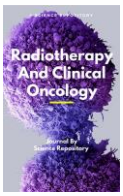

Available online at www.sciencerepository.org

Science Repository

Research Article

Assessment of muscle mass with computerised tomography in patients with incurable gastrointestinal cancer. A prospective single centre study

Sine Roelsgaard Obling[1, 2, 3*], Benedicte Vibjerg Wilson[4], Per Pfeiffer[5] and Jens Kjeldsen[1,2]

[1]*Department of Gastroenterology and Hepatology, Odense University Hospital, Denmark*
[2]*Department of Clinical Research, Faculty of Health Sciences, University of Southern Denmark*
[3]*OPEN; Odense Patient data Explorative Network, Odense University Hospital, Denmark*
[4]*Department of Gastroenterology and Hepatology, Herlev Hospital, Denmark*
[5]*Department of Medical Oncology, Odense University Hospital, Denmark*

ARTICLE INFO

Article history:
Received: 11 December, 2018
Accepted: 22 December, 2018
Published: 8 March, 2019

Keywords:
Skeletal Muscle Mass (SMM)
incurable cancer, sarcopenia
body composition
modified Glasgow Prognostic Score (mGPS)
BMI

ABSTRACT

Objective

Body composition is often affected in patients with incurable cancer, but the prevalence of sarcopenia is unknown. Our aim was to evaluate sarcopenia as predictor of overall survival in a cohort of patients with incurable gastrointestinal cancer and furthermore to evaluate if this cohort had different characteristics than patients, from an identical cohort who accepted participation in a RCT.

Design and methods

In this single centre study, we prospectively included a cohort of patients with incurable gastrointestinal cancer nutritionally at risk (NRS 2002≥2). Patients were screened but refused participation in an RCT testing supplemental HPN. To assess sarcopenia, data on skeletal muscle mass (SMM) from the cross-sectional area of L3 were assessed using computerized tomography scan (CT scan). SMM evaluation was included if a CT scan was available within 60 days from the inclusion date. Differences in survival were tested according to sarcopenia and modified Glasgow Prognostic Score (mGPS). Survival was compared between the patients who refused to participate in the RCT and patients who actually did participate.

Results

Eligible for inclusion were 187 patients, and 165 had a CT scan available for analysis. Most prevalent diagnosis was pancreatic cancer (52%), median age was 70.5 (41.2-89.4), median BMI 22.3 (14.4-36.8) and 99% were receiving chemotherapy. Sarcopenia was present in 78% of the overall cohort, more women (88%) than men (70%) were sarcopenic at inclusion. There was a positive correlation between BMI and SMM, but SMM accounted for only 8% of the variance in BMI.

Conclusions

Prevalence of sarcopenia was high in this cohort of patient with incurable gastrointestinal cancer; SMM did positively correlate to BMI, but only accounted for minor variations. mGPS was in the multivariate cox regression model predictive of survival and sarcopenia did not add to this elevated risk.

**Correspondence to: Sine Roelsgaard Obling, Department Gastroenterology and Hepatology, Odense University Hospital (OUH), Kloevervænget 13.2nd, DK-5000 Odense C; E-mail: sine.obling@rsyd.dk*

http://dx.doi.org/10.31487/j.RCO.2018.01.005

Introduction

Patients with incurable cancer often develop alterations in body composition, which has a negative impact on prognosis [1, 2]. The change in body composition in cancer patients often includes loss of muscle mass associated with functional disability and mortality [3-5]. Multifarious adverse effects of chemotherapy often increase these challenges [6-8]. As reported in a recent study by Choi et al. body composition has proved a prognostic factor in patients with incurable cancer [9]. Loss of skeletal muscle mass (SMM) is a result of impaired food intake, inflammation, and absence of physical activity. It is still uncertain if loss of muscle mass in patients with incurable cancer can be reversed and perhaps this will improve the outcome. However, it is likely that this is only possible in patients without severe inflammation and with a life expectancy above three months [10]. In a recent study by Feliciano et al [11] on patients with colorectal cancer the risk of death was nearly doubled in patients with sarcopenia and inflammation at time of diagnoses. In previous studies mGPS, based on 'crp' and 'albumin', has been valuable as a prognostic tool in patients with incurable cancer [12, 13].

Recruitment of patients with incurable cancer to clinical trials is often challenging and in a recent review on methodology, characterising clinical trials in palliative care, it was reported that only one third (36.8%) of the presented studies succeeded in including the number of patient estimated necessary in the sample size calculations [14].

It is questionable if patients participating in clinical trials have better outcomes, but recently an individual benefit of study participation was proven in young adults with cancer [15, 16]. Furthermore, another concern could be that patients participating in clinical trials basically have different demographic characteristics e.g. sex, age, and grade of disease, which may result in poor generalizability of study results.

