Early, integrated, specialised, palliative rehabilitation for patients with advanced cancer.

PhD Thesis

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Preface

My first encounter with specialised palliative care happened when I was in my first year of Oncology training and it immediately sparked a fire in me. I found the multidisciplinary and holistic approach towards patients and their families meaningful and professionally rewarding. Therefore it did not require many thoughts when Tove Bahn Vejlgaard contacted me on a later occasion to enquire about my willingness to undertake a PhD project on the early integration of palliative care into standard oncology treatment. I owe Tove my warmest thanks for trusting me with this project and paving the way for a dream come true.

I knew Lars Henrik Jensen as a colleague from the Department of Oncology and had no objections when he was brought in as a potential principal supervisor. I expected to get a supervisor with lots of enthusiasm and the ability to securely anchor the project within the Department of Oncology. I was given that and much more. I have received support and guidance, when needed, but I have also enjoyed a high degree of freedom to work independently and bring my own thoughts and perspectives forward. I would like to thank Lars Henrik heartedly - I could not have asked of anything more.

Furthermore, I was privileged that Mogens Grønvold agreed to co-supervise the project bringing his immense expertise in quality of life research in cancer and palliative care to the table. Mogens has been a patient and extremely competent supervisor and I am most grateful that he has made time in his busy schedule to guide me and share most generously his profound knowledge of the field. Due to the geographical restrictions most of the contact has been over e-mail but I have always felt most welcome whenever I have visited the Research Unit at Bispebjerg Hospital. I would therefore like to extent my thanks to all the staff at the Unit for allowing me to steel Mogens' time and always greeting this "foreigner" so warmly. A special thanks to Morten Aagaard Petersen for his always friendly and forthcoming attitude as well as a huge statistical contribution to the project and to Anna Thit Johnsen for taking on almost a mentoring role for me in the first phases of the project.

A very special thank goes to all the patients and family caregivers who were willing to participate in this project and trust me and the rest of the personnel involved with their personal data. It goes without saying that they are the very foundation of the work presented in this thesis. I would also like to thank the Patient and Relatives Council at Vejle Hospital for valuable advice, perspective, and discussions throughout the project.

I have many people to thank at Vejle Sygehus without whom this project would not have succeeded. All staff at the Palliative team, the Clinical Research Unit, and the Oncology Department has played an important part in the project. I send my special thanks to Gitte Eiberg Møller and Birgitte Skov Zellweger for their coordinating roles and to Karin Larsen for very competent help with linguistic editing and otherwise. I am grateful to Anette Hygum for both personal and professional support.

I thank the financial benefactors of the project for enabling us to transform the project from ideas and good intentions to real work that will hopefully contribute to bettering the quality of life of many more patients and families living with cancer.

Last but not least I would like to thank all my lovely research colleagues at "Bjerget" for creating such a wonderful working milieu. I have enjoyed working with you every day. I would also like to thank my family and friends for all their loving support. Words are not enough!

English summary

Title: Early, integrated, specialised, palliative rehabilitation for patients with advanced cancer.

Introduction: Early palliative care integrated in the standard care of advanced cancer patients is recommended by leading cancer organisations but is still not widely implemented. Rehabilitation and palliative care share the goal of improving quality of life, emphasize patient and family centred care, and focus on achieving patient goals through a multidisciplinary approach. Palliative rehabilitation can be defined as function-directed care aligned with the values of patients and caregivers facing serious illnesses and care which integrates rehabilitation, enablement, self-management, and self-care into the holistic model of palliative care. Research on palliative rehabilitation is sparse.

Aims: The aim of this PhD project was to investigate the effect of a 12-week palliative rehabilitation intervention on the quality of life of patients with newly diagnosed advanced cancer receiving anticancer treatment at Vejle Hospital. The project also evaluated how the intervention was utilized and evaluated by the participants.

Methods: A new ambulatory palliative rehabilitation clinic was opened under the existing specialised palliative care team. The clinic employed physicians, nurses, physiotherapists, psychologists, an occupational therapist, a dietician, a social worker, and a chaplain and offered individual consultations and a 12-week group programme combining educational sessions with physical exercise.

Patients newly diagnosed with advanced cancer and receiving standard care at the Department of Oncology could be randomised to standard care (control group) or standard care plus palliative rehabilitation (intervention group). The intervention group received at least two consultations in the palliative rehabilitation clinic and additional offers at the clinic dependent on individual needs.

All study participants completed three quality of life questionnaires (at baseline, after 6 and 12 weeks) measuring symptoms and problems. Patients were asked at baseline to prioritise a “primary problem” that they needed help with the most corresponding to a scale in the questionnaire. The primary outcome measure was the change since baseline in the “primary problem” measured as area under the curve across the 12 weeks. Secondary outcomes were the proportion of patients feeling helped with the “primary problem” and survival. Data on intervention components and participant evaluation was also collected.

Main results: 288 patients were randomised 1:1 and 279 patients were included in the modified intention-to-treat analysis with 146 patients in the standard care group and 133 patients in the palliative rehabilitation group.

The score of the "primary problem" improved significantly during the 12-week participation period in patients receiving palliative rehabilitation compared to the patients receiving standard oncology care alone. The estimated size of the absolute group difference was 3.0 (95% CI: 0.0-6.0, p=0.047). A sensitivity analysis of the change from baseline to 12 weeks later showed an absolute difference of 3.3 (95% CI 1.0-5.6; p=0.005). At 12 weeks significantly more patients in the group receiving palliative rehabilitation agreed that they had received help (75%) compared to the standard care group (51%), p=0.002.

The palliative rehabilitation intervention was received by 132. After the initial consultation 59 patients (45%) joined the group programme and 47 patients (35%) received supplementary individual consultations without participating in a group. The remaining 26 patients (20%) received no more than the two planned consultations.

Patients who joined the group programme participated in a median of 10 of the 12 sessions (range 1-13), and received a median of five supplementary consultations (range 0-21). Patients who received supplementary individual consultations without joining the group had a median of two contacts (range 1-18) in addition to the planned consultation.

In total, 411 supplementary individual consultations were held between patients in the intervention arm and members of the palliative rehabilitation team. The main themes were pain management, coping, and nutrition.

When intervention participants were asked, if they would recommend the intervention to others in the same situation, 93% agreed, 7% (n=7) partly agreed, and no one disagreed.

Survival was not affected by the intervention.

Conclusion and perspectives: Receiving palliative rehabilitation concurrently with standard oncology treatment significantly improved the quality of life of patients with newly diagnosed advanced cancer. The intervention was better than standard care in helping the patients with the problems they prioritized and was perceived as relevant and beneficial by the participants.

The results could be used to inform decision makers in Denmark and elsewhere about ways to improve healthcare for cancer patients.

Danish summary/ dansk resumé

Titel: Tidlig, integreret, specialiseret, palliativ rehabilitering til patienter med alvorlig kræftsygdom.

Introduktion: Tidlig, integreret palliativ indsats anbefales af førende kræftorganisationer som en del af standardtilbuddet til alvorligt syge kræftpatienter, men det har ikke vundet stor udbredelse. Rehabilitering og palliation har begge til formål at forbedre livskvalitet ved brug af tværfaglige teams og fælles beslutningstagning. Palliativ rehabilitering kan defineres som behandling, der retter sig mod at opretholde funktioner hos alvorligt syge mennesker med aktiv involvering af den syge og dennes familie samt de værdier, der optager dem. Man kan også tale om behandling, som inkorporerer et fokus på rehabilitering, aktivering, egenomsorg og uafhængighed i palliationens tilgang til det hele menneske. Det er hidtil lavet meget lidt forskning i palliativ rehabilitering.

Formål: Målet med dette PhD-projekt var at undersøge effekten af et 12 ugers palliativt rehabiliteringstilbud på livskvaliteten hos patienter med en alvorlig kræftsygdom, som netop havde startet medicinsk kræftbehandling på Vejle sygehus. Projektet undersøgte også, hvordan patienterne anvendte og tog imod det nye tilbud om palliativ rehabilitering.

Metoder: Det blev etableret et palliativt rehabiliteringsambulatorie under det specialiserede palliative team. De involverede faggrupper var læger, sygeplejersker, fysioterapeuter, psykologer, en ergoterapeut, en diætist, en socialrådgiver og en præst. Ambulatoriets tilbud var individuelle konsultationer og et 12 ugers gruppeprogram bestående af patient-/pårørendeskole og fysisk træning.

Der blev trukket lod blandt patienter fra onkologisk ambulatorie, som var nydiagnosticerede med alvorlig kræft og som ønskede at deltage i forsøget. Halvdelen skulle fortætte standardbehandlingen som vanligt (kontrolgruppe), og den anden halvdel fik tilbuddet om palliativ rehabilitering i tillæg til standardbehandlingen (interventionsgruppe). Interventionsgruppen modtog minimum to konsultationer i det palliative rehabiliteringsambulatorie og fik derudover et tilbud, der var sammensat til deres behov.

Alle forsøgsdeltagere udfyldte tre livskvalitetsspørgeskemaer (før lodtrækningen og efter 6 og 12 uger), som omhandlede forskellige symptomer og problemer. Før lodtrækningen blev de endvidere bedt om at prioritere et ”primært problem”, som de særligt ønskede hjælp til. Forsøgets primære endemål var ændringen over 12 uger målt som arealet under kurven på den skala i spørgeskemaet, som svarede til det ”primære problem”, patienten havde valgt. Andre endemål var overlevelse og andelen af patienter, som følte sig hjulpet med deres ”primære problem”. Der blev også indsamlet deltagerevalueringer og data om komponenterne i interventionen.

Hovedresultater: 288 patienter deltog i lodtrækningen og 279 patienter blev inkluderet i forsøgets hovedanalyse (146 i kontrolgruppen og 133 i interventionsgruppen).

I løbet af de 12 uger, forsøget varede, forbedrede scoren for det "primære problem" sig signifikant for de patienter, der modtog palliativ rehabilitering i sammenligning med dem, der alene modtog standardtilbuddet. Størrelsen på den anslåede forskel mellem grupperne var 3,0 (95% sikkerhedsinterval 0,0-6,0; p=0,047). Der blev også foretaget en sensitivitetsanalyse for forskellen fra det første til det sidste spørgeskema, og den viste en højsignifikant gruppeforskel på 3,3 (95% sikkerhedsinterval 1,0-5,6; p=0,005).

Efter 12 uger var der også signifikant flere af de patienter, der havde modtaget palliativ rehabilitering, der følte, de havde fået hjælp til deres "primære problem" (75%) i forhold til de patienter, der havde fået standardtilbuddet (51%), p=0,002.

132 patienter tog imod tilbuddet om to konsultationer i det palliative rehabiliteringsambulatorie. 59 patienter (45%) deltog desuden i gruppeprogrammet, og 47 patienter (35%) modtog ekstra individuelle konsultationer uden at deltage i gruppen. De resterende 26 patienter (20%) modtog udelukkende de to planlagte konsultationer.

Patienterne i gruppeprogrammet deltog mediant i 10 ud af de 12 gruppesessioner (fra 1-13), og modtog mediant fem supplerende, individuelle konsultationer (fra 0-21). Patienter, som udelukkende fik ekstra, individuelle konsultationer havde mediant to ekstra kontakter (fra 1-18).

I alt blev der afholdt 411 ekstra, individuelle konsultationer mellem forsøgsdeltagere i interventionsgruppen og personalet i det palliative rehabiliteringsambulatorie. Konsultationerne omhandlede især smertebehandling, følelsesmæssig håndtering af den svære livssituation, patienterne stod i, og rådgivning om ernæring.

Da forsøget var slut, og de forsøgsdeltagere, der havde modtaget det nye tilbud, blev spurgt, om de ville anbefale tilbuddet til andre i samme situation som dem selv, var 93% helt enige og 7% delvist enige. Ingen var uenige.

Der var ingen effekt på overlevelsen i de to grupper.

Konklusion og perspektiver: Patienter, der netop var blevet diagnosticeret med en alvorlig kræftsygdom, fik en forbedret livskvalitet af at modtage palliativ rehabilitering sideløbende med den medicinske kræftbehandling. Palliativ rehabilitering var bedre end standardbehandling til at hjælpe patienterne med de

problemer, de udvalgte som de væsentligste at få hjælp til. Patienterne opfattede tilbuddet som relevant og nyttigt.

Resultaterne kan anvendes til at informere beslutningstagere nationalt og internationalt og føre til forbedringer i behandlingen af alvorligt syge kræftpatienter.

List of original papers

The thesis is based upon the following papers:

1. A parallel-group randomized clinical trial of individually tailored, multidisciplinary, palliative rehabilitation for patients with newly diagnosed advanced cancer: the Pal-Rehab study protocol. Nottelmann L, Groenvold M, Vejlgaard TB, Petersen MA, Jensen LH. BMC Cancer. 2017 Aug 23;17(1):560. doi: 10.1186/s12885-017-3558-0.

2. A new model of early, integrated palliative care: palliative rehabilitation for newly diagnosed patients with non-resectable cancer. Nottelmann L, Jensen LH, Vejlgaard TB, Groenvold M. Supportive Care in Cancer. 2019 Jan 5th (published online ahead of print) doi: 10.1007/s00520-018-4629-8.
3. The effect of individually tailored, multidisciplinary, palliative rehabilitation for patients with newly diagnosed advanced cancer: the Pal-Rehab randomized controlled trial. Nottelmann L, Groenvold M, Vejlgaard TB, Petersen MA, Jensen LH. (Draft)

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Definitions

Palliative care

Palliative care is defined by the World Health Organization (WHO) in 2002 as an approach aiming to improve the quality of life (QoL) of patients and their families facing the problems associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual.[1]

Specialised palliative care is provided by healthcare professionals whose main task is to provide palliative care. Typically a multidisciplinary team of physicians, nurses, social workers, and chaplains deliver specialised palliative care. [2]

Early, integrated palliative care

Palliative care is often misconstrued as "end of life"-care only.[3] The term "early, integrated palliative care" has been introduced as palliative care delivered alongside disease modifying treatments and integrated in the standard treatment of the disease. The new concept of palliative care has been illustrated in the following figure:

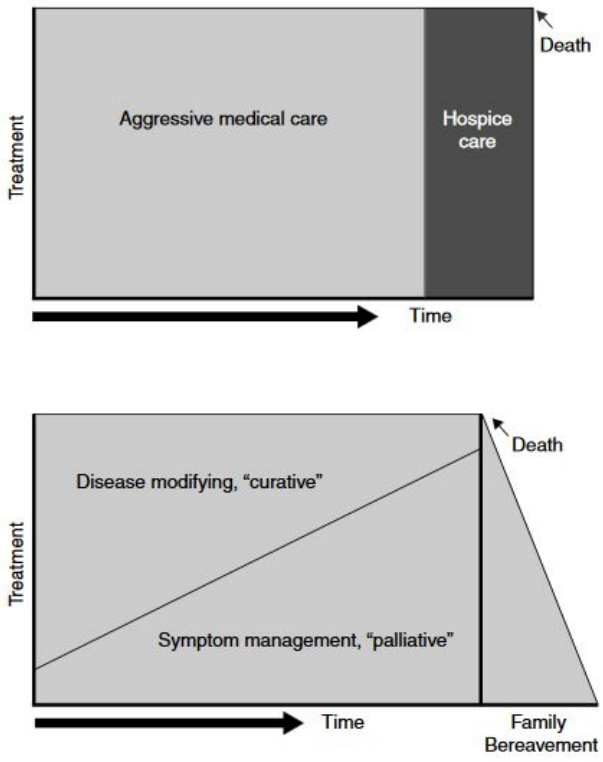

Figure 1. *Model of the older "transition model" versus the newer "trajectory model" of palliative care as defined by WHO in 2002. Source: Lynn & Adamson[4]. Reprinted with permission.*

Early integrated palliative care for patients with advanced cancer is recommended by international cancer organizations such as The American Society for Clinical Oncology (ASCO) and The European Society for Medical Oncology (ESMO).[5, 6]

Palliative rehabilitation

Rehabilitation is defined by WHO as a set of measures that assist individuals who experience, or are likely to experience, disability to achieve and maintain optimal functioning in interaction with their environments.[7]

Rehabilitation aims at improving and maintaining physical, mental, social and intellectual performance levels and preventing loss of functions related to activities of daily living (ADL) with the purpose of supporting independence and self-management.[8]
Typically, rehabilitation occurs for a specific period of time and can involve single or multiple interventions delivered by an individual or a team.[7]

Specialised palliative care and rehabilitation services may overlap in terms of the healthcare professionals involved and the overall aim of improving QoL. Both services apply a patient and family centred, multidisciplinary and team based approach founded in shared decision making.

No consensus exists for the fusion of the two types of services, but a few definitions have been proposed. Dietz identified and described four approaches to cancer rehabilitation in 1980: preventative, restorative, supportive, and palliative.[9] However, in this model the timing of the offer was central to the definition, and palliative rehabilitation was merely seen as “interventions that would allow terminal patients to live a high QoL physically, psychologically, and socially”. Patients and their families were predominately seen as receivers of support. Later definitions have put the patient and family caregivers in a more active role and avoided the understanding of “palliative” as synonymous with “end-of-life”.

In 2015 Tiberini and Richardson from the United Kingdom suggested a definition of rehabilitative palliative care as “a paradigm which integrates rehabilitation, enablement, self-management and self-care into the holistic model of palliative care” and “an approach that empowers people to adapt to their new state of being with dignity […] and cope constructively with losses resulting from deteriorating health”.[10] This definition thus puts emphasis on the content of the offer. American author Cheville mainly focused on the context of the offer in her 2017 suggestion of palliative rehabilitation as “function-directed care delivered in partnership with other disciplines and aligned with the values of patients who have serious and often incurable illnesses in contexts marked by intense and dynamic symptoms, psychological stress, and medical

morbidity, to realize potentially time-limited goals". [11] Whenever the term "palliative rehabilitation" is mentioned in this thesis it is in accordance with the definitions by Tiberini/Richardson and Cheville.

Advanced cancer

Advanced cancers can be locally advanced or metastatic. Locally advanced cancers have grown outside the organ they started in but have not spread to other parts of the body. Metastatic cancers have spread to other parts of the body via the bloodstream or lymph system.

Following a cancer diagnosis the patient is assessed for resectability and most often the first treatment for a locally advanced cancer will be operation whereas the first treatment for the majority of patients with metastatic disease will be systemic oncological treatment.

Background

Living with advanced cancer

In Denmark around 40,000 people are diagnosed with cancer and more than 15,000 people die of the disease each year.[12, 13] At the end of 2017, 325,000 Danes were living with a cancer diagnosis.[13] Since most people have close friends and family the number of people affected by cancer is even higher.

