiciteit en mortaliteit. Slechts weinig studies hebben de associatie tussen spiermassa en kwaliteit van leven onderzocht. Meer bewijs over deze potentiële associatie kan gebruikt worden voor toekomstige studies naar strategieën die als doel hebben de kwaliteit van leven te verbeteren. In hoofdstuk 5 analyseerden we de gelijktijdige veranderingen in spiermassa en ziekte-specifieke symptomen, dagelijks functioneren en algehele kwaliteit van leven van 221 patiënten die deelnamen aan een studie naar de behandeling van uitgezaaide dikkedarmkanker (de CAIRO3 studie). Onafhankelijk van de behandeling rapporteerden patiënten die spiermassa behielden, d.w.z. stabilisatie of toename, een significante en klinisch relevante toename van de algehele kwaliteit van leven, evenals een afname van vermoeidheid en pijn. Deze afname van vermoeidheid en pijn is van belang omdat beide frequent voorkomen in deze patiëntengroep, ze bepalend kunnen zijn voor de kwaliteit van leven en bekend staan als onafhankelijke voorspellers van overleving in verschillende oncologische populaties. Onze studie heeft bijgedragen aan de identificatie van spiermassa als een potentieel veranderbare factor die verband houdt met de kwaliteit van leven van patiënten met uitgezaaide darmkanker. Deze bevinding kan waardevolle informatie leveren voor toekomstige interventiestudies.

Hoofdstuk 6

Om na te gaan welke patiënten mogelijk een verhoogd risico hebben op verlies van spiermassa, hebben we onderzocht welke factoren geassocieerd waren met een verandering in spiermassa bij patiënten met uitgezaaide darmkanker tijdens de eerstelijns behandeling. Voor deze analyse is gebruik gemaakt van gegevens uit de CAIRO3 studie, die bestond uit patiënten die na zes initiële kuren met capecitabine, oxaliplatine en bevacizumab (CAPOX-B) combinatie therapie reageerden met stabiele ziekte of (partiële of complete) respons. Hierdoor konden we onze vraag onderzoeken in een populatie waar ziekteprogressie geen rol speelde. In hoofdstuk 6 staat beschreven dat een hogere spiermassa aan het begin van de systemische behandeling, het hebben van metachrone metastasen (d.w.z. het optreden van metastasen na diagnose van de primaire tumor) en actief roken aan het begin van de therapie factoren waren die onafhankelijk verband

hielden met verlies van spiermassa, terwijl lokale resectie van de primaire tumor vóór systemische therapie significant geassocieerd was met toename in spiermassa. Bovendien verloren patiënten met stabiele ziekte, gemeten na initiële therapie, significant meer spiermassa in vergelijking met patiënten die partiel of compleet respondeerden (d.w.z. dat de tumor in volume vermindert of niet meer meetbaar is) na de initiële therapie.

We veronderstellen dat spiermassa een rol zou kunnen spelen in de associatie tussen actief roken en een verminderde overleving bij oncologie patiënten. Onze resultaten ondersteunen de toegevoegde waarde van het bespreken van het rookgedrag en het faciliteren van ondersteuning bij stoppen met roken na de diagnose dikkedarmkanker, ter verbetering van klinische uitkomsten.

Hoofdstuk 7

Doorgaan met roken na de diagnose kanker is geassocieerd met een slechtere prognose. Dit kan worden toegeschreven aan meerdere factoren, waaronder een hogere prevalentie van tabak-gerelateerde co-morbiditeiten, meer spiermassa verlies, verhoogd risico op een tweede primaire tumor, en biologische interacties van tabak-gerelateerde carcinogenen. Er is toenemend bewijs voor verbeterde uitkomsten bij patiënten die op het moment van diagnose stoppen met roken. Daarom waren we geïnteresseerd in de mening van oncologen over de invloed van stoppen met roken, de huidige praktijk rondom ondersteuning bij stoppen met roken en de identificatie van mogelijke barrières voor het faciliteren van ondersteuning. Dit is de eerste studie waarbij ook onderscheid wordt gemaakt tussen de curatieve en palliatieve setting. Deze onderwerpen zijn uitgevraagd middels een online enquête onder 544 oncologen uit 16 Europese landen. In hoofdstuk 7 is beschreven dat de meeste oncologen van mening zijn dat het gebruik van tabak van invloed is op de behandelresultaten en dat interventies ter ondersteuning bij het stoppen met roken onderdeel zouden moeten uitmaken van de multidisciplinaire behandeling. Hoewel oncologen aangaven dat ze patiënten vragen naar de intentie om te stoppen met roken en daarnaast zelf het advies geven om te stoppen met roken, gaf slechts 23% aan zich voldoende opgeleid te voelen om de patiënt een effectieve interventie aan te bieden. Bovendien bespreken slechts weinig oncologen routinematig medicamenteuze opties en bieden zij patiënten weinig ondersteuning bij het stoppen. Gebrek aan tijd, middelen, opleiding en weerstand van de patiënt waren de voornaamste redenen voor oncologen om stoppen met roken niet te bespreken met hun patiënten. Deze redenen werden in dezelfde mate genoemd voor patiënten in de curatieve als de palliatieve setting. Aarzeling om een plezierige gewoonte weg te nemen en het niet geloven dat