It is generally accepted that mGPS is predictive for survival in patients with cancer, and some studies have suggested a worse prognosis if combined with sarcopenia. Aim of the present study was to evaluate the prevalence of sarcopenia in a cohort of patients with incurable gastrointestinal cancer and to evaluate the predictive value of sarcopenia for overall survival.

Patients and methods

Study design

Data were analysed from a prospective cohort of patients with incurable gastrointestinal cancer who were consecutively screened and offered participation in a RCT [17]. Patients were recruited in relation to the clinical randomized study of parenteral nutrition, in which they declined to participate. Extraction from the medical records and data entry in the database was completed by a physician and two specially trained nurses. Results from the RCT were not the scope of this work, and therefore these data are reported elsewhere [17].

Ethics

Ethical approval was obtained from the local Ethics Committee (S-20120094). Permission to use the data from the patients who declined to participate in the RCT was obtained from the Danish Patient Safety Authority (3 -3013-1763/1/). Patients who participated in the RCT all gave written informed consent. Permission for data handling and storage was obtained from the Danish Data Protection Act (16/24969).

Patients

Patients attending the Oncology Outpatient Clinic for clinical evaluation or scheduled treatment with chemotherapy were screened using NRS 2002 which is the mandatory screening tool used in the Danish Hospital setting. Patients were approached by the primary investigator or the project nurse during chemotherapy.

Inclusion criteria were: incurable gastrointestinal cancer (locally advanced or metastatic), age >18 years, WHO performance status (PS) 0-2 and nutritionally at risk according to NRS 2002 score ≥ 2) AND who declined to participate in the previously published RCT [17-19]. Exclusion criteria were; non-compliance, expected survival<3months, Short Bowel Syndrome or actual treatment with home parenteral nutrition. Chemotherapy was not an exclusion criterion. Patients were evaluated from May 2014 until November 2016 at a Danish University hospital.

Definitions

Baseline characteristics were recorded at the time of screening. Data on demographics, modified Glasgow Prognostic Score (mGPS), unplanned admissions and survival were obtained from patient's medical record. Computerised Tomography (CT) images completed for routine care; staging and follow up of the cancer were used for evaluation of SMM. Additionally, patients were asked the main reason for not wanting to participate in the RCT. Body surface Area (BSA) was calculated using the formula by Du Bois [20].

Sarcopenia

The term sarcopenia was in the study based exclusively on muscle mass since no data on muscle function was available. Analyses of muscle mass were included if a CT scan was available within 60 days from the inclusion date. Muscle mass was manually marked by hand by the same person, a trained radiographer for all scans, and evaluated using Osirix software (Osirix version 7.0. Pixmeo, Switzerland, 2015). The radiographer was blinded to the outcome including the overall survival.

CT images were analysed at the level of L3, using the cross-sectional area as a predictor of whole-body muscle mass. The cross-sectional area of SMM at the level of L3 is closely related to whole body muscle area [21]. To quantify the muscle, mass the Hounsfield unit threshold used was within the range -29 to + 150 HU [22, 23]. All tissue values were normalized for height (cm2/m2) and expressed as skeletal muscle index (SMI).

CT evaluated muscle mass and the criteria for sarcopenia was based on cut-offs from the study by Martin et al, with stratified definitions for sarcopenia accounting for BMI [4]. Threshold values with BMI <25 L3 skeletal muscle index ≤43 cm2/m2 for men and L3 skeletal muscle index ≤41 cm2/m2for women at BMI ≥25 threshold values were 53 cm2/m2 and 41 for men and women, respectively. To estimate the whole body muscle mass, the following equation was used in our study: total body fat-free mass (FFM) (kg) = 0.3* [skeletal muscle at L3 (cm2)] + 6.06 (r=0.94) [3].

Cachexia

At baseline all included patients had either anorexia or had had a marked weight loss >5%. Therefore, patients may all be characterized with some degree of cachexia [10]. Since no biomarkers of cachexia exist at the time being, we evaluated the patients using SMI and mGPS.

Survival analyses

Overall survival was estimated from date of refusal until the last day of observation. Overall survival was analysed according to sarcopenia and mGPS.

Unplanned admissions

Included were unplanned admissions due to incidents of acute illness from the time of screening/ inclusion to end of observation.

Statistical Analysis

Descriptive statistics are presented as median and range if not stated otherwise. For comparison of continuous outcome variables unrelated t-test or Mann-Whitney U test, (Wilcoxon two-sample test) was used when appropriate. Ordinal scale data was analysed using Fisher's exact test.

A multivariable logistic regression was used to analyse the association between unplanned admissions and SMI. Univariate and multivariate logistic regression was used to analyse variables associated with sarcopenia. Correlation between SMM and BSA as well as SMM and BMI were evaluated using Pearson's correlation coefficient.