A national Danish survey of 977 patients with mixed advanced cancer found that the participants were burdened by symptoms and problems related to living with cancer and were not offered the help they needed.[14, 15]

Timely referral to specialised palliative care (SPC) may improve patient related outcomes such as overall QoL, symptom burden, satisfaction with care, and lower healthcare utilization, [16] but it primarily depends on individual judgements by the referring clinician.[17] In Denmark referral to SPC happens late in the disease trajectory with a median survival time from the first contact with SPC of less than six weeks.[18]

Early palliative care in cancer

Early palliative care is not widely implemented in oncology and the optimal model of delivery and time for referral remains uncertain.[19]

Several clinical trials have investigated the effect of systematic, "earlier than usual" referral to specialised palliative care for outpatients with advanced cancer. At least sixteen randomised controlled trials (RCTs) have been published on the subject - the majority within the last five years.[20, 21, 30–35, 22–29] Three of the trials were not restricted to advanced cancer patients but included other types of advanced disease as well.[24, 34, 35]

In seven of the studies the intervention could be classified as specialised palliative care integrated in the standard disease-modifying treatment from the onset of an advanced cancer diagnosis (up to 100 days after diagnosis). [21, 22, 25, 26, 29, 31, 32] In other trials the study population was primarily selected by a perceived prognosis, e.g. an expected survival time of less than one year or between six and 12 months at the time of enrolment.[20, 23, 27, 28, 34, 35]

Early, integrated palliative care from the onset of an advanced cancer diagnoses

Although all seven studies representing early, integrated care for newly diagnosed patients with advanced cancer used patient reported outcomes, they differed in choice of outcome measures and findings. Four studies reported a single pre-specified primary outcome measure of change in health-related QoL over 12

weeks[22, 29, 31, 32] and three of them met their primary endpoint.[22, 29, 32] The fourth study found a greater improvement in QoL for intervention patients after 24 weeks.[31] Three studies reported a cluster of "key or primary outcome measures" and while one study found a mixed result with significant improvements on some but not all primary endpoints in the intervention group[21], two studies could not prove superiority of the early palliative care intervention.[25, 26]

The studies also differed markedly in terms of study participants, study design, and intervention components. Two studies exclusively enrolled patients with one cancer type, i.e. non-small lung cancer [22] and pancreatic cancer[29], respectively. The remaining studies investigated the effect of early palliative care in patients with mixed cancer types.[21, 25, 26, 31, 32] All studies were individual-randomized trials apart from one, which was cluster-randomised. [26]

Two interventions were led by nurses only[21, 26] and two other studies initiated with a nurse-led consultation but entailed the possibility of seeing a palliative care physician, if needed.[25, 32] In two studies, conducted at the same cancer-centre, the patients would meet with "a member of the palliative care team consisting of physicians and advanced-practice nurses".[22, 31] One study implied the use of a multidisciplinary team in addition to nurses and physicians, stating that the patient initially would meet with a "Palliative Care-specialist" (profession not specified) who could initiate other interventions concerning the patient's physical, psychological and spiritual needs.[29] None of the studies specifically mentioned the inclusion of other healthcare professionals besides nurses and physicians in the intervention.

Palliative rehabilitation

The national survey of 977 Danish patients with advanced cancer showed that the most dominant symptoms/problems reported were fatigue (73%), limitations to physical activity (65%), limitations to work and daily activities (58%) and worry (58%).[15] These results indicate that it is highly relevant to focus on alleviating impairments related to physical, social, and emotional functioning as well as specific symptoms in this patient group.

Cancer incidences are increasing worldwide and many patients are living longer with advanced cancer because of more effective treatments.[36] It is thus increasingly relevant also from a societal point of view to develop interventions to support the patients' independence and self-management.

The focus on the conceptual relation between palliative care and rehabilitation has increased in Denmark in recent years.[37, 38] International authors have also pointed out the value of rehabilitation interventions for patients with cancer as a chronic condition. [11, 39–47]

In the United Kingdom specialist palliative day-care defined as *"services that enhance the independence and quality of life of patients through rehabilitation, occupational therapy, physiotherapy, the management and monitoring of symptoms, and provision of psychosocial support"* has been offered since the 1970s.[48] The offers are ambulatory and mainly hospice-based and nurse-led.[48] A systematic review from 2005 of qualitative and quantitative studies evaluating specialist palliative day-care services found that it could not be established whether the offers led to improved symptom control or better health-related QoL.[48] There was, however, evidence of high patient satisfaction with the offers. The participants especially highlighted the social element of contact with staff and other patients, the possibility of taking part in a range of activities, and having their symptoms assessed when required. The studies included in the review were mainly observational and none of them used a randomised, controlled design. In 2015 Hospice UK published a report stating that "rehabilitative palliative care is an essential component of palliative care".[10] However, the amount of robust evidence on which to base this approach was still very limited.

A British RCT published in 2013 tested the effect of a complex rehabilitation intervention delivered by a hospice-based multidisciplinary team vs. usual care for patients with active progressive breast or haematological cancer and found a psychological benefit of the intervention.[49] The study only included 41 patients and does not represent an example of integrated care since the intervention took place after the termination of active anticancer treatment.

While research on palliative rehabilitation is sparse there is a growing body of literature on integrated and often multidisciplinary, function- and quality of life-directed interventions in patients with advanced cancer. American authors Rummans et al. applied a randomised, controlled design to test the effect of eight 90-minute multidisciplinary sessions over three weeks in 103 patients with advanced cancer undergoing radiotherapy.[50] The sessions were designed to impact physical, mental, social, emotional, and spiritual QoL and combined conditioning exercises, educational information, cognitive behavioural strategies, open discussions, and relaxation exercises. A control group received standard care as recommended by the radiation oncologist. The primary endpoint was overall QoL after four weeks, and the authors found that QoL slightly increased in the intervention group whereas it decreased significantly in the control group over the same period. In another RCT by members of the same author group 131 patients, also receiving radiation therapy for advanced cancer, were randomly assigned to a modified version of the above multidisciplinary intervention or standard care.[51] The sessions were also themed on the different domains of QoL and followed the same template as in the earlier study with some alterations to the specific themes addressed in the group sessions based on participant feedback. Six group sessions were offered instead of eight in the previous study and caregivers were invited to participate in four of the sessions. Again it was

found that the overall QoL was significantly higher in the intervention group at four weeks compared to the control group. Caregiver QoL was, however, not affected.

Another research group conducted an RCT comparing a 12 week multimodal intervention of nutritional support and physical exercise with the aim of improving QoL.[52] Patients with advanced cancer originating from the lung or gastrointestinal tract receiving standard care at a cancer centre in Switzerland were enrolled. Patients in the intervention group were offered a minimum of three nutritional counselling sessions and a twice a week physical exercise programme. The primary endpoint was overall QoL after 12 weeks and though the authors found that the primary endpoint did improve more in the intervention group than in the control group the difference was not statistical significant. The study did, however, suffer from very slow accrual and with the inclusion of 58 patients it did not meet the sample size calculations.

Aims and hypothesis

The overall hypotheses of the thesis

- Patients with advanced cancer in Denmark have unmet palliative and rehabilitative needs from the onset of their advanced cancer diagnoses.
- Early palliative care in the form of a multidisciplinary, palliative rehabilitation programme integrated in standard oncology care can improve QoL in newly diagnosed advanced cancer patients.

The hypothesized mechanism of an early palliative care model is shown in the figure below:

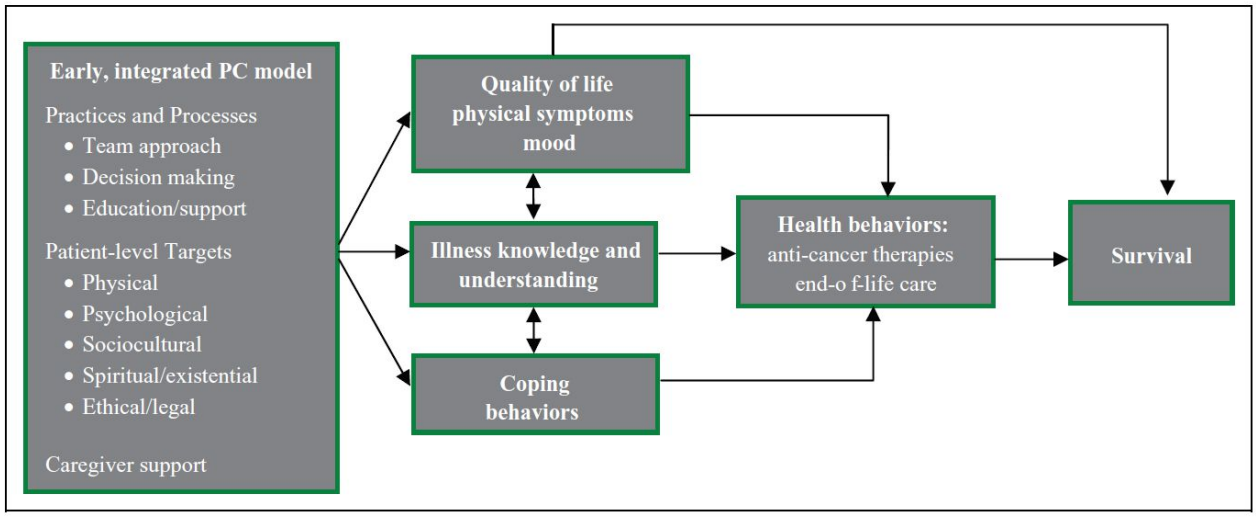

Figure 2. *Model of early, integrated palliative care (PC) in cancer. Source: Irwin et al. 2012*[53]*. Reprinted with permission.*

The hypotheses of the thesis were tested in an RCT investigating the effect of a 12-week palliative rehabilitation intervention on QoL of patients with newly diagnosed advanced cancer receiving anticancer treatment at Vejle Hospital. The palliative rehabilitation intervention would entail individual consultations and the possibility of entering a group programme combining educational sessions with physical exercise.

The aims of the thesis were addressed in three papers as follows:

Paper I

The aim of the protocol paper was to present and discuss the rationale, design, and methods of the RCT.

Paper II

The aim of the second paper was to present data on how the newly developed palliative rehabilitation intervention was utilized during the RCT and how it was received by the patients.

Paper III

The aim of the third paper was to test the probability of the null-hypothesis of no difference between the two study arms of the RCT and estimate the size of a potential group difference in QoL in the period between baseline and 12 weeks after randomisation.

In addition to the aims presented in the three papers this thesis also includes an analysis of survival as a distal goal of the early palliative care intervention (Fig. 2).

Material and methods

This section is based on papers I-III.

Study design

The study was a parallel group, two-arm randomised controlled trial with six- and 12-week follow-up measurements. Participants were randomised 1:1 to receive standard oncology care (control group) or palliative rehabilitation concurrently with standard care (intervention group).

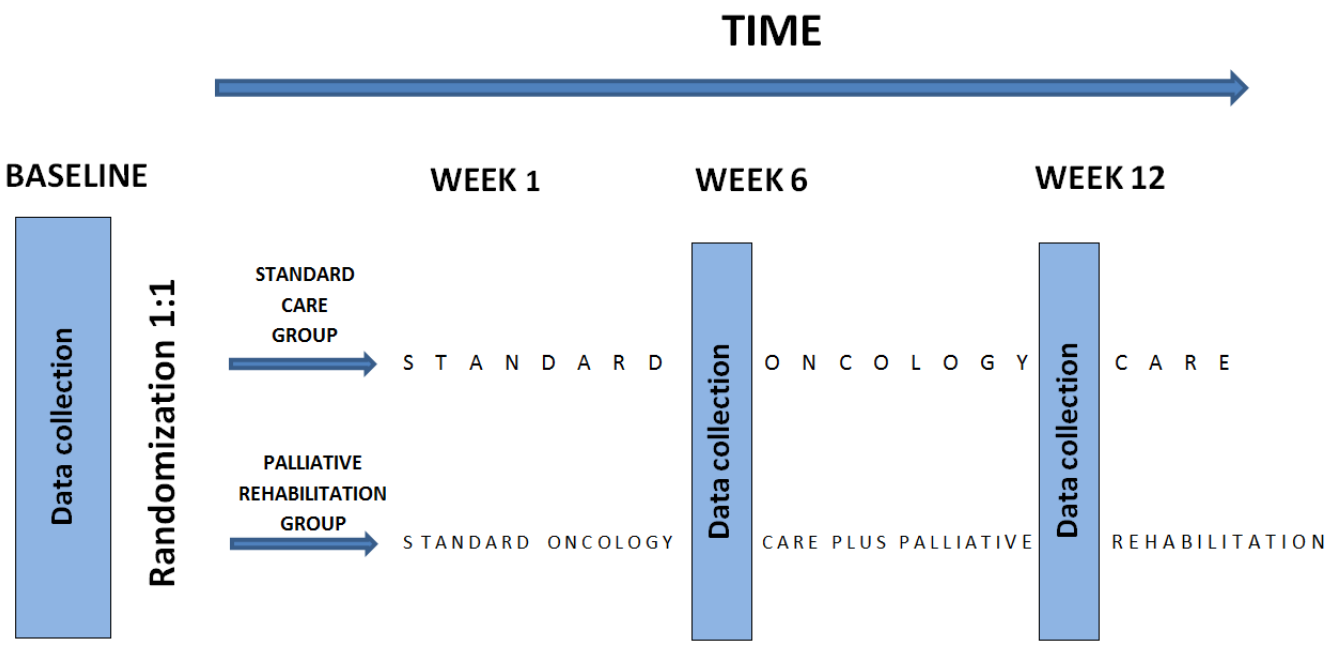

Figure 3. *Study outline.*

Setting and participants

Between December 2014 and December 2017 eligible patients were recruited from the Department of Oncology, Vejle hospital in the Region of Southern Denmark. The department houses three outpatient oncology clinics, one outpatient radiotherapy clinic, one bed ward, and one palliative care unit. Activities on a yearly basis include approximately 60,000 ambulatory visits with 9,300 chemotherapy administrations and 22,000 radiotherapy administrations. The outpatient oncology clinics treat adult patients with solid tumours originating from the lungs, breasts, prostate, colon, rectum, biliary tract, and the female reproduction tract.

Inclusion criteria were: 1) diagnosed with non-resectable cancer for the first time within the last eight weeks; 2) eligible for and accepting standard oncology treatment at the Department of Oncology, Vejle

Hospital, and 3) able to speak and understand Danish. Resectability was evaluated by a multidisciplinary team of surgeons, radiologists, and oncologists. Patients who had potentially resectable cancer depending on the success of the anticancer treatment were also deemed eligible. Patients with advanced prostate cancer are usually treated at the Department of Urology with endocrine treatment as a first choice, which means that a large group of patients with this disease were not eligible according to the inclusion criteria. Hence, the protocol was amended after 10 months (October 2015) to also include patients with advanced prostate cancer referred to the Department of Oncology for systemic treatment for the first time within the last eight weeks.

Patients who were not able to comply with study procedures were excluded from participation. Among the reasons were cognitive impairment, language barriers, and contact with a specialised palliative team within one year prior to enrolment.

Recruitment

A research assistant screened new referrals for potential eligibility. The staff at the oncology clinics was furthermore encouraged to inform the research assistant of any eligible patients diagnosed with non-resectable tumours during adjuvant treatment or follow-up.

Eligible patients received oral and written information about the study by the research assistant or a doctor or nurse at the oncology clinics.

Randomisation

When written consent to participation was given, either immediately or at a following visit, the patient completed the baseline questionnaire. The informant filled in a sheet of baseline characteristics and contacted an independent study nurse with access to the allocation list. The list was generated at randomizer.org before the enrolment began and kept strictly hidden from anyone involved in the recruitment of study participants. No stratification was used during randomisation. If a patient declined participation the following information was registered anonymously; age, sex, ECOG performance status[*], cancer diagnosis, living status (partnered or living alone), educational background, and reason for declining, if given.

[*] **ECOG performance status**: the Eastern Cooperative Oncology Group performance status ranging from 0-4 (5), where 0 is “Fully active, able to carry on all pre-disease performance without restriction” and 4 is “Completely disabled, cannot carry on any self-care, totally confined to bed or chair”(5 is ”dead”) [100]

When a patient was allocated to the intervention arm, the study nurse would notify a secretary in the palliative team, who would telephone the patient and schedule the initial consultation to take place within one week, if possible.

Standard care

Standard care was "treatment as usual" at the Department of Oncology and provided at the discretion of the treating oncologist. In addition to anticancer treatment the department offers psychosocial support and employs psychologists, social workers, and hospital chaplains. The department has guidelines for referral to dieticians or physiotherapists and for the screening of "palliative and rehabilitative needs". Every local municipality in the region of the hospital offers cancer rehabilitation.

Standard care was provided to all study participants regardless of allocation arm.

The intervention

Patients allocated to the intervention arm of the study were systematically offered palliative rehabilitation concurrently with standard oncology care.

Two consultations were offered in the outpatient palliative rehabilitation clinic. The first consultation was held with a physician and a nurse specialised in palliative care and took place as soon as possible after randomisation. The second consultation with a specialised palliative care nurse was a follow-up to the first consultation and took place six to seven weeks after randomisation. Participants were encouraged to bring family or other personal caregivers to the consultations. At the end of the first consultation participants were provided with the team's contact information and the names of their contact physician and nurse. They were informed that they were welcome to contact the team directly during the next 12 weeks, should the need occur.

A list was made of subjects to be covered at the first consultation. This was inspired by the template made for a trial on early palliative care by Temel et al. [22] The consultation addressed symptoms, mood, barriers to activities of daily living (ADL), illness and prognostic understanding, coping mechanisms, thoughts and goals for the future, a map of the patient's family and network, and individual needs of the family caregiver(s). If found relevant based on specific symptoms, a focused physical examination was performed. A plan was made for the next approximately 12 weeks in collaboration with the patient and family caregivers, was documented in the electronic patient record, and a copy was sent to the patient's general practitioner.

The offer was individually tailored to the needs of the patient and caregivers and reflected the offers of the palliative rehabilitation clinic including a group programme and individual consultations at the clinic or over the telephone.