stoppen de behandeluitkomsten beïnvloedt waren twee redenen die oncologen vaker rapporteerden voor de palliatieve setting. Ondank het groeiende bewijs voor positieve effecten van stoppen met roken op de overleving, is meer onderzoek nodig naar de rol van roken tijdens de behandeling, met name in de palliatieve setting. We zijn van mening dat rookgedrag routinematig besproken moet worden met oncologische patiënten in de klinische praktijk. Indien een oncologische patiënt rookt, dan zouden hem/haar geïndividualiseerde interventies, gegeven door experts, moeten worden aangeboden, bij voorkeur kort na de diagnose en vóór aanvang van de behandeling.

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LIST OF PUBLICATIONS

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Derksen JWG, Warren GW, Roodhart JML, Koopman M, May AM. Practice patterns and barriers to smoking cessation after a cancer diagnosis in the setting of curative vs. palliative cancer treatment: a survey of European oncologists. *Submitted*

Derksen JWG, Vink GR, Elferink MAG, Roodhart JML, Verkooijen HM, van Grevenstein WMU, Siersema PD, May AM †, Koopman M †, on behalf of the PLCRC study group. The Prospective Dutch Colorectal Cancer (PLCRC) Cohort: "real-world" data facilitating research and clinical care. *Submitted*

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Derksen JWG, Kurk SA, Peeters PHM, Dorresteijn B, Jourdan M, van der Velden AMT, Nieboer P, de Jong RS, Honkoop AH, Punt CJA, Koopman M, May AM. The association between changes in muscle mass and quality of life in patients with metastatic colorectal cancer. *Journal of Cachexia, Sarcopenia and Muscle*. 2020 Feb. DOI: 10.1002/jcsm.12562.

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Jeroen

“The greatest moments in life are not concerned with selfish achievements, but rather with the things we do for the people we love and esteem.” - Walt E. Disney

ABOUT THE AUTHOR

Jeroen (H.W.G.) Derksen was born on the 31st of August 1989, in Rhenen, the Netherlands, as our oldest of three sons. We, his parents, were about to start a Veterinary Practice of our own that year.



We are very happy and grateful that we have the opportunity to write something about Jeroen in his thesis.

Early on, competition swimming (at national level) was of paramount importance to Jeroen. Twice a day you could find him in the swimming stadium to complete his training exercises.

Competitive swimming gave way to competitive rowing at the Argo Rowing Club in Wageningen when he started studying Nutrition and Health at the Wageningen University & Research (WUR) in 2010.

He participated in organizing an international rowing competition at the Amsterdam rowing course "de Bosbaan" in cooperation with the Dutch Student Rowing Federation in 2013.

After completing his thesis at the Department of Human and Animal Physiology (WUR), and an internship at the Department of Cancer Epidemiology and Prevention Research (Alberta Health Services) in Calgary, Jeroen graduated as an MSc in Nutrition and Health in 2015.

In October 2015, Jeroen started working on his PhD project described in this thesis at the Department of Medical Oncology of the University Medical Center Utrecht under the supervision of Miriam Koopman, Anne May, Peter Siersema, and Jeanine Roodhart.

During this PhD project he also graduated as a MSc in Clinical Epidemiology with a thesis on changes in skeletal muscle mass and quality of life in metastatic colorectal cancer (2018).

Besides the passion for his work at the UMC Utrecht, Jeroen has one big other passion. Despite his busy life you can often find Jeroen in a kitchen, preparing the most wonderful and delicious creations.

Twan and Angélique Derksen



COLORECTAL CANCER SURVIVORSHIP
STEPS TOWARDS INTEGRATIVE ONCOLOGY
AND PATIENT-CENTERED CANCER CARE
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