Kaplan-Meier curves according to sarcopenia and to mGPS were presented for all patients participating in this study. Cox proportional hazards regression analyses were used to test for predictors of mortality in a subgroup of patients who had a valid CT scan within 60 days from inclusion. Results from the univariate analyses are presented, along with results from a multivariate Cox regression model including variables if $p<0.10$ in the univariate model. To test for strength of the model Harrell's C, concordance was performed after the regression analyses. Using Kaplan-Meier and Log-rank we compared the differences in overall survival according to RCT participation or not. All analyses were performed using Stata (Version15. Statistical software, College station, Texas: StataCorp LLC).

Results

Demographics

Five hundred and sixty-four patients with incurable gastrointestinal cancer were screened for participation in the RCT. Of these 323 patients did not fulfil the inclusion criteria; 245 (43%) were screened to have risk score <2, 30 (5%) were evaluated to be non-compliant, 14 (2%) had a life-expectancy<3 months, 12 (2%) had performance status 3, six (1) were already receiving HPN, five (1%) had Short Bowel Syndrome, and 11(2%) were not included for a unknown reason. A total of 187 patients who declined to participate in the RCT were included in the present study.

Twenty-three patients (12%) were scanned more than 60 days within the days of the interview and thus were not included in the Kaplan-Meier or the cox regression analyses on muscle mass and survival.
Half of the patients had pancreatic cancer, were median 71 years, and had a median BMI 22.3 and 99% were receiving chemotherapy at the time of observation.

Sarcopenia

Majority of the patients in our cohort had sarcopenia. We found a vast difference for the number of patients estimated to be malnourished using BMI (11%) and the patients estimated to be sarcopenic using computerized tomography scan at L3 level (78%). Sarcopenia was found in patients with BMI ranging from 14.7kg/m2 – 36.8 kg/m2. Median BMI in patients was 22.8 kg/m2 in patients with sarcopenia and 22.1 kg/m2 in patients without sarcopenia (*Table 2*). We found a strong positive correlation (Pearson's coefficient = 0.72, $p<0.01$) between

SMM and Body Surface Area (BSA), SMM explaining 52% of the variation in BSA. As well there was a small but significant positive correlation (Pearson's coefficient= 0.28, p<0.01) between SMM and BMI, SMM explaining only 8% of the variation in BMI.

Table 1: Demographics and characteristics of a population of 187 patients with incurable gastrointestinal cancer.

N (%)	**cohort**	**Percentage %**
Median (Range)		**Range**
N	187	
Sex		
Women	89	48
Men	98	52
Age	70.5	41.2-89.4
BMI	22.3	14.4–36.8
<18.5 (underweight)	21	11
18.5-24.9 (normal weight)	117	63
25.0-29.9 (overweight)	40	21
≥30 (Obese)	9	5
Tumour site		
Oesophagus	4	1.5
Stomach	34	18
Duodenum	2	1
Pancreas	96	52
Bile duct	14	7
Colorectal	34	18
NET	2	1
Unknown	1	0.5
Performance Status		
0	26	14
1	115	61
2	46	25
mGPS		
0	100	54
1	52	28
2	34	18
Palliative chemotherapy	186	99
No chemo	1	1
Single agent chemotherapy	42	22
Combination chemotherapy	144	77
Re-admissions		
No admissions	29	16
One admission	46	24
Two or more admissions	112	60

[a]*mGPS=Modified Glasgow Prognostic Score*

(0=albumin>35,crp<10,1=CRP>10, albumin>35, 2=CRP>10, albumin<35

In a simple logistic model, sex was the only risk factor for sarcopenia, but the significance disappeared when analysed in the multivariate model. In the multivariate model the risk of sarcopenia was significantly higher in women (OR 3.67, p<0.01).

We found no significant in survival according to sarcopenia (Figure 1)

Survival was in median 289 days (104-1109) and 212 days (6-980). In the cox regression model sarcopenia was not predictive of survival.

Table 2: CT evaluated muscle mass and the proportion of patients being sarcopenic and sarcopenic obese.