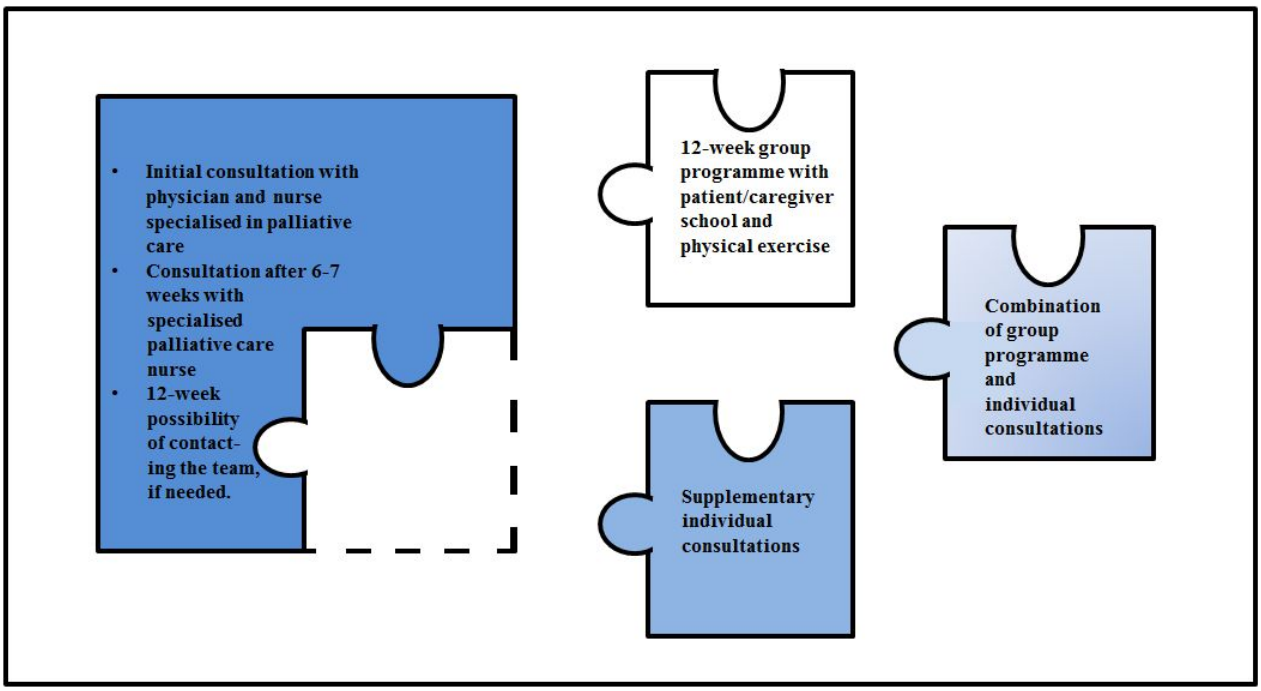

Figure 4. *The palliative rehabilitation offer.*

The multidisciplinary team

The specialised palliative care team at Vejle Hospital consists of physicians, nurses, physiotherapists, psychologists, and secretaries. The team was founded in 2005 and has predominately cared for patients and families in their homes near the end of life. For the purpose of offering palliative rehabilitation in an outpatient clinic the team was enhanced in 2013 by a part time occupational therapist, a dietician, a social worker, and a chaplain. The team has weekly meetings to discuss all new patients and caregivers at least once.

Training of the intervention providers

Members of the palliative rehabilitation team attended a one-day training session in facilitating health education and received a two-day visit by palliative rehabilitation clinicians from the Irish and British health systems.

The palliative rehabilitation group offer

The group offer was the main intervention, if relevant. However, an individually tailored intervention was offered if the participants could not identify themselves with a group setting or if they were assessed to be unfit for a group intervention, e.g. due to personal crisis or reduced social skills.

Patient and caregiver school

The patient and caregiver school was a 12-week course with weekly non-mandatory sessions. Each session was designed to stand alone to allow enrolment of participants on an ongoing basis. A facilitating nurse followed the group each time and assessed the need for supplementary individual consultations – either directly after the group sessions or at another time point if other members of the team were to be involved.

The weekly session began with a one-hour gathering for patients and caregivers in a group room with soft furnishings. The participants had been given an overview of the subjects and dates beforehand. Supplementary written material from each session was collected in a folder for the patients to take home. The first 20 minutes was held as an educational session and the remaining 40 minutes were allocated to debate, questions, and the exchange of personal experiences. All participants were informed about the importance of keeping things shared in the group strictly confident. Taking active part in the debates was voluntary. An overview of the subjects and responsible healthcare professionals can be seen in Table 1.

Table 1. Topics covered and the responsible healthcare professionals in the educational sessions of the patient and caregiver school.	
Topic	**Responsible healthcare professionals**
Body and movement	Physiotherapist and facilitating nurse
Sleep and tiredness	Two nurses (one being the facilitating nurse)
Breathlessness	Physiotherapist and facilitating nurse
Fatigue	Occupational therapist and facilitating nurse
Nutrition	Dietician and facilitating nurse
Coping with the patient role	Psychologist and facilitating nurse
Open session	Physician and facilitating nurse
Coping with the caregiver role	Psychologist and facilitating nurse
When life hurts	Hospital chaplain and facilitating nurse
Financial and social issues	Social worker and facilitating nurse
Open session	Psychologist and facilitating nurse
Rest and relaxation	Physiotherapist and facilitating nurse

Physical exercise

After the educational session a break gave the participants an opportunity to engage more informally, have a snack, and change clothes for the physical exercise programme that would last another hour. Caregivers were not invited to take part in the physical exercise but were encouraged to socialise in an adjacent lounge area.

The physical exercise programme, which was based on joined goal setting and individual tailoring, was a combination of aerobic exercises and dynamic resistance training. Before entering the group the patient would meet alone with the responsible physiotherapist. A panel of validated tests was applied to establish the patient's physical performance level; a six-minute walking test, hand grip strength measurement, and sit-to-stand ability.[54–56] The physiotherapist would help the patient set a specific, relevant, challenging but realistic and achievable goal for the 12-week intervention.[57]

If relevant, the physiotherapist would give the patient instructions for additional home exercises. At the end of the 12 weeks the panel of tests was repeated, the goal evaluated, and the patient was offered recommendations on how to maintain the obtained results.

Individual tailoring

All members of the palliative rehabilitation team were available for individual consultations with patients and caregivers – together or individually. Appointments with the hospital chaplain could not be arranged through the palliative rehabilitation clinic, but patients and caregivers could be encouraged to make a request at the oncology clinic or their local church, if appropriate.

Patients and caregivers were referred back to the Department of Oncology after 12 weeks, or when the group programme was finalised. However, all interventions initiated in the palliative rehabilitation clinic were followed through, and if the patients and caregivers were assessed to still have a need for specialised palliative care they remained with the team.

Data collection

All study participants were asked to fill out the European Organisation for Research and Treatment of Cancer Quality of Life Core Questionnaire (EORTC QLQ-C30) version 3.0., before randomisation and after six and 12 weeks. The questionnaire consists of 30 items measuring different domains of QoL through five function scales (physical, role, emotional, cognitive, and social function), three multi-item scales (fatigue, pain, and nausea and vomiting), one global health status/QoL scale, and six single-item scales measuring dyspnoea, insomnia, appetite loss, diarrhoea, and financial difficulties. The questionnaire starts with five items forming the physical function scale. It continues with 23 items measuring the remaining symptoms and functions. At this point the respondent is asked to recall the severity of the symptoms and problems within the last week. Response categories for the magnitude of each symptom or problem are “not at all”, “a little”, “quite a bit” or “very much”. Finally, two seven-point response scales ranging from 0 (very poor) to 7 (very good) form the global health status/QoL scale.

In the present study the patients were asked at baseline to choose a “primary problem” that they needed help with the most from a list of 12 symptoms or problems. A 13th option was “none of the above”(see Appendix).

The 12 different potential “primary problems” corresponded to the 12 different domains in the EORTC QLQ-C30 that the intervention was thought to impact to the largest extent. Diarrhoea, financial difficulties, and Global health status could not be chosen as a “primary problem”.

Extra items were added to the existing scales so that each scale corresponding to a “primary problem” would be made up of at least four items. The extra items came from a calibrated list of items (item bank) developed for computer adapting testing (CAT) of EORTC QLQ-C30. [58] In all, the questionnaire used in the study included 54 EORTC items.

At six and 12 weeks the participants were asked on a separate sheet if they had received help with the "primary problem" (yes/no).

In the intervention arm the dates of all contacts with the palliative rehabilitation team were registered on a separate contact sheet immediately after the contact also stating the type of contact, the responsible healthcare professional(s), and whether or not caregivers were present. The responsible healthcare professional would also make a note of the contact in the electronic patient file. One main theme was assigned to each individual non-mandatory consultation by means of a retrospective review of the notes in the electronic patient files.

At the end of the study period participants in the intervention arm were asked a few extra questions evaluating the offer. Did they agree, partly agree, or disagree with the statements: "The intervention made a positive difference to me" and "I would recommend the intervention to others in a situation like mine". The evaluation form for participants in the group programme also included the following statements; "It was a positive experience to spend time with others in the same situation" and "The physical exercise programme improved my wellbeing".

The intervention was not expected to cause any serious event, but adverse event were nonetheless registered prospectively.

Data management

All study documents were pseudonymised using unique identification numbers and handled confidentially. Questionnaires for the primary outcome analysis were double-entered manually by blinded personnel using the Research Electronic Data Capture programme (REDCap) [59]and merged afterwards.

The rest of the data forms were entered into REDCap once. A random sample of 5% of the identification numbers was selected by an independent research nurse for a second check. If a form turned out to have an error, the previous and subsequent forms were also checked.

A codebook was used to keep track of variables and labels, and all decisions concerning data handling were documented in a data management log book.

Statistical data were saved on a secure SharePoint site owned by the Region of Southern Denmark.

Outcomes

Primary outcome measure

The primary outcome measure was the change since baseline for the problem prioritized by the patient (paper III).

Thus, if a patient chose pain as the "primary problem", the pain score was used in the analysis of the primary outcome, etc. If the patient chose "none of the above" or did not choose any of the 13 options the global health status/QoL scale was used in the analysis.

Secondary outcome measures

The secondary outcome measures included in this thesis are survival and group comparisons of whether or not the patients felt they had been helped with their "primary problem" at six and 12 weeks after baseline (paper III). A description of how the intervention was utilized during the RCT and evaluated by the participants is also included (paper II).

Sample size calculation, power and significance level

Scales based on the EORTC CAT item banks are analysed using item response theory (IRT) based T-scores without a fixed lower and upper limit but centred to have a mean of 50 and a standard deviation (SD) of 10 in the European general population.[60] At the time of designing the trial no data was available for sample size calculation based on the IRT-based scoring system and hence, sample size was estimated based on other studies using the original EORTC QLQ-C30 and a chosen SD of 25. With a power of 90% to detect a minimal clinically important group difference (MCID) of 10 points for the primary outcome, the sample size was calculated to be 266 (133 in each study arm). It was decided to aim for a sample size of 300 to allow for approximately 10% drop-out. The significance level was set at 5%.

Statistical analyses

Analysis of the primary outcome

A modified intention-to-treat (ITT) analysis was conducted meaning that patients who withdrew their consent after randomisation, died before 12 weeks, did not have a baseline assessment, or were enrolled on the basis of a screen failure were excluded from the primary outcome analysis. The statistician carrying out the analyses of the primary outcome was blinded to intervention allocation.

Each outcome was estimated as the change from baseline to the weighted mean of the six and 12-week follow-up measured as area under the curve (AUC) for the EORTC-scale representing the "primary problem"

chosen by the patient. The analyses were performed as multiple regressions adjusted for the variables believed to be of predictive importance, i.e. baseline ECOG performance status, sex, age, intention of the oncology treatment (potentially curative or non-curative), primary diagnosis, living status (partnered or living alone), educational background, and "primary problem". Multiple imputations were based on the same potentially predictive baseline variables.[61]

The decision to adjust for potentially predictive variables in the main analysis was made before any analyses were conducted but was a change from the statistical analysis plan published in paper I. The new decision was based on recommendations from Kahan et al. stating that covariate adjustments should be routinely incorporated into the analysis of randomised trials.[62]

As sensitivity analyses, the primary analysis was repeated for the change from baseline to the six and 12-week follow-up, respectively.

Explorative analyses were performed as tests for interactions between the intervention variable and the potentially predictive variables used in the primary analysis. The analyses were made on observed data using a linear regression model.

All the above analyses were made with SAS® statistical software version 9.4. [63]

Remaining analyses

The remaining analyses, as mentioned below, were performed using the statistical package, STATA, version 14 (StataCorp 2015, Texas, USA).

Components of the intervention and the participant evaluation in the intervention arm of the study were analysed using descriptive statistics (paper II). The same methods were applied in the analysis of reasons for declining participation. The median and range were used to describe continuous variables and number and percentages were used for categorical variables.

Baseline characteristics were described using mean value and standard deviation for continuous variables and number and percentages for categorical variables (paper III). Differences in baseline characteristics of participants and non-participants were analysed using Chi-squared test on categorical variables and Wilcoxon rank sum test on continuous variables (paper III).

Group comparisons of whether or not the patients felt that they had been helped with their "primary problem" six and 12 weeks after baseline were made with Chi squared tests on observed data (paper III). Patients who did not choose a "primary problem" were excluded from the analysis.

The survival analysis included all patients, except those excluded due to withdrawn consent or screen failure. Dates of death were obtained from the Danish Civil Registration System[64] on June 11, 2018, i.e. three months after the 12-week follow-up of the last study participant. Groups were compared using the Kaplan-Meier plot and log-rank test. A Cox regression model using the same potentially predictive variables as in the questionnaire analyses was used for estimation of a hazard ratio.

Ethics and approvals

All study procedures were conducted according to The Helsinki Declaration by the World Medical Association[65] and the protocol was approved by The Regional Committee on Health Research Ethics for Southern Denmark on April 2, 2014 (Project ID S-20140038).

The trial was registered with ClinicalTrials.gov after enrolment of one study participant (NCT02332317). The Danish Data Protection Agency approved the data collection, storing, and processing.

Participation in the study did not limit the access to specialised palliative care and nothing was done to prevent patients in the control group from being referred to specialised palliative care at the discretion of the oncologist.

Patient and caregiver involvement in the research process

Patients and patient representatives were involved during preparation, operation, and dissemination of the trial. In the preparation phase the intervention model was being tested on 84 patients referred to the specialised palliative team while still receiving chemotherapy. Feedback from patients, caregivers, and staff was collected systematically and changes were applied to the model based on their feedback (paper II). In parallel with the development of the intervention model the study design and set-up was discussed thoroughly and approved by the hospital's Patient and Relatives Council. A smaller group of the Council volunteered to meet up on a separate occasion to discuss how best to communicate about palliative care to patients with newly diagnosed advanced cancer. In the dissemination phase of the study the Council contributed with pointing out and adding perspective to the results of the trial they found to be most relevant and also making suggestions for knowledge dissemination.

Results

Paper I was published before the study was finalised and did not entail any results. As a consequence, this section is based on Papers II and III.

Between Dec 3, 2014 and Dec 22, 2017, 1,303 patients were screened of which 804 were eligible. A total of 288 patients with newly diagnosed advanced cancer were randomly assigned to receive standard oncology care (n=149) or the same care supplemented with palliative rehabilitation (n=139). Ultimately, 279 patients were included in the modified intention-to-treat analysis with 146 patients in the standard care group and 133 patients in the palliative rehabilitation group. The trial profile appears from Fig. 5.

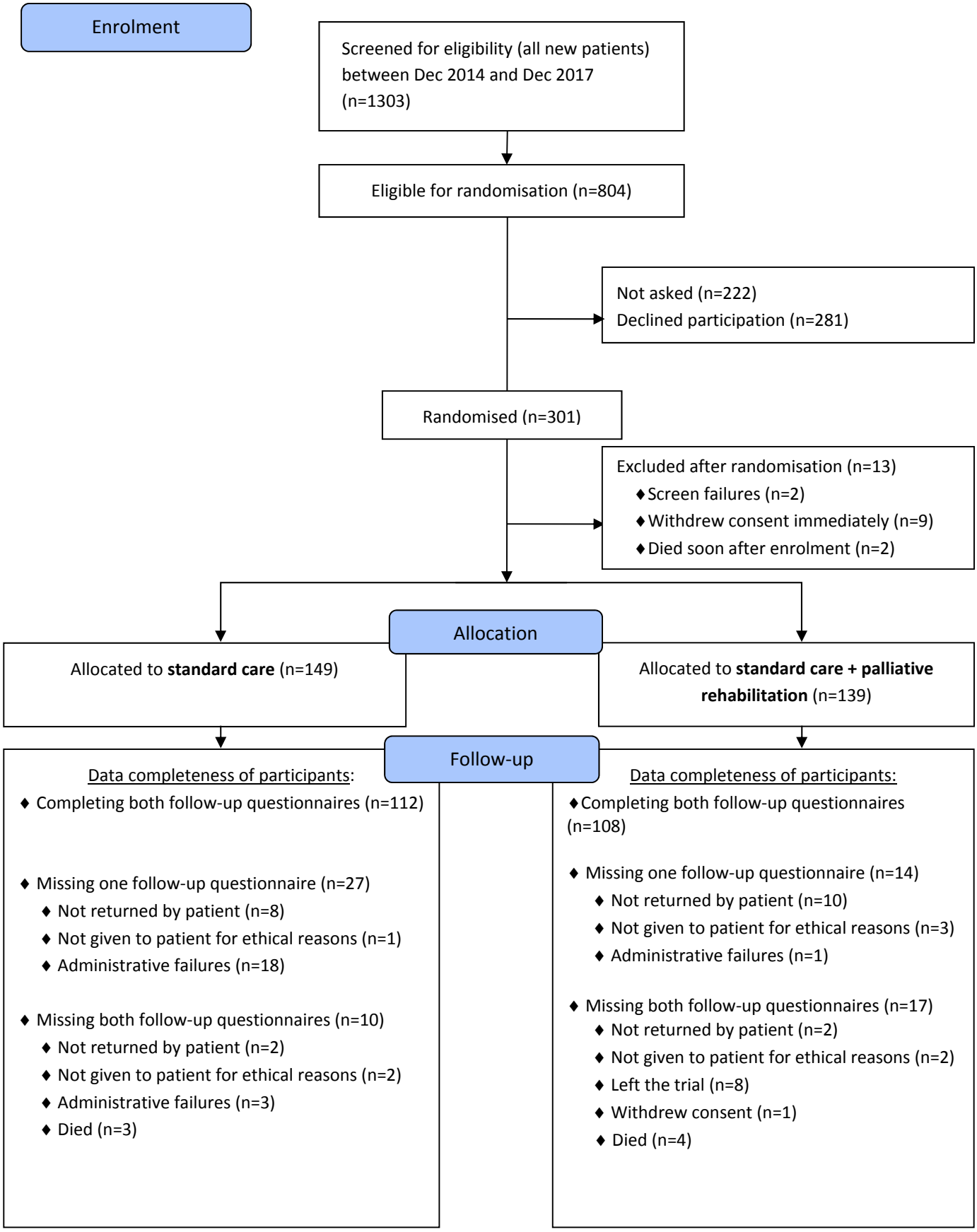

Figure 5. *Trial profile.*

Baseline characteristics

Baseline characteristics, “primary problems” chosen at baseline, and baseline values of the EORTC-scales (T-scores) appear from Table 2.

Table 2. Baseline characteristics and "primary problems"

	Palliative rehabilitation group (N=139)	Standard care group (N=149)
Time from diagnosis to enrolment (days), mean (SD)	35 (16)	36 (16)
Age (years), mean (SD)	66 (9)	66 (10)
Age groups (years), N (%)		
≥60	111 (80)	115 (77)
18-59	28 (20)	34 (23)
Male sex, N (%)	80 (58)	89 (60)
Cancer site, N (%)		
NSCLC	37 (27)	45 (30)
Colorectal cancer	38 (27)	39 (26)
Prostate cancer	25 (18)	28 (19)
SCLC	17 (12)	16 (11)
Breast cancer	11 (8)	8 (5)
Gynaecological cancer	5 (4)	5 (3)
Other	6 (4)	8 (5)
ECOG performance score [a)], N (%)		
0	53 (38)	65 (44)
1	69 (50)	66 (44)
2	17 (12)	18 (12)
Education (years), N (%)		
≤10	15 (11)	23 (15)
11-12	32 (23)	35 (23)
≥13, not university	79 (57)	73 (49)
Academic	10 (7)	15 (10)
Missing	3 (2)	3 (2)
Living status, N (%)		
Married or partnered	96 (69)	114 (77)
Living alone	43 (31)	35 (23)
Intention of oncological treatment, N (%)		
Non-curative	113 (81)	124 (83)
Potentially curative	26 (19)	25 (17)
Status of disease, N (%)		
Distant metastases present	116 (83)	129 (87)
Locally advanced	23 (17)	20 (13)
Brain metastases present, N (%)	8 (6)	7 (5)
Bones the only metastatic site, N (%)	11 (8)	14 (9)

Primary problem chosen by patients, N (%)		
"None of the above" [b)]	35 (25)	40 (27)
Emotional function	15 (11)	19 (13)
Physical function	10 (7)	22 (15)
Fatigue	11 (8)	18 (12)
Pain	16 (12)	9 (6)
Insomnia	12 (9)	11 (7)
Role function	11 (8)	11 (7)
Dyspnoea	11 (8)	3 (2)
Appetite loss	5 (4)	4 (3)
Nausea and vomiting	4 (3)	4 (3)
Cognitive function	4 (3)	4 (3)
Social function	1 (1)	3 (2)
Constipation	1 (1)	1 (1)
Missing	3 (2)	-
Baseline values for EORTC short form scales [c)], mean (SD)		
Global health status/Quality of life	50 (11)	50 (10)
Emotional function	51 (8)	53 (8)
Physical function	45 (10)	46 (10)
Fatigue	54 (9)	53 (8)
Pain	51 (9)	48 (8)
Insomnia	51 (9)	49 (8)
Role function	41 (10)	44 (10)
Dyspnoea	54 (11)	52 (10)
Appetite loss	56 (12)	55 (11)
Nausea and vomiting	55 (11)	54 (9)
Cognitive function	50 (8)	49 (9)
Social function	49 (7)	50 (7)
Constipation	52 (9)	50 (9)
Diarrhoea	53 (10)	52 (9)
Financial difficulties	49 (5)	50 (7)

Baseline characteristics and "primary problems" of 288 patients with newly diagnosed advanced cancer randomly assigned to receive standard oncology care (n=149) or an additional offer of palliative rehabilitation (n=139)
The sum of percentages may not total 100 because of rounding.
a) ECOG Performance status ranges from 0 to 4, with 0 = able to carry out all normal activity without restriction and 4 = completely disabled; totally confined to bed or chair.
b) "none of the above" marked by the patient on a list of 12 possible "primary problems" and a 13th option being "none of the above".
c) Baseline values for EORTC short form scales for 279 patients included in the modified intention-to-treat analysis. T-scores centered with European mean value=50 (SD=10). A score > 50 for a functional scale represents a higher level of functioning than the European mean and a score >50 for a symptom scale represents a higher level of symptomatology/ problems than the European mean.

Abbreviations: SD= standard deviation, NSCLC= Non-small cell lung cancer, SCLC= Small cell lung cancer, ECOG= Eastern Cooperative Oncology Group, EORTC= European Organization for Research and Treatment of Cancer.

Participants and non-participants

A total of 582 patients were invited to participate in the trial of whom 281 declined. The reasons for declining are shown in Fig. 6. The category “unknown” was used when the patient did not offer a reason for declining.

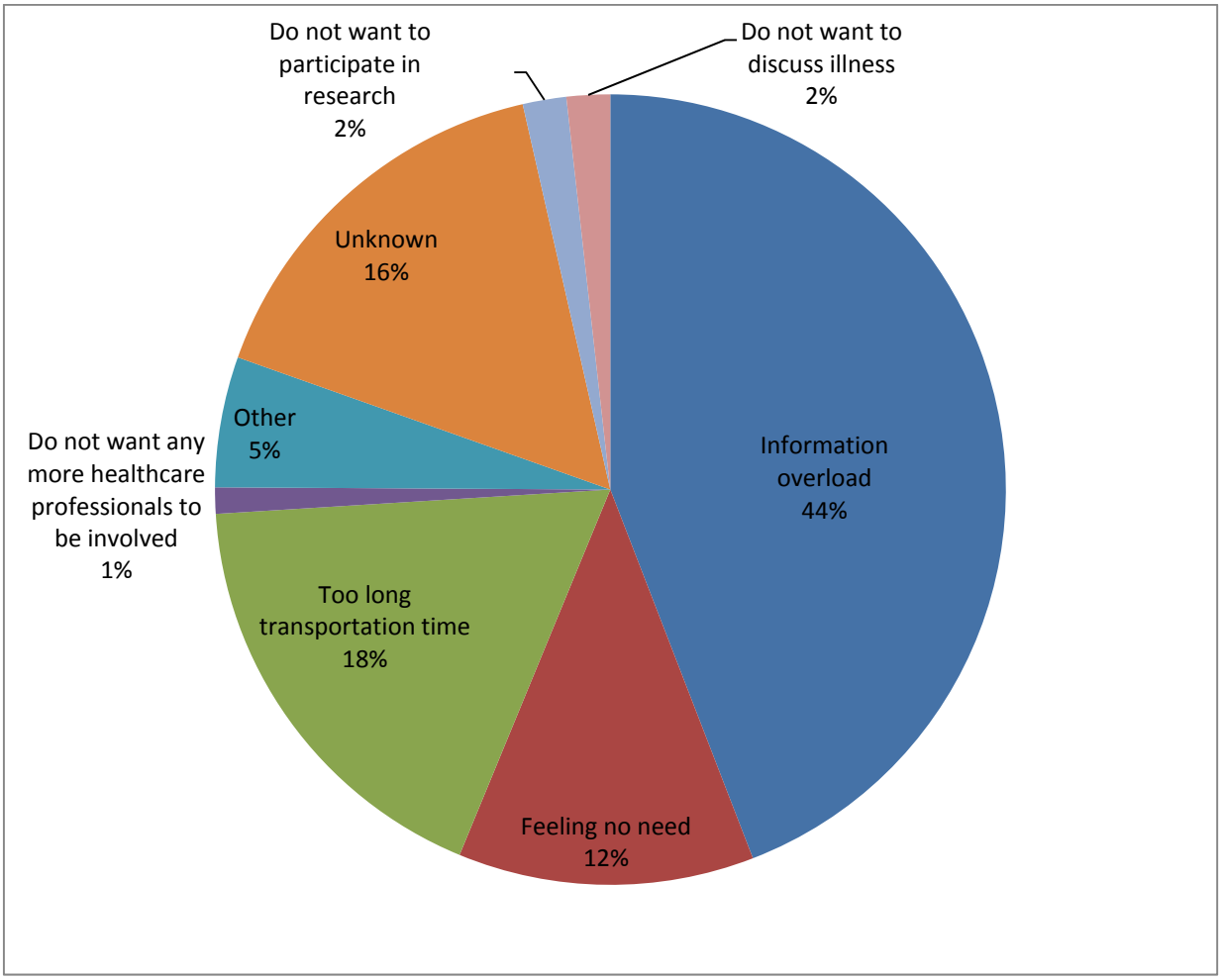

Figure 6. *The reasons stated by 281 patients for declining participation up front.*

Differences in baseline characteristics between participants and non-participants can be seen in Table 3.

Table 3. Baseline characteristics of 288 participants and 290 non-participants [a)]

	Participants (N=288)	Non-participants (N=290)	P-value
Age (years), mean (SD)	66 (10)	70 (8)	<0.001
Male sex, N(%)	169 (59)	163 (56)	0.580
Cancer site, N(%)			0.001
Lung cancer	115 (40)	158 (55)	
Colorectal cancer	77 (27)	46 (16)	
Prostate cancer	53 (18)	46 (16)	
Breast cancer	19 (7)	8 (3)	
Gynaecological cancer	10 (3)	15 (5)	
Other	14 (5)	16 (6)	
ECOG performance status[b)], N (%)			0.506
0	118 (41)	104 (36)	
1	135 (47)	145 (51)	
2	35 (12)	38 (13)	
Education (years), N (%)			<0.001
≤10	38 (13)	48 (25)	
11-12	67 (24)	77 (40)	
≥13, not university	152 (54)	61 (31)	
Academic	25 (9)	9 (5)	
Living status, N (%)			0.325
Married or partnered	210 (73)	200 (69)	
Living alone	78 (27)	89 (31)	

The sum of percentages may not total 100 because of rounding.
Differences in categorical variables were tested with Chi-squared test. Difference in age was tested with Wilcoxon rank sum test.

a) Non-participants declined participation (n=281) or regretted giving consent to participate (withdrew consent immediately (n=9))
b) ECOG Performance status ranges from 0 to 4, where 0 = able to carry out all normal activity without restriction and 4 = completely disabled; totally confined to bed or chair.
Abbreviations: SD, standard deviation; ECOG, Eastern Cooperative Oncology Group.

Non-participants were patients who declined participation upfront (n=281) or regretted giving consent immediately (n=9). Non-participants were older, less likely to have colorectal cancer, more likely to have lung cancer and had received fewer years of education. No differences were found in relation to sex, performance status, and living status. The analyses were repeated comparing the 279 patients included in the primary analysis with the non-participants without altering the results.

Data completion

In the standard care group 112 (75%) completed all three study questionnaires compared to 108 (78%) in the palliative rehabilitation group (Fig. 5).

In the standard care group 146 patients and 438 questionnaires were included in the modified intention-to treat analyses. Of those, 41 questionnaires were based on imputed values (9.4%) (Fig. 5). In the intervention group 133 patients and 399 questionnaires were included in the analyses of which, 38 were reconstructed using multiple imputations (9.5%).

How was the intervention model utilized during the RCT? (paper II)

Of the 139 patients allocated to the intervention arm, seven left the trial before the initial consultations. Thus, 132 patients were seen in the palliative rehabilitation out-patient clinic after allocation to the intervention arm.

The initial consultation took place a median of 11 days after randomisation (range 1-42 days) and the follow-up consultation took place a median of 50 days after randomisation (range 39-77 days).

After the initial consultation 59 patients (45%) joined the group programme and 47 patients (35%) received supplementary individual consultations without participating in a group. The remaining 26 patients (20%) received no more than the initial and the follow-up consultation (Table 4).

Of the 132 patients seen for the initial consultation, 97 had chosen a specific “primary problem” at baseline (73%), 33 had chosen “none of the above” (25%), and two had a missing value for “primary problem” (Table 4).

Table 4. The intervention received by 132 participants in the intervention arm.

	Intervention received			
	Initial and follow-up consultation only N	Group programme (with or without individual contacts). N	Supplementary individual contacts without group programme. N	**Total N (%)**
A specific "primary problem" chosen*	12	51	34	97
"None of the above" chosen as primary problem	12	8	13	33
Missing value for "primary problem"	2	-	-	2
Total N (%)	**26 (20)**	**59 (45)**	**47 (35)**	**132 (100)**

*Primary problem chosen by patients from a list of 12 possible problems correlating to scales in EORTC QLQ-C30 or "none of the above".

Patients who joined the group programme participated in a median of 10 of the 12 sessions (range 1-13), and received a median of five supplementary consultations (range 0-21). The vast majority (n=49) of group participants received one or more supplementary individual consultations, and thus only ten patients received the group intervention only. Half of the participants (n=29) in the group programme were accompanied by a family or friend caregiver in the educational sessions.

Patients who received supplementary individual consultations without joining the group had a median of two contacts (range 1-18) in addition to the scheduled initial and follow-up consultation.

In total, 411 supplementary individual consultations were held between patients in the intervention arm and members of the palliative rehabilitation team. The two mandatory consultations and other scheduled elements like the test and introduction with a physiotherapist before joining the group programme were not included in the 411 consultations. Details appear from Fig. 7.

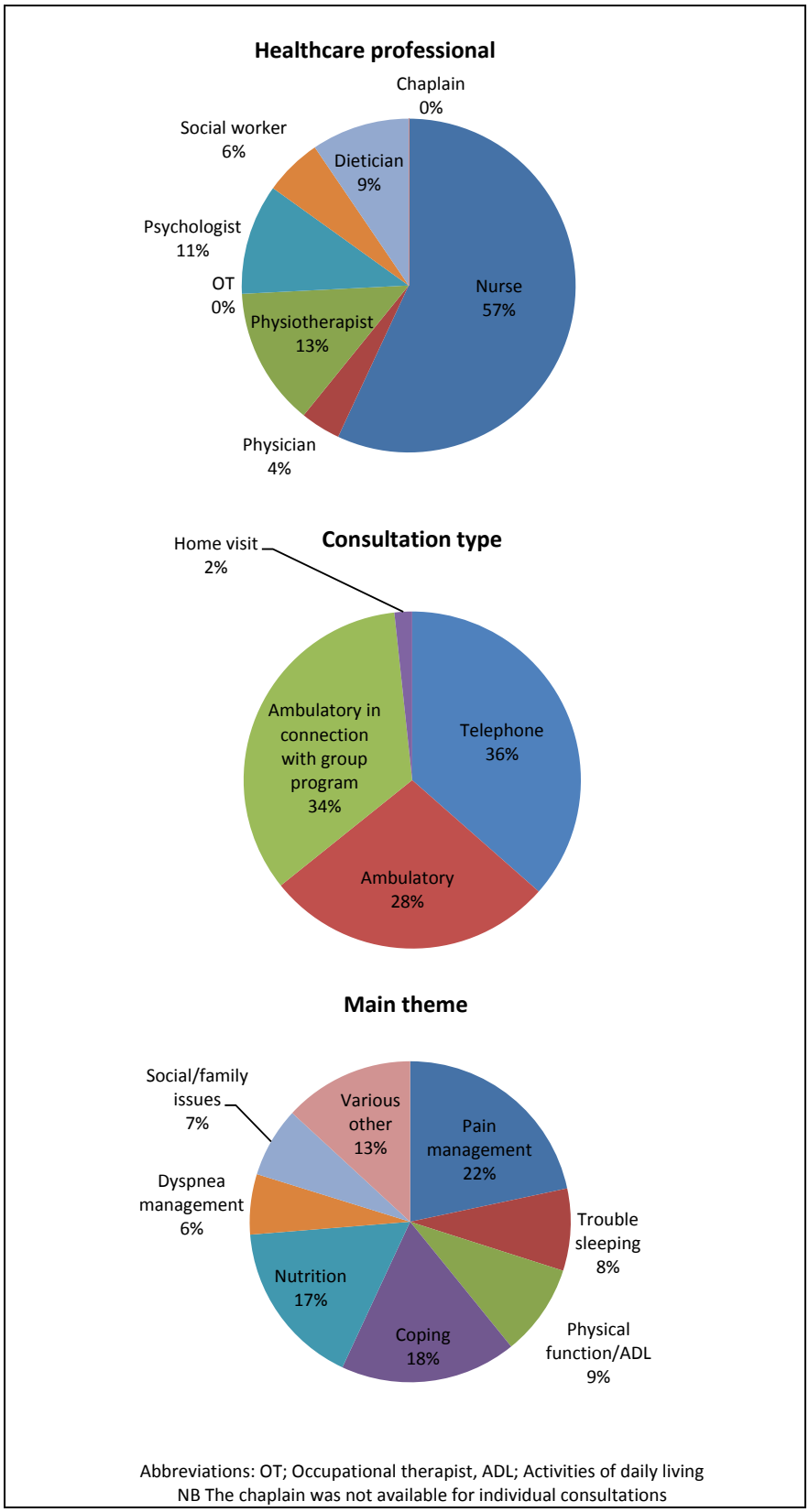

Figure 7. *411 supplementary individual consultations distributed by responsible healthcare professional, type of consultation, and main theme*.

Approximately half of the participants (n=67) brought at least one family or friend caregiver to the palliative rehabilitation outpatient clinic for the initial consultation. Subsequently, 16 of these caregivers received one or more individual consultations (median 2, range 1-9). Solo consultations with caregivers were held by psychologists (n=18), nurses (n=12), and social workers (n=9).

Almost half of the patients (n=60) had contacts with the palliative rehabilitation team beyond the 12-week study period. Of individual consultations and group sessions 18% and 26%, respectively, took place after 12 weeks at which point measurements for the primary endpoint were collected.

The majority of the participants (84%) were discharged from the palliative rehabilitation clinic after having received the planned intervention. The remaining patients either died during the intervention period (3%) or were evaluated as having an ongoing need for specialised palliative care (13%).

Primary endpoint (paper III)

The score of the "primary problem" improved during the 12-week participation period in patients receiving palliative rehabilitation compared to those receiving standard oncology care alone. The estimated size of the absolute group difference was 3.0 with a 95% confidence interval (CI) for the difference ranging from 0.0 to 6.0. The probability of obtaining the group difference found by the analyses, if there was no true difference, was less than the 5% set as the significance level, namely p=0.047.