	Non-participants	RCT participants	P	Missing (N)
N	163	47		(24/0)
SMI[a] (cm^2/m^2)	37.6 (23.4-52.9)	37.4 (18.4-54.5)	0.60	(24/0)
Women	34.5 (23.4-47.6)	32.7 (18.4-47.2)		
Men	41.6 (28.7-52.9)	39.5 (29.9-54.5)		
FFM[b]	39.8 (25.4-62.5)	38.4 (22.0-55.6)	0.24	(24/0)
Women	34.2 (25.4-44.5)	31.7 (22.0-42.2)		
Men	46.5 (32.2-62.5)	41.6 (33.8-55.6)		
CT sarcopenic[c]			0.73	(24/0)
ALL	128 (78)	38(81)		
Women	67 (88)	15 (88)		
Men	61 (70)	23 (77)		
Sarcopenic obese[d]			0.34	(24/0)
Not sarcopenic, not obese	34 (21)	8 (17)		
Sarcopenic Obese	7 (4)	-		
Obese	1 (1)	1 (2)		
Sarcopenic	121 (74)	38 (81)		

Data were presented as Median (Range) N (%)

[a] SMI= Skeletal Muscle Index, CT measured muscle mass at L3 divided by height^2.

*[a]FFM = Fat free mass= 0.3*CT musclemass(kg) + 6.06 (1)*

[b]Sarcopenic = SMI <43 for men and SMI <41 for women at BMI 20-24.9; SMI<53 for men, SMI<41 for women at BMI≥25kg/m

c[d] Sarcopenic and obese, obesity = BMI ≥30kg/m^2

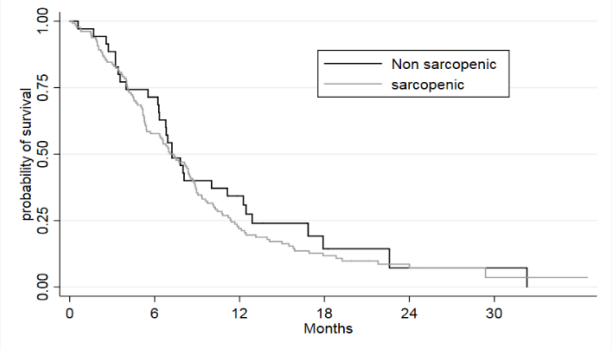

Figure 1: Overall survival according to sarcopenia. No significant difference was found.

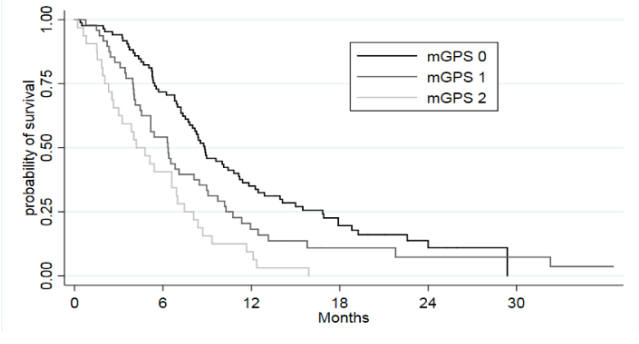

Figure 2: Overall survival according to mGPS. Significant difference was found when tested using cox regression.

Overall survival and mGPS

At six months 72%, 54% and 41% were still alive with mGPS 0, mGPS 1 and mGPS 2, respectively. At twelve months 35%, 21% and 9% were still alive with mGPS 0, mGPS 1 and mGPS 2, respectively (Figure 2). Median survival was for mGPS 0 268 days, mGPS 1 193 days, and for mGPS 2 136 days.

In the univariate and the multivariate cox regression analyses a significant worse outcome was found in patients with mGPS 1 (HR 1.59, 95% CI 1.07-2.38, p<0.03) and mGPS 2 (HR 2.39, 95% CI 1.52-3.73, p<0.01) and in patients with PS 1 (HR 1.71, 95% CI 1.01-2.90, p<0.05) and PS 2 (HR 4.28, 95% CI 2.37--7.73, p<0.01), whereas no predictive value of sarcopenia, age or sex was found (Table 3).

Table 3: Univariate and multivariate Cox regression analyses including patients with incurable cancer and an available CT scan for evaluation of skeletal muscle mass (SMM) within 60 days and an available mGPS

		Number	Survival		Crude model			Adjusted Model[a]	
		N	Median survival	HR	95% CI	P	HR	95% CI	P
		164	(Range)						
Non-		35	219 (18-980)						
sarcopenic		129	219 (6-1109)	1.16	0.78-1.74	0.45	0.98	0.63-1.51	0.92
Sarcopenic[b]									
Performance	0 (ref)	24	316 (59 -1109)						
	1	98	262 (6-891)	1.60	0.96-2.67	0.07	1.71	1.01-2.90	0.04*
	2	42	122 (15-788)	3.93	2.23-6.92	<0.01**	4.28	2.36-7.74	<0.01**
Age		165	219 (6-1109)	1.01	0.99-1.02	0.38	1.00	0.98-1.02	0.92
Sex	Men	86	209 (12-980)						
	Women	78	250 (6-1109)	0.78	0.56-1.08	0.14	0.77	0.54-1.10	0.15
mGPS[c]	0 (ref)	15	268 (12-891)						
	1	117	193 (23-1109)	1.48	1.01-2.17	0.05	1.59	1.01-2.90	0.05
	2	32	136 (6-482)	2.69	1.75-4.13	<0.01**	4.28	2.37-7.74	<0.01**