In the original sample estimation, the minimal clinically important difference was set at 10 (SD=25) corresponding to a Cohen's effect size of 0.4 (10/25). The standard deviation of the absolute group difference found in the study (area under the curve) was 11.6 and the observed effect size was therefore 0.26 (3.0/11.6), which is generally considered a small difference. [66]

Sensitivity analysis

The change from baseline to six weeks showed a non-significant group difference for the primary outcome of 1.3 (95% CI: -0.9-3.6; p=0.23412) whereas the change from baseline to 12 weeks showed a highly significant group difference of 3.3 (95% CI: 1.0-5.6; p=0.005). Both were in favour of the palliative rehabilitation intervention.

Exploratory analysis

The explorative analyses of interactions showed no association between the effect of the intervention and the potentially predictive variables included in the multiple linear regression model except for a borderline significant effect for sex (better effect for females, p=0.0501) and a significant effect for "intention of

oncology treatment" (better effect for patients receiving treatment with non-curative intent than for those treated with potentially curative intent, p=0.0384).

Survival

At the time of follow-up for survival 48% (n=139) of 289 participants had died. The median follow-up time was 418 days (range 3-1229 days). There was no significant difference in overall survival between the standard care group and the palliative rehabilitation group (Fig.8.). The Hazard ratio for death in the palliative rehabilitation group compared to the standard care group was 1.3 (95% CI: 0.9-1.9; p=0.173).

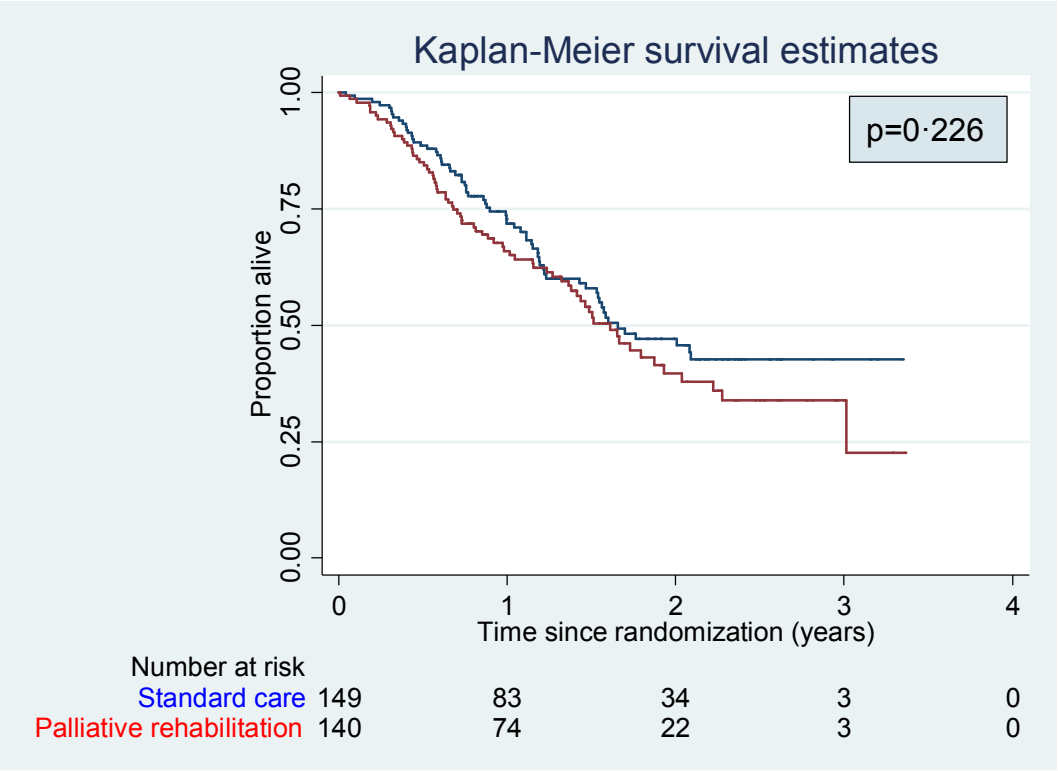

Figure 8. *Overall survival. P-value is reported using Chi^2 log rank test for equality of survival functions.*

Patient evaluation (paper II and III)

Whether or not the participants in the two study arms felt helped with the primary problem chosen at baseline was evaluable for 178 participants at six weeks after randomisation (n=89 in each study arm) and on 159 participants at 12 weeks (n=80 in the control group and n=79 in the intervention group). At six weeks, 60% in the palliative rehabilitation group agreed that they had received help with their primary problem vs. 48% in the standard care group, p=0.133. At 12 weeks significantly more patients in the group

receiving palliative rehabilitation agreed that they had received help (75%) compared to the standard care group (51%), p=0.002.

Twelve weeks after enrolment, 122 of the 132 participants in the intervention arm were eligible for evaluation (four died before 12 weeks, one withdrew consent, and five were not given the evaluation form because the staff considered it inappropriate in the situation). The evaluation form was completed by 80% of the eligible participants (n=97) of which 80% (n=78) agreed that the intervention had made a positive difference, 15% (n=15) partly agreed, and 4% (n=4) disagreed. When asked, if they would recommend the intervention to others in the same situation, 93% (n=90) agreed, 7% (n=7) partly agreed, and no one disagreed.

For participants in the group programme 82% (n=46) of the respondents agreed that it had been positive to spend time with others in the same situation, 17% (n=9) partly agreed, and 1% (n=1) disagreed. When asked if the physical exercise programme had improved their well-being 88% (n=49) agreed, 9% (n=5) partly agreed, no one disagreed, and two did not answer the question.

Adverse events (paper III)

Two adverse events were registered during the study, both among patients receiving palliative rehabilitation: one participant felt the physical exercise worsened his nausea, and one said the questions asked in the initial consultation in the palliative rehabilitation outpatient clinic added to her emotional distress.

Cross-over

One patient from the control group was referred by the treating oncologist to receive specialised palliative care in the study period.

Discussion

This PhD project evaluated a new offer of palliative rehabilitation and the effect of offering systematic palliative rehabilitation to patients with newly diagnosed advanced cancer concurrently with standard treatment. In this section the main results of the study are discussed against available literature, and methodological and ethical considerations are presented.

The study was designed as a trial of early specialised palliative care, but it also incorporated elements of cancer rehabilitation. The main facts of the intervention in this trial differing from other trials of early palliative care are that 1) it was designed to be time-limited while also being able to identify patients and families in the need of ongoing support; 2) it included healthcare professionals not generally actively involved in early palliative care trials, especially physiotherapists, occupational therapists, and dieticians; and 3) it entailed the opportunity of participating in a group programme combining physical exercise with educational sessions on topics related to living with cancer.

In the Danish context two other randomised, controlled trials (the DanPact and the DOMUS trials) have investigated the effect of systematic referral to specialised palliative care in recent years.[30, 33] Although both trials define themselves as "early delivery", neither of them tested the effect of systematic referral to early palliative care soon after diagnosis. Thus, in the DOMUS trial anticancer treatments had to be exhausted or very limited. The present trial is therefore the first Danish trial to investigate the effect of systematic early palliative care from the onset of an advanced cancer diagnosis and possibly the first randomised controlled trial in the world to investigate the effect of early palliative rehabilitation. To the knowledge of this author it is also the first trial to test the effect of a palliative care intervention on an individualised primary outcome chosen by the patient.

Main results

The main result of this study was that adding a palliative rehabilitation intervention to standard oncology care improved the QoL of patients with newly diagnosed advanced cancer. Furthermore, the intervention was perceived as relevant and beneficial by the participants.

The effect size found in the primary outcome analysis was small. It is difficult to estimate the smallest clinically meaningful difference between groups in trials on QoL, but it has been defined as "*the smallest difference which patients perceive as beneficial"* by King in 1996.[67] She also stated that large group differences are unlikely in randomised clinical trials using EORTC QLQ-C30, especially when the new type of care is compared to usual care instead of "no care". [67] For the present trial the smallest difference perceived as beneficial by the patients is not known. It is a fact, however, that after 12 weeks significantly

more patients in the intervention arm than in the control group felt that they had been helped with the "primary problem" identified at baseline.

The overall results of the present study add to the evidence presented in a recent review and meta-analysis published by the Cochrane group. [68] The review investigated the effect of early palliative care interventions for adults with advanced cancer and concluded that early palliative care may have more beneficial effects on QoL and symptom intensity than standard care.[68] The authors also noted that even though only small effect sizes were found they could be clinically meaningful in a population with an expected further decline in QoL.

The present study was sufficiently powered and successful in balancing the two study arms in terms of most baseline characteristics. However, more patients in the intervention arm had received 13 or more years of education, which is normally considered a positive prognostic factor. On the other hand, more patients in the intervention arm than in the control group lived alone and had an ECOG performance status >0, which may be negative prognostic indicators. Differences were more marked in terms of the "primary problems" chosen at baseline in each group (Table 2). The exploratory analysis found no relation between the outcome of the study and any of the potentially predictive factors that were unevenly balanced. However, true subgroup analyses were not performed since the sample size was not planned to evaluate outcomes by different baseline characteristics.

A heterogeneous group of patients with mixed advanced cancer was studied and the cancer site was not found to affect the primary outcome. This differs from the findings in another early palliative care study by Temel et al. from 2016 with exploratory subgroup analyses showing marked differences in QoL of patients with lung and gastrointestinal cancer.[31] Whether early palliative care should be tailored to different types of cancer should be explored further in future research.

The intervention model of the present study was adaptable to the individual needs of the patients. Almost half of the participants chose to enter the group programme even though it meant extra weekly visits to the hospital. Time and transportation are known potential barriers in cancer care.[69] Adherence to the group programme in the present study was very high with attendance at a median of 10 of the 12 group sessions, and the group participants found it beneficial to spend time with others in the same situation similar to the findings of a 2005 review of palliative day services.[48]

It is noteworthy that approximately 25% in each study arm chose "none of the above" when asked at baseline to choose a "primary problem" that they needed help with the most. It is unknown whether the

patients did not feel any need for help or that they wanted to prioritise something that was not included in the 12 possible “primary problems”. The experience from the initial consultation in the intervention arm was that many patients were unsure of what type of help they could potentially get, and whether other patients were more deserving of taking up the time and resources of the palliative rehabilitation team. Thus, it was often in a combination of patient thoughts and expectations, assessment by the palliative rehabilitation clinician, and knowledge of available and potential beneficial interventions, that a true need was established. More than half of the patients in the intervention arm who had chosen “none of the above” as a primary problem (64%) eventually received more than the scheduled initial and follow-up consultations (Table 4).

When the results of the trial were presented to the Hospital’s Patient and Relatives Council the interpretation of the results that a large group of patients were hesitant in expressing a need before they knew what they could be offered resonated very well with the Council. They highlighted the finding that more than half of this group of patients eventually were given more than the mandatory elements in the intervention as the most important finding of the study.

In the exploratory analysis the primary problem chosen by the patients did not affect the outcome of the main analysis and patient satisfaction was very high across the different “primary problems” and interventions.

Since many caregivers lack support in their caregiver role[70] and supporting the caregivers was anticipated to reflect positively on patient outcomes, the intervention was designed to meet the needs of family caregivers, too (Fig.2). Family caregivers were only approached if the patients invited them in, which was the case in approximately half of the initial consultations. Similarly, only half of the participants in the group programme brought a family or friend caregiver along, which means that the full potential of the intervention in supporting of family caregivers was probably not met. It is unknown why many patients did not involve their family in the intervention. Despite our effort to encourage participants to bring a family or friend caregiver, some of them believed that participating in a research project only involved them and that it was best to come alone. Specific caregiver outcomes were not registered in this study.

Different models of delivering early palliative care have been tested in the literature as partly described in the “background” section of this thesis. Many have been nurse-led, and nurses were also the healthcare professionals mainly involved in the present study (Table 1 and Fig. 7). However, all patients were discussed minimum once at a multidisciplinary conference and the responsibility for the intervention was shared by all team members. Even though no data was collected to explore the contribution of each type of

healthcare professional in terms of the overall result, they all took part in the individual consultations, the patient and caregiver school, and in team discussions.

The question of how early palliative care impacts patient outcomes remains open. Interestingly, the Cochrane review concluded that the type of model applied to provide early palliative care did not affect the results.[68] A newly published secondary analysis of the 2017 trial by Temel et al.[31] was performed with the aim of defining the effective components of early palliative care.[71] Data from 2,921 visits were analysed concluding that visits focusing on coping, treatment decisions, and advance care planning were associated with better patient outcomes. The major themes of the supplementary individual consultations in the present trial were pain management, coping, and nutrition (Fig. 7). Pain management and coping were also found to be major themes in the evaluation of the defining elements of early palliative care by Hoerger et al. mentioned above.[71]

The fact that nutritional advice accounted for a large part of the individually tailored interventions in the present trial emphasizes the need for focusing on nutrition in relation to the QoL of patients with advanced cancer.[72] Symptom management, psychosocial support, and nutritional support were all potentially part of the standard care if found relevant by the treating oncologist, which implies that a more systematic approach is required to cover the needs of all patients with advanced cancer.

Physical exercise programmes also form a part of the standard care if the patients are referred by the treating oncologist. In Denmark the programmes are mainly offered in community based settings as part of cancer rehabilitation.[73] The benefit of physical exercise programmes for patients with advanced cancer has been explored in reviews and found both feasible and beneficial to patient well-being and QoL.[46, 74] Nevertheless, cancer rehabilitation services are generally underused for patients with advanced cancer.[75] In the present trial 88% of the respondents from the group programme agreed that the physical exercise had improved their well-being. The staff at the palliative rehabilitation clinic had the impression that patients often were referred to the community based cancer rehabilitation offers at the end of the 12-week group programme as part of the encouragement to stay active (data not collected).

The present study did not show an effect of the intervention on survival unlike two previous trials,[22, 27] but the result is consistent with three other newly published trials.[29, 30, 32] Less than half of the participants (48%) had died at the time of data cut-off making it difficult to predict the final impact on survival. Involvement of patients and caregivers in treatment decisions resulting in less aggressive treatment towards end of life has been suggested as the mechanism behind a possible survival benefit of early palliative care.[22, 27] The intervention of this study was time-limited and applied at the beginning of the

disease trajectory. The hypothesis was that it could still affect survival as demonstrated in Fig.2. A potential explanation to the lacking survival benefit in the present study is that shared decision making in patient communication is already a general focal point at the Department of Oncology, Vejle Hospital.[76] Also, the specialised palliative team is integrated in the department resulting in successful coordination of treatment towards the end of life. Data collection on these issues was not within the scope of this study.

All in all, a correlation between early palliative care and potential survival benefit must be considered uncertain, which is consistent with the findings of two recent systematic reviews.[68, 77]

Methodological considerations

Intervention design

In Denmark, including at Vejle Hospital, specialised palliative care has usually been delivered much closer to the end of life than what was intended in this study. Therefore the intervention used in this trial was designed to specifically address the symptoms and problems thought to be of relevance to a population newly diagnosed with advanced cancer. However, the hypothesis was that the intervention also needed to support the enablement and self-management of the participants as well as enhance their self-efficacy for future challenges related to living with cancer. The decision on which elements to include in the design of the intervention was based on clinical experience in the palliative team and a literature search, which was last updated in November 2013.

Early, integrated palliative care and rehabilitation services are complex health interventions with several interacting components undertaken in complex environments.[78] Therefore the new intervention model was tested on patients referred to the palliative team during chemotherapy in the year before initiation of study enrolment (paper II).

During the test phase it was concluded that the intervention itself was feasible and acceptable for the test population. Based on the results of the study presented above this was also true for the study population. The intervention was safe given the very limited number of adverse events observed in the trial period.

The study design might have improved if estimations on retention, rates of recruitment, and timing and delivery of the intervention had been considered more thoroughly, e.g. through interviews with representatives of the intended study population. However, the study design was discussed with the Patient- and Relatives Council of the Hospital. There is always a risk that patients volunteering to be interviewed are the most resourceful and that he patients who would be more difficult to enrol in a future study would be underrepresented.

Study participants were not enrolled until the intervention was found robust and could be offered with the highest possible consistency during the trial period.

Choice of patient group

Patients with newly diagnosed non-resectable cancer were chosen as the population to be studied as opposed to patients with incurable cancer. The hypothesis was that all patients who were ineligible for surgery following their cancer diagnosis and who were then forced to live with the cancer and the uncertainty of their future health could potentially benefit from early palliative rehabilitation. However, exploratory analyses of the primary outcome indicated that the intervention was more effective in patients receiving oncology treatment with non-curative intent than in patients receiving treatment with potentially curative intent. This finding should be explored further in future research.

Choice of study design

The study design was an individually-randomised controlled trial, which is considered to provide the strongest evidence of whether or not there is a relationship between an intervention and an outcome in clinical research.[79] Randomised design and multivariate analyses minimise the risk of confounding factors. The intervention was tested at a single centre because it was newly developed.

It has been suggested that cluster randomised design where centres instead of individuals are randomised might be more appropriate when investigating public health and healthcare programmes because they are generally implemented at organisation rather than individual level. [80] However, an individual-randomised design has a better potential to ensure comparability of the two study arms, especially in a study like the present where it was assumed that everybody was given the same standard treatment and the intervention being tested was a supplement. This is also discussed under “potential sources of bias”.

A key question in evaluating complex interventions is how the intervention works.[78] Another choice of design could therefore have been a mixed methods design with the randomised controlled trial supplemented by qualitative methods. Methods such as semi-structured interviews might have been helpful in understanding the change process and isolating effective components of the intervention.

Choice of measurement instrument

Healthcare professionals are poor judges of patients’ QoL[81] and the measurement instrument was therefore required to collect the data directly from the patients. A questionnaire was chosen because of its ability to collect data in the same way in both study arms without interpretation of the patient‘s response by a clinician or interviewer.

EORTC QLQ-C30 is a cancer-specific questionnaire validated and widely used in cancer and palliative care research.[82, 83] It incorporates different function and symptom scales relevant to the study population and is sensitive to differences among patients, treatment effects, and changes over time. [84]

Choice of outcome measurements

QoL can be used as a measure in clinical trials when focus is on the patient rather than the disease.[85] For this trial a standardized measurement tool with predetermined domains of QoL was used and it can therefore be argued that health status or health-related QoL was measured rather than QoL in a broad sense.[86]

The CONSORT group (Consolidated Standards of Reporting Trials) recommends the choice of a single primary outcome measure for a randomised controlled trial to avoid the problems of interpretation associated with multiplicity of analyses. [87]
On the other hand, the authors of the "New Medical Research Council guidance" on designing and evaluating complex medical interventions state that "*Identifying a single primary outcome may not make best use of the data, and may not provide an adequate assessment of the success or otherwise of an intervention which may have effects across a range of domains*. A *range of measures will be needed, and unintended consequences picked up where possible".*[78]

A single primary outcome measure was chosen for the present study. Taking into account the multidimensionality of palliative rehabilitation and the individual construct of QoL[86] the primary outcome was patient-individualised. Patients were asked to choose a "primary problem" they needed help with the most. In order to structure the process and establish sensible measurements the participants were given a list of 12 different possible "primary problems" and a 13th option of "none of the above". Patients may experience multiple symptoms and problems, but they may not perceive them as equally important. Likewise, some patients with newly diagnosed advanced cancer may not experience a wide range of symptoms and problems, but receiving help with the one(s) they do experience is still very relevant. Asking the patients to prioritize ideally made the primary outcome measurement relevant to all participants. Also, it meant avoiding summing up all the different symptoms and problems in the EORTC scales which could potentially dilute the effect measurement. These facts are considered a strength of the approach. The main weakness is that priorities can change over time in response to the course of the disease or adaptation to the life altering circumstances.[86] Furthermore, as this is a new approach, it may require additional explanations in publications, etc.

Since it is assumed that each item is an equally strong estimator of the latent variable, extra items were added to the scales in the questionnaire with fewest items in order to increase the reliability of the scale and improve the precision of the scale score.[84]
The extra items were chosen by members of the palliative rehabilitation team to ensure they were relevant to the intervention offered. The number of items to include was considered carefully due to the potential frailty of some of the study participants. The mental burden relating to being newly diagnosed with a serious illness and initiating anticancer treatment was also a factor. Too many items in the questionnaire could potentially result in unmanageable data loss if the patients were overwhelmed by the extent of the questionnaire.

Survival was chosen as a secondary outcome measure based on the hypothesized mechanism of effect illustrated in Fig.2 and because of previous studies of early integrated palliative care showing a survival benefit as discussed above.

Timing of measurements

The timing of measurements is, perhaps especially in a palliative care trial, a trade-off between attrition and time for the intervention to have an effect. Follow-up at six- and 12 weeks was chosen to capture changes taking place relatively soon as well as those appearing later. The intervention was designed to last 12 weeks, but in reality the patient behaviour was different from what was anticipated in the study design. The initial consultation was supposed to take place within a week but actually took place after a median of 11 days because of the patients' conflicting schedules. Also, some patients who were informed about the group intervention at the initial consultation needed time to consider and therefore entered the group after the follow-up consultation. All in all it meant that a significant proportion of the intervention took place after the 12-week measurements. A measurement at a later time point, e.g. after 18 weeks, could have captured the vast majority of the intervention, but it is unclear whether the data loss at that time would have been too large for a meaningful analysis.

Three previous trials on the integration of early palliative care into standard oncology care also showed a significant improvement in QoL at 12 weeks[22, 29, 32] whereas three others found improvements at later time points.[21, 28, 31] The sensitivity analysis performed in the present study showed a greater and more significant group difference when the primary analysis was repeated for the change from baseline to 12 weeks not including the six-week measurement. Thus, early palliative care may become more efficient with time and at least 12 weeks are required for a group difference to be detected.

Statistical considerations

Area under the curve

The summary measure of AUC was applied for the primary outcome to sum up the longitudinal measurements to a single value. Thus, the problems with multiplicity that could occur by comparing the groups at each time point was avoided as was an under or overestimation of group differences that could occur from testing at any specific time point.

Other randomised controlled trials measuring the QoL of cancer patients by patient reported outcomes have used the same approach.[30, 88, 89] In the present trial the measurements at six- and 12 weeks were collected despite the fact that the intervention continued for longer than 12 weeks in many cases. This was done to comply with the principle of equal measurements in the two study arms. Multiple imputations were used to replace missing values and thus ensuring an AUC could be made for each individual included in the analyses.

Missing data

The method chosen for dealing with missing data was pre-specified, and a certain amount of missing data was expected and accounted for in the sample size calculation. Multiple imputations were based on the baseline variables anticipated to be of prognostic importance. Hence, patients were not excluded from the analyses due to incomplete data. Imputations were not used in the case of incompleteness due to death since this would make no sense as would not speculations about any problems they might have experienced.[90]

Patients who withdrew consent could not be included in the analyses due to data legislations. Until November 2016 every patient allocated to the intervention arm who declined the initial consultation was automatically handled as a case of “consent withdrawn”. From that time on patients were asked for permission to keep them in the study without receiving the intervention and all but one consented to stay in the study and were consequently included in the analyses. Optimally, this approach should have been applied from the beginning.

Attrition is inevitable in palliative care trials [91] and is discussed further in the sections below. Some of the attrition in the study was non-random because it was associated with allocation to the intervention arm. This is discussed further under “Potential sources of bias” and “Ethical considerations”. Other types of attrition such as patients not returning the questionnaire for unknown reasons were equally distributed in the two study arms and not likely to impact the end result (Fig. 5).

Potential sources of bias

Despite the randomised controlled design and the use of blinding whenever possible, there are still sources of bias to consider in the present trial.

A potential consequence of the missing data described above is attrition bias in the case of the patients leaving the study not being similar to the ones staying. Together with the risk of selection bias that was the reason for investigating differences in baseline characteristics between participants and non-participants (Table 3). It is a general problem that RCTs in palliative care may evaluate those who are the least ill and/ or the best able to cope.[92, 93] In the present trial it was found that participants were younger, had received more years of education, and were less likely to suffer from lung cancer, which is often associated with worse outcomes. Importantly, there were no differences in ECOG performance status, sex, and living status. Co-morbidity was not registered in this trial.

The primary outcome measure was based on self-reported data, which is a potential source of bias in a non-blinded study because of the participants' expectations about the trial. However, the patients chose the "primary problem" before randomisation, and at follow-up they were asked if they felt they had been helped with that problem. They were not explicitly told that the primary effect of the study would be measured on a selected group of questions incorporated in the questionnaire they were given.

Performance bias also cannot be ruled out, since the allocation was not blinded to the personnel after randomisation. For instance, it is possible that participants allocated to the intervention arm were given less psychosocial support as part of their standard care because of their attachment to the palliative rehabilitation team. Likewise, patients in the control group may have been given "more than usual" psychosocial support or offered better symptom control. The staff in the oncology clinic may have perceived the patients receiving palliative rehabilitation as more privileged and wanted to compensate the control group, or perhaps the patients became more aware of their needs through completion of the questionnaires and therefore were in a better position to raise their most imminent needs during the following consultations in the oncology clinic.

A cluster-randomised design may have minimised performance bias in that centres instead of individuals would have been randomised. The same would apply if the patients in the control group were put on a waiting list and offered the intervention at a later time point.

External validity

The flexibility of the intervention model was a strength of the study in terms of making the intervention relevant to the participants and meaningful to the clinicians. This, however, can also be seen as a weakness

as it makes it even more complex to make assumptions about the effective components and may weaken the study's generalisability. The same is true for the study having been conducted at a single site only as discussed earlier. On the other hand, the model of delivery has been described and published in detail (paper II), and the healthcare professionals involved are found at most centres delivering cancer treatment – at least in Denmark and other Western countries.

The Danish population is quite homogeneous which may limit generalisability. Also an intervention that has proven effective in the Danish Healthcare System may not be easily transferrable to other set-ups because of marked differences in models of organisation, financing etc.

The differences in baseline characteristics between participants and non-participants presented in Table 3 should also be taken into account when evaluating the generalisability of the findings.

Timing of the intervention

The timing of the palliative rehabilitation intervention soon after an advanced cancer diagnosis was chosen based on the aim of palliative care to prevent and relieve suffering by means of early identification and treatment of symptoms and problems.[1]

The timing was inspired by the study on early palliative care by Temel et al. published in 2010.[22] The successful study used inclusion criteria of an advanced cancer diagnoses within eight weeks before enrolment and also shared the aim of improving QoL over 12 weeks. A study published in 2015 showed better patient outcomes when the palliative intervention was initiated soon after diagnosis as opposed to three months later.[27]

Rehabilitation services tend to be more effective in the early stages of cancer related functional loss, a time when patients and clinicians perhaps focus too narrowly on treating the malignancy and may postpone interventions relating to the maintenance of function or prevention of functional impairments.[11] The desire to stay mobile may contribute to improved and prolonged QoL and likewise, inactivity may play a critical role in the interaction between symptom burden and functional decline.[41, 75]

Theoretically, there are therefore sound arguments for initiating a palliative rehabilitation intervention as early as possible, but the optimal timing should be explored in further research.

The subject of timing is discussed further in the section "Ethical considerations" below.

Ethical considerations

It has been a matter of discussion whether research in palliative care is unethical.[94, 95] Patients with advanced cancer should receive evidence based treatment to the same extent as any other patient group. Therefore, when a knowledge gap is identified it may even be unethical not to pursue the issue in a research project. A newly published commission work by 30 international experts in oncology, palliative care, public health, and psycho-oncology concluded that there is now a strong consensus for integration of oncology and palliative care in contemporary cancer care, but the contents and constructs of implementation are lacking worldwide.[19] High quality research complying with international standard ethics is needed to drive the implementation and ensure pursuit of the most effective models of delivery. With that in mind, palliative care still carries a stigma of death, hopelessness and dependency, which must be taken into account when designing and setting up palliative care trials.[96] Zimmermann et al. approached 48 patients and 23 caregivers who had recently participated in an early palliative care trial with the purpose of qualitatively assessing their attitudes and perception of palliative care.[97] They found that the negative stigma persisted even after a positive experience with an early palliative care intervention and concluded that more education of the general public, patients, and healthcare providers was needed.

In the preparation phase of the present study it became evident that being referred to an offer with the word “palliative” in the title was a barrier for a number of patients and caregivers. The discussions with a smaller group of representatives from the Patient and Relatives Council in the early phases of the trial also unveiled the stigma attached to the term “palliative” and the importance of nurturing the concepts of hope and independence when talking to patients and caregivers. One of the methods chosen to approach this challenge was the design of a pocket card for the staff responsible for informing potential study participants (appendix). The card offered suggestions for phrases addressing the stigma of “palliative care” and reframing the concept to the present intervention. In addition, repeated staff meetings were held throughout the recruitment phase where successes and barriers to recruitment were discussed, including the staff’s own personal perception of palliative care. With these means none of the invited patients attributed their reluctance to participate to the word “palliative”. Only 2% of the patients explicitly said that they did not want to participate in research (Fig. 6) and another 2% did not want to discuss illness. It is, of course, not possible to conclude anything about the 16% who did not explain their decline to participate. Also, gatekeeping by the staff intended to inform eligible study participants still cannot be ruled out.[98]

After enrolment in the study attrition was skewed by 18 patients allocated to the intervention arm either regretting giving consent immediately or declining the secretary’s offer of an appointment for the initial consultation in the palliative rehabilitation clinic. Together with the large proportion of patients declining

participation during enrolment it raises the question of whether the timing of the intervention was a barrier and maybe even unethical. The reasons given by the 18 patients were the same as the reasons patients gave for not participating, namely feeling too overwhelmed by their present situation and the amount of information given by different healthcare professionals (n=15) and feeling no need (n=3). It is important to bear in mind that participants in the intervention arm were required to show up at the hospital for at least two consultations in addition to the ones already scheduled in connection with their anticancer treatment. Patients in the control group only needed to complete questionnaires. It is therefore likely that the attrition had more to do with the timing and demands of the intervention than the subject studied. Also, it is worth noting that only one person withdrew the consent after having met the palliative rehabilitation team and that patient satisfaction in the intervention arm was very high.

Conclusions

The present study investigated the effect of adding systematic palliative rehabilitation to standard oncology care in patients with newly diagnosed advanced cancer. Palliative rehabilitation was evaluated using a patient-individualised outcome measure and was successful in improving the QoL of the patients participating in the study. The intervention was ethically justified and let to a high degree of patient satisfaction.

The proportion of patients who felt they had been helped with the “primary problem” prioritized at baseline was significantly higher in the group receiving palliative rehabilitation as compared to the standard care group after 12 weeks. Survival was not affected.

The intervention was highly flexible to individual needs and after the initial consultation in the palliative rehabilitation clinic almost half of the patients (45%) chose to enter the clinic’s 12-week group programme with patient and caregiver school in combination with physical exercise. Participation in the group programme was supplemented with individual consultations in most cases. The remaining participants either received the two planned consultations in the palliative rehabilitation clinic only (20%) or received additional individual consultations without participation in the group programme (35%).

The main themes of the supplementary individual consultations were pain management, coping, and nutrition.

The study was planned and conducted with involvement of patient and caregiver representatives.

The results of the study are in line with the literature on early, integrated palliative care but offer additional knowledge of a new implementation model adding a focus on enablement and self-management to the holistic concept of palliative care.

Perspectives and future research

The results of this trial indicate that early palliative rehabilitation for patients with advanced cancer is relevant, feasible, and beneficial. The results could therefore be used to inform decision makers in Denmark and elsewhere about ways to improve healthcare for cancer patients.

Additional analyses of the data collected during the present trial could potentially shed more light on the effect of offering systematic palliative rehabilitation. These include:

- Analyses of the secondary outcomes mentioned in paper I: the effect on symptoms of depression and anxiety, all EORTC-scales, and an economic evaluation of healthcare utilization in the two study arms.
- Subgroup testing – was the intervention more effective in the participants in the group programme compared to the ones getting an individually tailored intervention only? Was there a dose-response effect?

Future research on palliative rehabilitation should consider the timing of the intervention and the study measurements carefully. Collecting data on caregiver outcomes and supplement the patient reported outcome data with test results, e.g. from the physical performance tests of the group programme should also be considered. A mixed methods design should be considered in order to better understand the process and results in order to identify the most effective components.

The intervention of this study should ideally be tested in a multicenter trial, preferably in an international setting.

Finally, in the future when hopefully more trials of palliative rehabilitation have been conducted the results of this trial should be analysed in a systematic review including meta-analyses and trial sequential analyses of all relevant randomised clinical trials. Preferably, these analyses should be based on depersonalized individual patient data.[99] The digital data from the present study will be transferred to the Danish National Archives for long term archiving and will be freely available to other researchers as long as the donors are asked prior to any publications based on the data.

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Appendix

List of appendixes

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Appendix 1

Written information for potential study participants and informed consent form

Deltagerinformation og samtykkeerklæring ved deltagelse i en videnskabelig undersøgelse

Et kontrolleret, randomiseret studie om tidlig integreret, specialiseret palliativ rehabilitering til patienter med nydiagnosticeret, ikke primært resektabel kræftsygdom.

En undersøgelse, der skal belyse effekten af palliativ rehabilitering til mennesker, der lever med kræft.

Version 1
17. februar 2014

Deltagerinformation

Med denne information vil vi spørge dig, om du vil deltage i en videnskabelig undersøgelse?
Før du beslutter dig for at deltage, får du mundtlig information af læge eller sygeplejerske, ligesom du bør tage dig god tid til at læse denne information. Spørg lægen eller sygeplejersken, hvis der er noget, du ønsker en nærmere forklaring på.

Sammen med denne deltagerinformation har du også fået udleveret folderen "Før du beslutter dig", hvor du kan få yderligere oplysninger om deltagelse i forsøg.

Meningen med denne skriftlige information er, at du i fred og ro skal kunne overveje situationen og drøfte den med dine nærmeste. Du er velkommen til at tage pårørende med til samtalen i afdelingen, og der vil her være mulighed for at stille spørgsmål. Efter samtalen har du ret til betænkningstid på mindst et døgn, og vi vil anbefale, at du benytter dig af denne ret.

Vi vil gerne understrege, at det er frivilligt at deltage i undersøgelsen og du skal vide, at du kan afbryde forsøget, når som helst du måtte ønske det. Du skal vide, at lægen ligeledes kan afbryde forsøget, hvis det skønnes påkrævet af hensyn til dit velbefindende. Uanset om du siger "ja" eller "nej" eller fortryder senere, vil vi give dig den bedst mulige behandling for din sygdom.

Undersøgelsen foregår i et samarbejde mellem onkologisk afdeling, Vejle Sygehus og Palliativt Team, Vejle Sygehus.
Det skal pointeres, at den behandling du vil modtage i onkologisk afdeling er standardbehandlingen. Hvis du vælger ikke at deltage i undersøgelsen, vil du få tilbudt den samme behandling for din sygdom. Den behandling, der indgår i forsøget er altså noget, der gives ved siden af den vanlige behandling.

Der skal deltage 300 patienter i undersøgelsen.

Hvad går undersøgelsen ud på?

Formål og definition
Denne undersøgelse omhandler palliativ rehabilitering. Palliativ indsats betyder lindring af symptomer og problemer, der kan opstå i forbindelse med en kræftsygdom. Rehabilitering betyder genopbygning af tabte funktioner eller forebyggelse af yderligere funktionstab.

Du har for nyligt taget imod et tilbud om behandling i onkologisk afdeling i Vejle. Formålet med dette forsøg er at undersøge, om mennesker i din situation har gavn af at få et individuelt tilpasset palliativt rehabiliteringsforløb sideløbende med den behandling, der gives mod sygdommen i onkologisk afdeling. I forsøget vil vi også undersøge eventuel effekt på overlevelse og udgifter til sundhedsvæsenet.

Palliativ rehabilitering varetages af tværfagligt personale som læger, sygeplejersker, fysioterapeuter, psykologer, socialrådgivere m.fl. som tilsammen kan støtte og hjælpe patienter i forbindelse med mange af de problemstillinger af fysisk, social, psykologisk og eksistentiel art, som kan opstå ved alvorlig sygdom.
Palliativ rehabilitering kan foregå en-til-en eller i grupper – alt efter hvilke problemstillinger, det drejer sig om.

Baggrund
Baggrunden for forsøget er, at der mangler gode, systematiske undersøgelser af, om det samlet set hjælper mennesker, der lever med kræft at få et palliativt rehabiliteringstilbud. Vi ved heller ikke, om det har betydning, hvornår i sygdomsforløbet, man får tilbuddet. Det er derfor vigtigt at skaffe ny viden for systematisk at kunne vurdere, om man skal ændre på behandlingen til mennesker i din situation fremover.