[a]*Adjusted model including sarcopenia, mGPS, performance, age and sex.*

[b]*Sarcopenic = L3 skeletal muscle index ≤52.4 cm2/m^2 for men and for women L3 skeletal muscle index ≤38,5*

[c]*m2/m^2* cmGPS=Modified Glasgow Prognostic Score; (0=albumin>35,crp<10,1=CRP>10, albumin>35, 2=CRP>10, albumin<35

Unplanned admissions

Unplanned admissions were frequent and only 15% were not admitted at all. Number of admissions ranged from 1 to 9 per patient. A limited number of patients had more than four admissions (9%). We did not identify any predictors of risk of admission.

Discussion

In this study mGPS was a strong predictor of survival, and there was no predictive value of sarcopenia. Sarcopenia was found in patients with a wide range of BMI's. We found a strong positive correlation between SMM and BSA. Length of survival was not dependent on RCT participation. Finally, we did not find that patient with sarcopenia had a higher risk of admissions.

At baseline majority of the patients had sarcopenia, and sarcopenia had a predictive value for overall survival but only in the univariate cox regression model. Compared to the patients who declined to participate in the previously reported RCT by Obling et al. the patients in this cohort were similar regarding tumour site, performance and sex [15]. SMM did not differ between the two cohorts, and neither did the percentage of

patients with sarcopenia. Participants in the RCT testing sHPN were younger, had lower BMI, but did not have a better outcome than the ones who refused participation.

The prevalence of sarcopenia in this study was higher than in previously published studies. This is not surprising, since the included patients were all screened to be nutritionally at risk at inclusion, with either eating disabilities or preceding loss of weight. The discrepancy between number of patients being underweight and the number being sarcopenic highlights the need for the use of other parameters than BMI to assess the nutritional encounters. Using Body Mass Index (BMI) or weightloss as criteria for study inclusion may not be accurate in patients with cancer, since fluid imbalance will affect these parameters [24]. As well, it may be considered if the screening tool NRS 2002, originally developed for the use in hospitalized patients, is sufficiently accurate to identify the patients before the severe decrease in muscle mass or the decline in mGPS.

Drug distribution is affected by body composition, which may be the reason for patients with sarcopenia being more susceptible to toxicity during chemotherapy than patients without sarcopenia [6, 7, 25]. In a cohort of colon cancer patients receiving combination chemotherapy, lean body mass was evaluated to be a significant predictor of neuropathy and toxicity [26]. Furthermore, a previous study on patients with non-metastatic colon cancer receiving chemotherapy found an association between toxicity and low SMI [27]. Prescription of chemotherapy as single agent or combination therapy is dependent on performance status but not on mGPS or sarcopenia. Dosage of chemotherapy is at the time being, calculated from BSA, which may not be accurate since SMM only explained half of the variation in BSA [20]. BSA did not correspond perfectly to the muscle mass findings, which make us consider if other parameters should be included when calculating chemotherapy dosage to minimize the risk of toxicity. Nutritional status and impaired mobility were predictive of overall survival in a recent study [28]. A study on aging patients with cancer suggested a multivariate model including functional capacity to prevent toxicity [29]. Also, the review by Hopkins et al. suggests using muscle mass to individualize the chemotherapy and to a greater extent avoid side effects [30].

mGPS and not sarcopenia was in this study predictive of survival in opposition to previously reported findings. The large number of patients with sarcopenia and the inclusion of patients at different stages of advanced cancer disease may have influenced the results. It is possible that some patients stopped losing weight and some had an ongoing weight loss depending on tumour burden and inflammatory status. In a recent prospective observational study on 67 patients with metastatic colorectal cancer, muscle area (CT measured) decreased significantly during palliative chemotherapy and the loss of muscle mass was independently associated with survival [1]. As reported in a recent study by Choi et al body composition has proved as a prognostic factor in patients with incurable cancer and sarcopenia receiving chemotherapy [9]. In that study there was a predictive value of loss of muscle mass during chemotherapy, whereas BMI did not show any significant value.

Prognostication in patients with incurable cancer is important since there is a correlation between life expectancy and symptom burden. Patients with fewer and less severe symptoms often have longer life expectancy [31]. In a previous study on patients with incurable cancer it was shown that a high symptom burden was associated with prolonged hospitalization and higher number of readmissions [32]. Malnutrition, which was found in 41% of the total population screened for inclusion in this study, leads to a wide range of symptoms. It seems logical to treat the symptoms accompanying malnutrition in an attempt to prevent the burdensome hospitalizations.