Hvad indebærer det at deltage i forsøget?
Forsøget starter med en lodtrækning. På basis af denne lodtrækning vil halvdelen af deltagerne fortsætte med at modtage standardbehandling, dvs. den behandling, som du har aftalt med onkologisk afdeling (kontrolgruppen). Den anden halvdel vil også fortsætte med at modtage standardbehandling, dvs. den behandling, som du har aftalt med onkologisk afdeling, men vil derudover blive henvist til Palliativt team på Vejle Sygehus, som står for det palliative rehabiliteringstilbud (interventionsgruppen).
Det betyder, at selv om du siger 'ja' til at deltage, er det ikke sikkert, at du bliver henvist til et palliativt rehabiliteringstilbud. Du vil blive orienteret om lodtrækningens udfald af en projektsygeplejerske.

Uanset om du kommer i kontrol- eller interventionsgruppen, vil du blive bedt om at udfylde et **spørgeskema** i starten, et igen efter cirka syv uger og igen efter cirka tretten uger.

Personer, som kommer i kontrolgruppen, følger den plan, de har lagt med onkologisk afdeling og kan naturligvis ændre og påbegynde ny behandling efter aftale med læger på sygehuse og andre steder.

Personer, som kommer i interventionsgruppen, følger også den plan, de har lagt sammen med onkologisk afdeling, men vil derudover blive indkaldt til en opstartsamtale i Palliativt Team, Vejle Sygehus. Her vil det sammen med dig blive vurderet, hvilket palliativt rehabiliteringstilbud, der eventuelt passer til dig. Hvis du får et tilbud, løber det over seks uger. Du vil under alle omstændigheder blive indkaldt til en ny samtale og evaluering seks uger efter den første samtale. Selvom du henvises til et palliativt rehabiliteringstilbud, vil du stadig være tilknyttet din praktiserende læge og de afdelinger, du plejer.
Forsøget slutter, når det palliative rehabiliteringstilbud har varet **to gange seks uger**. Hvis du kommer i interventionsgruppen, kan du fortsætte med at være tilknyttet det Palliative Team efter forsøgets afslutning, så længe dette vurderes hensigtsmæssigt af lægerne i teamet. Du vil samtidig kunne fortsætte med din vanlige behandling.

Indhentning af oplysninger
I forbindelse med forsøget vil vi indhente og gennemgå relevante journaler og udvalgte registeroplysninger for alle personer, der deltager i undersøgelsen. Materialet gennemgås, med henblik på at kunne undersøge og dokumentere, hvilke behandlinger, der er blevet givet, om der er opstået nogle alvorlige bivirkninger, og hvilke typer af kontakter, du har haft med sundhedsvæsenet. Alle oplysninger om dig opbevares forsvarligt.
Fremtidige analyser, der ikke har med dette forsøg at gøre, kan kun udføres efter godkendelse fra Videnskabsetisk Komité

Eventuelle bivirkninger og risici

Der er ikke på forhånd nogen forventede bivirkninger, der knytter sig særligt til dette forsøg. Al den behandling, du vil modtage, anvendes i forvejen af den del af sundhedsvæsenet, du kommer i kontakt med og sker efter en individuel vurdering af din situation.

Hvad betyder forsøget for dig selv eller andre?

Hvis du kommer i interventionsgruppen betyder deltagelse i forsøget nogle ekstra besøg på sygehuset. Det er ikke muligt på forhånd at sige, hvor mange besøg, det drejer sig om, da det tilrettelægges i samarbejde med dig. Der vil dog som minimum være tale om to samtaler i Palliativt Team. Til gengæld tilbydes du den bedst mulige støtte og behandling af dine eventuelle problemer/ symptomer.
Overordnet set er håbet, at forsøgets resultater vil bidrage til, at Sundhedsvæsenet opnår mere viden om, hvorvidt det gør en forskel for mennesker, der lever med kræft, at få et palliativt rehabiliteringstilbud og i så fald hvordan. Dette kan muligvis ændre praksis for mennesker i din situation i fremtiden.

Ophør med deltagelsen

Det er frivilligt at deltage, og du kan på et hvert tidspunkt trække dig ud af undersøgelsen.
Hvis lægen, der er ansvarlig for denne undersøgelse, skønner det nødvendigt, kan hun undervejs i behandlingen tage dig ud af undersøgelsen. Lægen kan også på et hvilket som helst tidspunkt afslutte undersøgelsen, hvis der foreligger en medicinsk begrundelse, en sikkerhedsrisiko eller et krav fra myndighederne. Du vil i så fald straks blive informeret derom, og vi vil drøfte muligheder for den fremtidige behandling med dig.

Hvem kan få oplysninger?

Alle oplysninger om dig i denne undersøgelse opbevares fortroligt i henhold til dansk lovgivning (Persondataloven). Lægerne og det personale der behandler dig, vil få adgang til oplysningerne i indtil 10 år efter forsøgets afslutning. Tavshedspligt er gældende for alt personale, og din identitet bliver ikke afsløret, selvom vi offentliggør resultaterne af undersøgelsen.

Sundhedsstyrelsen og andre relevante myndigheder, GCP-enheden samt personale, der indsamler og kontrollerer data vil ligeledes have adgang til din journal i op til 10 år med henblik på kontrol og inspektion.

Resultaterne af undersøgelsen forventes at kunne gøres op i år 2016. Du er velkommen til at kontakte undertegnede til den tid for at få et uddrag af resultaterne.

Forsikring, erstatning og økonomi

Ved deltagelse i dette forsøg er du omfattet af "Lov om klage og erstatningsgang inden for sundhedsvæsenet", og der kan som altid klages via Patientklagenævnet efter almindeligt gældende regler.

Ingen af de involverede sygeplejersker, læger eller forskere har nogen kommerciel interesse i undersøgelsen.

Der gives ikke vederlag eller andre ydelser til forsøgsdeltagere.

Undersøgelsen er godkendt af Videnskabsetisk Komité, ligesom den anmeldes til Datatilsynet.

Hvad nu?

Hensigten med denne skriftlige information er, at du i fred og ro skal kunne overveje sagen, før du taler nærmere om den med personalet i onkologisk afdeling. Når du har fået svar på alle spørgsmål, kan du beslutte dig. Tag den tid du behøver og husk, at din beslutning skal være helt frivillig og at den når som helst kan fortrydes.

Med venlig hilsen
Lars Henrik Jensen
Overlæge, MD Ph.d

Onkologisk Afdeling
Vejle Sygehus
Tlf.: 7940 5000
Email: kfe.onko@rsyd.dk

Samtykkeerklæring

Pal-Rehab

Et kontrolleret, randomiseret studie om tidlig integreret, specialiceret palliativ rehabilitering til patienter med nydiagnosticeret, ikke primært resektabel kræftsygdom.

Erklæring fra forsøgsdeltageren

Jeg har fået skriftlig og mundtlig information og jeg ved nok om formål, metode, fordele og ulemper til at sige ja til at deltage.

Jeg ved, at det er frivilligt at deltage, og at jeg altid kan trække mit samtykke tilbage uden at miste mine nuværende eller fremtidige rettigheder til behandling.

Jeg giver samtykke til at deltage i forskningsprojektet og til, at oplysninger om mig indsamles med henblik på brug i forskning.

Jeg har fået en kopi af dette samtykkeark samt en kopi af den skriftlige information om projektet til eget brug.

Patient navn: _____
BLOKBOGSTAVER

Dato og patientunderskrift: _____
Dato Underskrift

Erklæring fra den informationsansvarlige

Jeg erklærer, at forsøgsdeltageren har modtaget mundtlig og skriftlig information om forsøget og har haft mulighed for at stille spørgsmål til mig. Efter min overbevisning er der givet tilstrækkelig information til, at der kan træffes beslutning om deltagelse i forsøget.

Informationsansvarlig: _____
BLOKBOGSTAVER

Dato og underskrift, informationsansvarlig: _____
Dato Underskrift

Afdelingens kopi

Samtykkeerklæring

Pal-Rehab

Et kontrolleret, randomiseret studie om tidlig integreret, specialiceret palliativ rehabilitering til patienter med nydiagnosticeret, ikke primært resektabel kræftsygdom.

Erklæring fra forsøgsdeltageren

Jeg har fået skriftlig og mundtlig information og jeg ved nok om formål, metode, fordele og ulemper til at sige ja til at deltage.

Jeg ved, at det er frivilligt at deltage, og at jeg altid kan trække mit samtykke tilbage uden at miste mine nuværende eller fremtidige rettigheder til behandling.

Jeg giver samtykke til at deltage i forskningsprojektet og til, at oplysninger om mig indsamles med henblik på brug i forskning.

Jeg har fået en kopi af dette samtykkeark samt en kopi af den skriftlige information om projektet til eget brug.

Patient navn: _____
BLOKBOGSTAVER

Dato og patientunderskrift: _____
Dato Underskrift

Erklæring fra den informationsansvarlige

Jeg erklærer, at forsøgsdeltageren har modtaget mundtlig og skriftlig information om forsøget og har haft mulighed for at stille spørgsmål til mig. Efter min overbevisning er der givet tilstrækkelig information til, at der kan træffes beslutning om deltagelse i forsøget.

Informationsansvarlig: _____
BLOKBOGSTAVER

Dato og underskrift, informationsansvarlig: _____
Dato Underskrift

Udfyldes af Forskningsenheden

Patientnummer ☐☐☐ **Patient-initialer** ☐☐☐

Appendix 2

Pocket card for recruitment

Inklusionskriterier
Patienten skal:

- være diagnosticeret med ikke primært resektabel kræftsygdom indenfor de seneste 8 uger (tæller fra den dag, patienten har fået besked)
- kunne tilbydes og acceptere behandling i Onkologisk afdeling, Vejle Sygehus
- være over 18 år
- læse og forstå dansk
- give skriftligt og mundtligt informeret samtykke.

Eksklusionskriterier

- forløb i palliativ enhed inden for det seneste år
- vurderes ikke at kunne kooperere til forsøget
- manglende skriftligt samtykke

Kontaktperson ved inklusion:
Den KFE-sygeplejerske, der er tilknyttet dit team.
Øvrige kontakter:
Overordnet ansvarlige i KFE er Gitte (66709)
Daglig forsøgsleder Lise, LN (40265209)
Overordnet forsøgsansvarlige LHJ (66802)

Lommekort Pal-Rehab

Forslag til formulering ved informationssamtale
"Vi er ved at undersøge, om det hjælper at blive undersøgt og behandlet af specialister i understøttende og lindrende behandling allerede når man begynder et behandlingsforløb for en kræftsygdom. Alle får den almindelige understøttende behandling, men vi trækker lod om at få den ekstra vurdering."

Kan evt. suppleres med:
"Den vurdering, der trækkes lod om, omhandler en palliativ rehabiliteringsindsats. Måske er du vant til at forbinde ordet "palliation" med hjælp til meget alvorligt syge mennesker, men her er der tale om en helt ny tilgang og en indsats, der er målrettet starten af et sygdoms- og behandlingsforløb".

Herefter udleveres det skriftlige informationsmateriale og folderen "Før du bestemmer dig".
Patienten opfordres til at læse materialet grundigt igennem og stille afklarende spørgsmål.

NB! Ingen grund til at gå i detaljer omkring tilbuddet – det gør Palliativt team ud fra en samtale og samlet vurdering, når patienten møder i Kræftpatienternes Hus.

Appendix 3

Baseline questionnaire

Udfyldes af forskningsenheden: Initialer ☐☐☐ Deltagernummer ☐☐☐

Label:

EORTC QLQ-C30

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

Dato for udfyldelse af dette skema (dag, måned, år): ☐☐ ☐☐ ☐☐☐☐

		Slet ikke	Lidt	En del	Meget
1.	Har du nogen vanskeligheder ved at udføre anstrengende aktiviteter, som f.eks. at bære en tung indkøbstaske eller en kuffert?	1	2	3	4
2.	Har du nogen vanskeligheder ved at gå en lang tur?	1	2	3	4
3.	Har du nogen vanskeligheder ved at gå en kort tur udendørs?	1	2	3	4
4.	Er du nødt til at ligge i sengen eller at sidde i en stol om dagen?	1	2	3	4
5.	Har du brug for hjælp til at spise, tage tøj på, vaske dig eller gå på toilettet?	1	2	3	4

I den forløbne uge:

		Slet ikke	Lidt	En del	Meget
6.	Var du begrænset i udførelsen af enten dit arbejde eller andre daglige aktiviteter?	1	2	3	4
7.	Var du begrænset i at dyrke dine hobbyer eller andre fritidsaktiviteter?	1	2	3	4
8.	Har du været begrænset i udførelsen af dine huslige opgaver?	1	2	3	4
9.	Har du været begrænset i at tage dig af personlige eller husholdningsmæssige økonomiske anliggender (f.eks. betaling af regninger)?	1	2	3	4
10.	Havde du åndenød?	1	2	3	4
11.	Havde du åndenød, når du hvilede dig?	1	2	3	4
12.	Fik du åndenød, når du udførte moderate aktiviteter som at gå to etager op ad trappe eller bære noget let på jævnt terræn?	1	2	3	4
13.	Havde du problemer med at puste ud?	1	2	3	4
14.	Har du haft smerter?	1	2	3	4

Vær venlig at fortsætte på næste side

I den forløbne uge:	**Slet ikke**	**Lidt**	**En del**	**Meget**
15. Vanskeliggjorde smerter dine daglige gøremål?	1	2	3	4
16. Har du måttet blive i sengen om dagen på grund af smerter?	1	2	3	4
17. Havde du brug for at hvile dig?	1	2	3	4
18. Har du trængt til hyppige eller lange hvileperioder?	1	2	3	4
19. Har du haft en følelse af en overvældende og langvarig mangel på energi?	1	2	3	4
20. Har du haft besvær med at sove?	1	2	3	4
21. Har din søvn været hvileløs?	1	2	3	4
22. Har du været vågen i lange perioder i løbet af natten?	1	2	3	4
23. Har du følt dig træt (ikke udhvilet), når du vågnede?	1	2	3	4
24. Er du vågnet tidligere end du ønskede på grund af smerter?	1	2	3	4
25. Har du følt dig svag?	1	2	3	4
26. Har du savnet appetit?	1	2	3	4
27. Har du tvunget dig selv til at spise?	1	2	3	4
28. Har du haft behov for opmuntring fra andre for at spise?	1	2	3	4
29. Har du syntes, at mad var frastødende?	1	2	3	4
30. Har du haft kvalme?	1	2	3	4
31. Har du kastet op?	1	2	3	4
32. Har kvalme eller opkastning vanskeliggjort dit arbejde eller andre daglige aktiviteter?	1	2	3	4
33. Har du spist mindre på grund af kvalme eller opkastning?	1	2	3	4
34. Har du haft forstoppelse?	1	2	3	4
35. Har du følt trang til at have afføring uden at du kunne?	1	2	3	4
36. Har din afføring været så hård, at det gjorde ondt at komme af med den?	1	2	3	4
37. Har du, efter at du har haft afføring, haft en fornemmelse af, at du ikke var "færdig"?	1	2	3	4
38. Har du haft diarré (tynd mave)?	1	2	3	4

Vær venlig at fortsætte på næste side

I den forløbne uge:

	Slet ikke	Lidt	En del	Meget
39. Var du træt?	1	2	3	4
40. Har du haft svært ved at koncentrere dig om ting som f.eks. at læse avis eller se fjernsyn?	1	2	3	4
41. Har du haft svært ved at udføre to opgaver samtidig, f.eks. føre en samtale, mens du laver mad?	1	2	3	4
42. Følte du dig anspændt?	1	2	3	4
43. Var du bekymret?	1	2	3	4
44. Følte du dig irritabel?	1	2	3	4
45. Følte du dig deprimeret?	1	2	3	4
46. Har du haft svært ved at huske?	1	2	3	4
47. Har du haft svært ved at huske aftaler eller møder?	1	2	3	4
48. Har din fysiske tilstand eller medicinsk behandling vanskeliggjort dit familieliv?	1	2	3	4
49. Har din fysiske tilstand eller medicinsk behandling vanskeliggjort din omgang med andre mennesker?	1	2	3	4
50. Har du som følge af din fysiske tilstand eller medicinsk behandling følt dig isoleret fra familie eller venner?	1	2	3	4
51. Har din fysiske tilstand eller medicinsk behandling fået dig til at skændes med familie eller venner?	1	2	3	4
52. Har din fysiske tilstand eller medicinsk behandling medført økonomiske vanskeligheder for dig?	1	2	3	4

Ved de næste 2 spørgsmål bedes du sætte en ring omkring det tal mellem 1 og 7, som passer bedst på dig

53. Hvordan vil du vurdere dit samlede helbred i den forløbne uge?

1 2 3 4 5 6 7

Meget dårligt Særdeles godt

54. Hvordan vil du vurdere din samlede livskvalitet i den forløbne uge?

1 2 3 4 5 6 7

Meget dårlig Særdeles god

Det næste spørgeskema er udformet med henblik på at hjælpe personalet med at finde ud af mere om, hvordan du har det.

Læs hvert spørgsmål og **sæt kryds ved det svar, der kommer tættest på, hvordan du har haft det i den sidste uge**.