A general understanding is that patients with cancer participating in clinic trials have an improved outcome because of the increased attention from the project workers [33, 34]. This was not confirmed by the results from our study. Overall survival was not significantly different in the patients who participated in this study compared to patients participating in the RCT. We could not confirm the previous reported findings of a superior outcome for the patients participating in RCT in terms of survival [35].

Although patients and their relatives do expect the professionals to take care of weight loss during cancer treatment [36] many patients did not want to participate in the clinical trial offering dietary counselling and supplemental home parenteral nutrition under circumstances of randomization. Reasons for not wanting to participate in the RCT varied, and we found no pattern in the reasoning. Almost one third of the patients stated being too stressed or overwhelmed as the main reason for not participating. Patients with incurable cancer in general experience high rates of stress due to the insecurity of the course of disease. From previous studies it is documented that patients in palliative care abstain from participation in clinical trials if the intervention is thought to be complex with risk of side –effects and if the support from the relatives is non-existent [37, 38].

The population studied was heterogenetic in terms of diagnoses and therefore also in type of chemotherapy. Patients were analysed at different stages of disease and were only included if nutritionally at risk. Previous studies have stated sarcopenic obesity as a negative predictor of mortality in patients with incurable cancer [39, 40]. In our study population only, a minority were obese since the patients were preselected, and therefore subgroup analysis including sarcopenic obesity was impossible.

In future studies addressing outcome and therapeutic intervention in patients with incurable cancer including nutritional status, muscle mass and muscle function could improve characterization of patient groups and may perhaps improve individual dosing of chemotherapy resulting in less toxicity.

Conclusion

We found a high prevalence of sarcopenia in this cohort of patients with incurable cancer. The high prevalence of sarcopenia found was surprising and make us wonder if a diminished nutritional state in patients with incurable cancer is not recognized and not treated. mGPS was a strong predictor of survival and sarcopenia did not add to this elevated predictive value of mGPS.

Acknowledgements

Radiographer, Katrine Herbst Hansen, analysed the CT scans and we appreciate the large amount of work invested in this project as well as the important collaboration with Jon Asmussen, Consultant in department of Radiology. Special thanks to our specialist nurses, Lene Scheby and Jeanette Bjerre Callesen who assisted in screening patients for inclusion, and who retracted data from patient medical records and entered data into the database.

Data availability

Data are available from the correspondent author upon request

Statement of authorship

Authors contributed equally to the design of the study. SRO collected the data and analysed and interpreted the data in close collaboration with BW, PP and JK. SRO, BW, PP and JK drafted and critically revised the manuscript. Final draft of the manuscript was approved by all contributing authors.

Conflicts of interest

Primary investigator received funding from the Danish national Cancer society and Baxter International Corporation to run the RCT.

Funding sources

Funding was received from the Danish Cancer Society, the Region of Southern Denmark, Odense University Hospital, Baxter Healthcare Corporation “Broedrene Hartmanns fond”, “Grosserer M. Brogaard and Hustru’s fund”, “Aase and Ejner Danielsen’s fund”, “Knud and Edith Eriksens memorial fund” “Inge and Joergen Larsen’s memorial fund” and “Odense University Hospital; consultants council scholarship”.

References

1. Blauwhoff-Buskermolen S, Versteeg KS, de van der Schueren MA, den Braver NR, Berkhof J, et al. (2016) Loss of Muscle Mass During Chemotherapy Is Predictive for Poor Survival of Patients With Metastatic Colorectal Cancer. *J Clin Oncol* 34: 1339-1344. [Crossref]
2. Park I, Choi SJ, Kim YS, Ahn HK, Hong J, et al. (2016) Prognostic Factors for Risk Stratification of Patients Recurrent or Metastatic Pancreatic Adenocarcinoma Who were Treated with Gemcitabine-Based Chemotherapy. *Cancer Res Treat* 48: 1264-1273. [Crossref]
3. Tan BH, Birdsell LA, Martin L, Baracos VE, Fearon KC (2009) Sarcopenia in an Overweight or Obese Patient Is an Adverse Prognostic Factor in Pancreatic Cancer. *Clin Cancer Res* 15: 6973-6979. [Crossref]
4. Martin L, Birdsell L, MacDonald N, Reiman T, Clandinin MT, et al. (2013) Cancer Cachexia in the Age of Obesity: Skeletal Muscle Depletion Is a Powerful Prognostic Factor, Independent of Body Mass Index. *J Clin Oncol* 31: 1539-1547. [Crossref]
5. Miyamoto Y, Baba Y, Sakamoto Y, Ohuchi M, Tokunaga R, *et al*. (2015) Negative Impact of Skeletal Muscle Loss after Systemic Chemotherapy in Patients with Unresectable Colorectal Cancer. *PloS one* 10: e0129742. [Crossref]
6. Arrieta O, De la Torre-Vallejo M, Lopez-Macias D, Orta D, Turcott J, et al. (2015) Nutritional Status, Body Surface, and Low Lean Body Mass/Body Mass Index Are Related to Dose Reduction and Severe Gastrointestinal Toxicity Induced by Afatinib in Patients With Non-Small Cell Lung Cancer. *oncologist* 20: 967-974. [Crossref]
7. Barret M, Antoun S, Dalban C, Malka D, Mansourbakht T, Zaanan A, et al. (2014) Sarcopenia is linked to treatment toxicity in patients with metastatic colorectal cancer. *Nutr Cancer* 66: 583-589. [Crossref]
8. Prado CM, Lima IS, Baracos VE, Bies RR, McCargar LJ, et al. (2011) An exploratory study of body composition as a determinant of epirubicin pharmacokinetics and toxicity. *Cancer Chemother Pharmacol* 67: 93-101. [Crossref]
9. Choi Y, Oh DY, Kim TY, Lee KH, Han SW, et al. (2015) Skeletal Muscle Depletion Predicts the Prognosis of Patients with Advanced Pancreatic Cancer Undergoing Palliative Chemotherapy, Independent of Body Mass Index. *PloS one* 10: e0139749. [Crossref]
10. Fearon K, Strasser F, Anker SD, Bosaeus I, Bruera E, *et al*. Definition and classification of cancer cachexia: an international consensus. *Lancet Oncol* 12: 489-495. [Crossref]
11. Feliciano EMC, Kroenke CH, Meyerhardt JA, Prado CM, Bradshaw PT, *et al*. (2006) Association of Systemic Inflammation and Sarcopenia With Survival in Nonmetastatic Colorectal Cancer: Results From the C SCANS Study. *JAMA oncol* 3: e172319. [Crossref]
12. Pantano Nde P, Paiva BS, Hui D, Paiva CE (2016) Validation of the Modified Glasgow Prognostic Score in Advanced Cancer Patients Receiving Palliative Care. *J Pain Symptom Manage* 51: 270-277. [Crossref]
13. Crumley AB, McMillan DC, McKernan M, McDonald AC, Stuart RC (2006) Evaluation of an inflammation-based prognostic score in patients with inoperable gastro-oesophageal cancer. *Br J Cancer* 94: 637-641. [Crossref]
14. Bouca-Machado R, Rosario M, Alarcao J, Correia-Guedes L, Abreu D, et al. (2017) Clinical trials in palliative care: a systematic review of their methodological characteristics and of the quality of their reporting. *BMC Palliat Care* 16: 10. [Crossref]
15. Johanna Nattenmüller, Raoul Wochner, Thomas Muley, Martin Steins, Simone Hummler, et al. (2017) Prognostic Impact of CT-Quantified

Muscle and Fat Distribution before and after First-Line-Chemotherapy in Lung Cancer Patients. *PloS one* 12: e0169136. [Crossref]

16. Hough R, Sandhu S, Khan M, Moran A, Feltbower R, et al. (2017) Are survival and mortality rates associated with recruitment to clinical trials in teenage and young adult patients with acute lymphoblastic leukaemia? A retrospective observational analysis in England. *BMJ open* 7: e017052. [Crossref]
17. Obling SR, Wilson BV, Pfeiffer P, Kjeldsen J (2017) Home Parenteral nutrition increases fat free mass in patients with incurable gastrointestinal cancer. Results of a randomised controlled trial**.** *Clin Nutr*. [Crossref]
18. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, et al. (1982) Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol* 5: 649-655. [Crossref]
19. Kondrup J, Rasmussen HH, Hamberg O, Stanga Z (2003) Nutritional risk screening (NRS 2002): a new method based on an analysis of controlled clinical trials. *Clin Nutr* 22: 321-336. [Crossref]
20. Du Bois D, Du Bois EF (1989) A formula to estimate the approximate surface area if height and weight be known. 1916. *Nutrition* 5: 303-311. [Crossref]
21. Mourtzakis M, Prado CMM, Lieffers JR, Reiman T, McCargar LJ, et al. (2008) A practical and precise approach to quantification of body composition in cancer patients using computed tomography images acquired during routine care. *Appl Physiol Nutr Metab* 33: 997-1006. [Crossref]
22. Mitsiopoulos N, Baumgartner RN, Heymsfield SB, Lyons W, Gallagher D, et al. (1985) Cadaver validation of skeletal muscle measurement by magnetic resonance imaging and computerized tomography. *J Appl Physiol* 85: 115-122. [Crossref]
23. Heymsfield SB, Wang Z, Baumgartner RN, Ross R (1997) Human body composition: advances in models and methods. *Annu Rev Nutr* 17: 527-558. [Crossref]
24. Roeland EJ, Ma JD, Nelson SH, Seibert T, Heavey S, et al. (2017) Weight loss versus muscle loss: re-evaluating inclusion criteria for future cancer cachexia interventional trials. *Support Care Cancer* 25: 365-369. [Crossref]
25. Prado CM, Baracos VE, McCargar LJ, Reiman T, Mourtzakis M, et al. (2009) Sarcopenia as a determinant of chemotherapy toxicity and time to tumor progression in metastatic breast cancer patients receiving capecitabine treatment. *Clin Cancer Res* 15: 2920-2926. [Crossref]
26. Ali R, Baracos VE, Sawyer MB, Bianchi L, Roberts S, et al. (2016) Lean body mass as an independent determinant of dose-limiting toxicity and neuropathy in patients with colon cancer treated with FOLFOX regimens. *Cancer Med* 5: 607-616. [Crossref]
27. Cespedes Feliciano EM, Lee VS, Prado CM, Meyerhardt JA, Alexeeff S (2017) Muscle mass at the time of diagnosis of nonmetastatic colon cancer and early discontinuation of chemotherapy, delays, and dose reductions on adjuvant FOLFOX: The C-SCANS study. *Cancer* 123: 4868-4877. [Crossref]
28. Soubeyran P, Fonck M, Blanc-Bisson C, Blanc J-F, Ceccaldi J, *et al*. (2012) Predictors of Early Death Risk in Older Patients Treated With First-Line Chemotherapy for Cancer. *J Clin Oncol* 30: 1829-1834. [Crossref]
29. Hurria A, Togawa K, Mohile SG, Owusu C, Klepin HD, *et al*. (2011) Predicting Chemotherapy Toxicity in Older Adults With Cancer: A Prospective Multicenter Study. *J Clin Oncol* 29: 3457-3465. [Crossref]
30. Hopkins JJ, Sawyer MB (2017) A review of body composition and pharmacokinetics in oncology. *Expert Rev Clin Pharmacol* 10: 947-956. [Crossref]
31. Kaasa S, Hjermstad MJ, Loge JH (2006) Methodological and structural challenges in palliative care research: how have we fared in the last decades? *Palliat Med* 20: 727-734. [Crossref]
32. Nipp RD, El-Jawahri A, Moran SM, D Arpino SM, Johnson PC, *et al*. (2017) The relationship between physical and psychological symptoms and health care utilization in hospitalized patients with advanced cancer. *Cancer* 123: 4720-4727. [Crossref]
33. Vist GE, Bryant D, Somerville L, Birminghem T, Oxman AD (2007) Outcomes of patients who participate in randomized controlled trials compared to similar patients receiving similar interventions who do not participate. *Cochrane Database Syst Rev* 16: Mr000009. [Crossref]
34. Peppercorn JM, Weeks JC, Cook EF, Joffe S (2004) Comparison of outcomes in cancer patients treated within and outside clinical trials: conceptual framework and structured review. *Lancet* 363: 263-270. [Crossref]
35. Julian-Reynier C, Genève J, Dalenc F, Genre D, Monnier A, *et al*. (2007) Assessment of Care by Breast Cancer Patients Participating or Not Participating in a Randomized Controlled Trial: A Report With the Patients' Committee for Clinical Trials of the Ligue Nationale Contre le Cancer. *J Clin Oncol* 25: 3038-3044. [Crossref]
36. Reid J, McKenna HP, Fitzsimons D, McCance TV (2010) An exploration of the experience of cancer cachexia: what patients and their families want from healthcare professionals. *Eur J Cancer Care (Engl)* 19: 682-689. [Crossref]
37. White CD, Hardy JR, Gilshenan KS, Charles MA, Pinkerton CR (2008) Randomised controlled trials of palliative care - a survey of the views of advanced cancer patients and their relatives. *Eur J Cancer* 44: 1820-1828. [Crossref]
38. Ling J, Rees E, Hardy J (2000) What influences participation in clinical trials in palliative care in a cancer centre? *Eur J Cancer* 36: 621-626. [Crossref]
39. Prado CMM, Lieffers JR, McCargar LJ, Reiman T, Sawyer MB, et al. (2008) Prevalence and clinical implications of sarcopenic obesity in patients with solid tumours of the respiratory and gastrointestinal tracts: a population-based study. *Lancet Oncol* 9: 629-635. [Crossref]
40. Rollins KE, Tewari N, Ackner A, Awwad A, Madhusudan S, et al. (2016) The impact of sarcopenia and myosteatosis on outcomes of unresectable pancreatic cancer or distal cholangiocarcinoma. *Clin Nutr* 35: 1103-1109. [Crossref]. [Crossref]