1) **Jeg føler mig anspændt:**

- Næsten hele tiden ☐
- Meget af tiden ☐
- Engang imellem ☐
- Slet ikke ☐

2) **Jeg nyder stadig de ting, som jeg tidligere har nydt:**

- Helt, som jeg plejer ☐
- Ikke helt så meget ☐
- Kun lidt ☐
- Næsten ikke ☐

3) **Jeg er bange for, at der skal ske noget frygteligt:**

- Helt bestemt og meget voldsomt ☐
- Ja, men det er ikke så slemt ☐
- Lidt, men det bekymrer mig ikke ☐
- Slet ikke ☐

4) **Jeg kan le og se det morsomme i en situation:**

- Lige så meget, som jeg plejer ☐
- Ikke helt så meget nu ☐
- Helt klart ikke så meget nu ☐
- Slet ikke ☐

5) **Jeg gør mig bekymringer:**

- En stor del af tiden ☐
- Meget af tiden ☐
- Engang imellem, men ikke så tit ☐
- Kun lejlighedsvis ☐

6) **Jeg føler mig glad:**

- Slet ikke ☐
- Ikke så tit ☐
- Nogle gange ☐
- Det meste af tiden ☐

Fortsæt venligst på næste side

7) **Jeg kan sidde roligt og føle mig afslappet:**

- Helt bestemt ☐
- Som regel ☐
- Ikke så tit ☐
- Slet ikke ☐

8) **Jeg føler det som om jeg fungerer langsommere:**

- Næsten hele tiden ☐
- Meget ofte ☐
- Nogle gange ☐
- Slet ikke ☐

9) **Jeg føler mig bange, som om jeg har "sommerfugle i maven" :**

- Slet ikke ☐
- Lejlighedsvis ☐
- Temmelig tit ☐
- Meget ofte ☐

10) **Jeg har mistet interessen for mit udseende:**

- Fuldstændig ☐
- Jeg er ikke så omhyggelig, som jeg burde være ☐
- Måske er jeg knap så omhyggelig som før ☐
- Jeg er lige så omhyggelig, som jeg altid har været ☐

11) **Jeg føler mig rastløs, som om jeg hele tiden skal være i bevægelse:**

- Virkelig meget ☐
- Temmelig meget ☐
- Ikke særlig meget ☐
- Slet ikke ☐

12) **Jeg glæder mig til ting, som skal ske:**

- Lige så meget som før ☐
- Noget mindre, end jeg plejer ☐
- Helt klart mindre end tidligere ☐
- Næsten ikke ☐

13) **Jeg får en pludselig fornemmelse af panik:**

- Særdeles tit ☐
- Temmelig ofte ☐
- Ikke særlig ofte ☐
- Slet ikke ☐

14) **Jeg kan nyde en god bog eller et radio/TV-program:**

- Ofte ☐
- Nogle gange ☐
- Ikke særlig tit ☐
- Meget sjældent ☐

Kære forsøgsdeltager.
Da det er første gang i forsøget, du udfylder spørgeskemaet, vil vi også bede dig tage stilling til dette spørgsmål:

Hvilket symptom eller problem er det vigtigst for mig at få hjælp til på nuværende tidspunkt? (sæt kun **et** kryds):

Symptom/problem	**Sæt (kun et) X**
Begrænsninger i fysisk funktion	
Begrænsninger i arbejde og daglige aktiviteter	
Begrænsninger i det sociale liv	
Hukommelses- og koncentrationsbesvær	
Følelsesmæssige problemer (bekymring, irritation, depression, anspændthed)	
Fatigue (træthed og svaghed)	
Smerter	
Åndenød	
Appetitløshed	
Kvalme	
Forstoppelse	
Søvnproblemer	
Ingen af ovenstående valgmuligheder	

Appendix 4

Paper I

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BMC Cancer

STUDY PROTOCOL Open Access

A parallel-group randomized clinical trial of individually tailored, multidisciplinary, palliative rehabilitation for patients with newly diagnosed advanced cancer: the Pal-Rehab study protocol

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Abstract

Background: The effect of early palliative care and rehabilitation on the quality of life of patients with advanced cancer has been only sparsely described and needs further investigation. In the present trial we combine elements of early, specialized palliative care with cancer rehabilitation in a 12-week individually tailored, palliative rehabilitation program initiated shortly after a diagnosis of advanced cancer.

Methods: This single center, randomized, controlled trial will include 300 patients with newly diagnosed advanced cancer recruited from the Department of Oncology, Vejle Hospital. The patients are randomized to a specialized palliative rehabilitation intervention integrated in standard oncology care or to standard oncology care alone. The intervention consists of a multidisciplinary group program, individual consultations, or a combination of both. At baseline and after six and 12 weeks the patients will be asked to fill out questionnaires on symptoms, quality of life, and symptoms of depression and anxiety. Among the symptoms and problems assessed, patients are asked to indicate the problem they need help with to the largest extent. The effect of the intervention on this problem is the primary outcome measure of the study. Secondary outcome measures include survival and economic consequences.

Discussion: To our knowledge the Pal-Rehab study is the first randomized, controlled, phase III trial to evaluate individually tailored, palliative rehabilitation in standard oncology care initiated shortly after an advanced cancer diagnosis. The study will contribute with evidence on the effectiveness of implementing early palliative care in standard oncology treatment and hopefully offer new knowledge and future directions as to the content of palliative rehabilitation programs.

Trial Registration: Clinicaltrials.gov Identifier: NCT02332317, registered retrospectively on December 30, 2014. One study participant had been enrolled at the time.

Keywords: Palliative care, Early integrated care, Rehabilitation, Supportive care, Advanced cancer, Quality of life research, Patient involvement, Randomized clinical trial, Cost-effectiveness, Study protocol

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Background

Early integrated palliative care

Studies have shown that cancer patients have unmet palliative needs (e.g. physical, social, emotional, and cognitive challenges related to living with cancer) [1].

Palliative care is applicable early in the course of illness and in conjunction with other therapies [2] but is often thought to address "end-of-life"-needs only; perhaps especially in the eyes of professionals involved in oncology, who often play the role of referring the patients to specialized palliative care when all other treatment options are exhausted [3]. Many patients and caregivers associate palliative care with hopelessness and giving up [4]. As a result many patients are not referred to specialized palliative care until late in the disease trajectory [5].

According to The World Health Organization (WHO, 2002) palliative care should not only be considered for the dying but for all patients and families living with a life threatening illness [2] and thus be an integrated part of the treatment at an early stage of the disease. This approach is known as early integrated palliative care. The recommendations are very general and lack specifications about the timing and content of the early, integrated palliative care intervention.

The American Society of Clinical Oncology released a provisional clinical opinion in 2012 about the integration of palliative care into standard oncology care [6] based on seven randomized clinical trials. The conclusion in this expert opinion was that, *while evidence clarifying optimal delivery of palliative care to improve patient outcomes is evolving[…] strategies to optimize concurrent palliative care and standard oncology care, with evaluation of its impact on important patient and caregiver outcomes (*e.g. *quality of life, survival, health care services utilization, and costs and on society, should be an area of intense research.*

This provisional clinical opinion has just been updated reflecting the change in evidence since the previous guideline [7]. The Expert Panel still concludes that more research is needed, especially with inclusion of patients with advanced cancer in early-phase clinical trials.

Several studies have investigated the integration of specialized palliative care into clinical oncology for patients with advanced cancer with promising results. The studies differ, however, in outcome measures, study participants, and timing and contents of the early palliative intervention.

A Canadian study published in 2009 [8] was the first to test the hypothesis that patients with advanced cancer who were offered specialized palliative care shortly after the diagnosis in conjunction with standard care would be more informed and participate more actively in their treatment plan and care. The hypothesis was that this would lead to better quality of life (QoL), better symptom control, lower depression rate and lower health expenses compared with the patients who received standard treatment. A total of 322 patients with newly diagnosed advanced breast, lung, gastrointestinal or genitourinary cancer were randomized. The intervention was a telephone based educational and supportive program led by specialized nurses. The weekly sessions were designed to empower patients to articulate palliative and end-of-life needs to their oncologist. The results showed significantly better self-reported QoL and lower depression rates in the intervention group compared to the control group, whereas no improvement in symptom control or decrease in health expenses was shown.

In an American single center study published in 2010–12 [9–11], 151 patients with newly diagnosed metastatic non-small cell lung cancer were randomized to standard care or standard care plus a palliative care intervention. The intervention was at least one monthly consultation with a specialized palliative care physician and nurse. The primary outcome measure was QoL 12 weeks after randomization. Other outcome measures were anxiety and depression, and health care expenses. The study was not designed to show differences in survival, but the analysis was made post hoc. The result of the study was significantly higher self-reported QoL of the patients who had received the palliative intervention. The intervention group also showed significantly fewer symptoms of anxiety and depression after 12 weeks and even a significantly longer mean survival of 11.6 months vs 8.9 months despite less aggressive active treatment in the intervention group.

The question of timing was evaluated in a large study of early versus delayed initiation of a palliative care intervention published in 2015 [12]. Patients ($N = 207$) with advanced cancer were randomly assigned to receive an in-person specialized palliative care consultation, structured telehealth nurse coaching sessions (once per week for six sessions), and monthly follow-up either early after enrollment or 3 months later. The outcome measures were group differences in QoL, symptom impact, mood, 1-year survival, and resource use. The study showed that the patient-reported outcomes and resource use of early entry participants were not statistically different from that of the late entry participants; however, their 1-year survival was significantly improved compared to those who began 3 months after enrollment.

Other studies of early, integrated, specialized palliative care have pointed to improved QoL [13], better patient and caregiver satisfaction with care, and a high level of satisfaction with the integrated model amongst oncologists due to patient satisfaction, reduction of symptom burden, and time saved in the clinic [14, 15].

Rehabilitation of patients with advanced cancer

The average survival time of patients with advanced cancer, calculated from the date of diagnosis until death, is

improving [16], which makes the discussion of rehabilitation of this group of patients increasingly relevant.

Specialized palliative care is a multidisciplinary approach aiming at relieving suffering in all its dimensions throughout the course of life-threatening disease and for everyone closely affected by the disease [2]. Rehabilitation aims at improving and maintaining physical, mental, social and intellectual performance levels and preventing loss of functions related to activities of daily living (ADL) with the purpose of supporting independence and self-management [16].

The overlap between specialized palliative care and rehabilitation becomes clear when assessing the resources and needs of the individual patient and caregiver, especially early in the disease trajectory. Specialized palliative care and rehabilitation involve many of the same health professionals and can be combined in an ambulatory setting [16].

In Great Britain the "Palliative Day Care Centers/ Services" have existed for decades combining specialized palliative care and rehabilitation. The physical frame is often a hospice. Group activities play a pivotal role with a combination of group discussions of issues related to living with cancer and physical exercise. A review of 15 quantitative and qualitative studies about" Palliative Day Care Centers/Services" conclude that they provide a high degree of patient and caregiver satisfaction and that the possibility of forming relations with the staff and other patients is of great importance [17]. Whether the patients experienced better symptom control or better health related QoL from participating in the services was not clear.

A phase II study from Norway published in 2006 tested the effect of an individually tailored twice-a-week 6-week physical exercise program on physical performance and QoL in patients with incurable cancer and a life expectancy of less than one year [18]. The conclusion was that the exercise program was not only feasible; it also significantly improved the physical and emotional functioning of the patients and reduced fatigue. However, the study population was quite small and did not include a control group.

An American study published in 2015 tested the effect of a multidisciplinary QoL-directed intervention on patients' adherence to the planned chemoradiation treatment [19]. A cohort of 61 patients with advanced localized gastrointestinal cancer was formed by pooling the results of two randomized, controlled trials using the same intervention. Twenty-nine patients were randomized to participate in sessions of exercise, education, and relaxation two or three times a week for six or eight weeks, and 32 patients received standard medical care. The study found a significantly higher proportion of patients completing the "as planned" cancer treatment and significantly fewer requiring hospitalization in the intervention group compared to the control group, and the results were still statistically and clinically significant when the analyses were completed for the subgroup who received neoadjuvant chemoradiation treatment.

Aim of this study

The overall experience with early, integrated, specialized palliative care and rehabilitation of advanced cancer patients is positive, but the evidence is still sparse and more research is required.

The Pal-Rehab study combines elements of early, integrated, specialized palliative care with elements of rehabilitation in an individually tailored intervention in patients with advanced cancer.

The aim of this study is to elucidate whether a 12-week individually tailored, palliative rehabilitation program initiated shortly after an advanced cancer diagnosis reduces physical and emotional symptoms/problems and improves QoL. The patient chooses the main symptom/problem to be focused on. Impact on survival and economic consequences measured as health service utilization will also be evaluated.

Methods/design

Study design

The study is a phase III, controlled, randomized trial with 300 patients allocated 1:1 to an intervention or a control group at the Department of Oncology, Vejle Hospital. The department offers treatment to adult patients with pulmonary, breast, prostate, colorectal, anal and biliary tract cancer, as well as cancers of the female reproductive organs. On a yearly basis there are around 57,000 outpatient visits and 23,000 radiotherapy fractions and 9300 chemotherapy treatments are administered. Geographically, the patients have up to 1½ hours of transport time by car to the hospital.

Newly diagnosed advanced cancer patients initiating oncologic treatment who consent to participate will be randomized to an individually tailored palliative rehabilitation program alongside their standard oncology care (disease specific treatment) or to standard oncology care alone. Study measures and timepoints can be seen in Fig. 1.

Study participants

Three hundred patients will be recruited according to the selection criteria (Table 1).

Patients are eligible if the first choice of treatment is systemic and complete surgical removal of the malignant tissue is either ruled out or depends on the success of the systemic treatment. Patients with advanced prostate cancer are often seen at other departments than the Oncology Department following the diagnosis, but they

	STUDY PERIOD					
	Enrollment	Allocation	Post-allocation			Close-out
TIMEPOINT	$-t_1$	0	W1	W6-7	W12	3 months after enrollment of last patient
ENROLLMENT:						
Eligibility screen	X					
Informed consent	X					
Randomization		X				
ALLOCATION:						
Intervention group			←	—	→	
• Consultation with specialized palliative care physician and nurse			X			
• Consultation with specialized palliative care nurse				X		
• Multidisciplinary team conference			X			
Control group			←	—	→	
ASSESMENTS:						
Baseline characteristics	X					
EORTC QLQ-C30 and HADS	X			X	X	
Contact sheet for intervention group			←	—	→	
Survival						X
Health care utilization						X

Fig. 1 Study outline

are considered eligible when they are referred to systemic treatment at the Oncology Department for the first time.

Enrollment procedure and baseline data collection

Eligible patients are informed about the project by a doctor or nurse in the outpatient clinic.

Table 1 Selection criteria

Inclusion criteria
1. First-time non-resectable cancer diagnosed less than 8 weeks before enrollment. Patients with prostatic cancer are eligible, if referred to systemic oncologic treatment for the first time less than 8 weeks before enrollment (e.g. due to failure of anti-hormone treatment).
2. Eligible for systemic oncologic treatment at Vejle Hospital and accepts treatment.
3. ≥ 18 years of age.
4. Reads and understands Danish
5. Written and orally informed consent.

Exclusion criteria
1. Other contact with a specialized palliative care unit within 1 year of enrollment.
2. Inability to comply with the protocol due to cognitive or other impairment.

Patients who have signed the informed consent form are asked to complete a baseline questionnaire. Baseline characteristics of the patient (WHO performance status, diagnosis, age, gender, time of primary diagnosis, cancer stage, marital status, and educational background) are registered. Randomization is subsequently performed by the clinical trial unit using a randomization list from randomizer.org [20]. Patients are randomized 1:1 to the intervention or control group with no further stratification used during randomization. The randomization list is blinded from anyone involved in informing potential study participants.

If a patient does not wish to participate, the reason is noted, if possible, and the following characteristics are registered anonymously; diagnosis, age, gender, WHO performance status, cancer stage, marital status and educational background.

The intervention

The intervention combines elements of specialized palliative care with rehabilitation of cancer patients and is a multidisciplinary assessment of symptoms/problems,

QoL, and potential barriers to activities of daily living (ADL) in patients receiving standard oncologic treatment.

The intervention is tailored to the individual patient and since rehabilitation is best described as a process containing specific actions [21], the bundle of actions is investigated rather than single components.

As suggested by Wade [22] the intervention is categorized into five main descriptors; the target population, goals of the intervention, activity or process, resources used, and context (Table 2).

Within one week after randomization patients allocated to the intervention are seen in the outpatient clinic by a physician and nurse specialized in palliative care. The themes covered in the first consultation are shown in Table 3.

Table 3 Content of the first intervention consultation

- Gaps between wishes for ADL and the patient's current situation
- Prognostic awareness
- Problems with the "patient/caregiver-role"
- Sleeping disorders
- Tiredness and fatigue
- Problems with memory or concentration
- Lack of appetite, weight loss
- Pain, respiratory problems, constipation, and other frequent symptoms
- Anxiety, worry, sadness
- Feeling of meaninglessness in the current situation
- Coping mechanisms of patients and caregivers and potential differences
- Problems of a socio-economic character or family issues
- Problems concerning work life

At the end of the first consultation a plan for the following 12 weeks is made together with the patient and caregivers based on their needs and wishes. The intervention provided reflects the offers of the specialized palliative care team to outpatients, i.e. individual consultations at the hospital, telephone consultations, and/or a palliative rehabilitation group program consisting of weekly group discussions followed by one hour of physical exercise, also in groups. If the group program is relevant to the patient, this will be the main intervention. Caregivers are welcome in the group discussions dealing with a new theme every week for 12 weeks. A dedicated, specialized palliative care nurse guides the group, and other

Table 2 Description of the individually tailored palliative rehabilitation intervention

Target population	Patients with newly diagnosed non-resectable cancer
Goals of the intervention	Immediate goals • To help patients and caregivers with symptoms/problems identified through questionnaires and a specialized palliative care consultation • To improve overall QoL through symptom control, improvement of physical performance level, and better understanding of the disease and related symptoms Distal/general goals • To improve survival and reduce health service utilization by early recognition of symptoms and problems, improvement of physical performance level and ability to complete "as planned" cancer treatment, and support of patient and caregiver empowerment in future treatment decisions
Activity/process	• Individual consultations • Group educational program for patients and caregivers • Group physical exercise program for patients • Contact to other health departments, the primary sector, local municipality and employer, if relevant and the patient consents
Resources	• Human resources A specialized palliative care team consisting of physicians, nurses, physiotherapists, psychologists, a dietician, an occupational therapist, a social worker, and a hospital chaplain • Physical resources A consultation room, a group room, and a group exercise room. • Time resources The initial specialized palliative care consultation has a duration of approximately one hour plus on average 15 min for the multidisciplinary team conference. The follow-up consultation with a specialized palliative care nurse takes about 30–45 min The group educational program and physical exercise program lasts two and a half hours once a week for twelve weeks. Additional resources are based on individual needs and wishes of patients and caregivers and will be assessed retrospectively
Context	• Scientific context Investigation of early, integrated palliative care and rehabilitation for advanced cancer patients • Organizational structures The specialized palliative care team is organized under the Department of Oncology

health professionals involved in the group program join in depending on the subject. The headlines of the group discussions reflect the themes covered in the first consultation (Table 3) and patients and caregivers receive an overview, when they join the group. Weekly attendance is not mandatory. A patient participating in the group physical exercise program meets with a specialized palliative care physiotherapist beforehand and an individual exercise program is tailored following a series of tests. When the 12-week program has been completed, the patient is examined by the same physiotherapist and receives tailored advice on future physical activity.

During the 12-week group program the patients and caregivers will have supplementary individual consultations if needed, together or separately. At the end of the program they are offered a final evaluation with the same physician and nurse they met at the first consultation.

Caregivers participating in the group program are encouraged to share their thoughts and experiences with each other in a separate room while the patients do the physical training.

If the patient/caregiver prefers or is better suited for individual consultations instead of the group program, this will be accommodated.

If no further intervention is initiated after the first consultation, the patient and caregivers are provided with contact details and may approach the palliative team any time during the next 12 weeks without a new referral.

All patients and caregivers in the intervention group are discussed at least once at a multidisciplinary team conference. A midway follow-up consultation with a specialized palliative care nurse is held six to seven weeks after randomization.

In order to describe the intervention in detail a "contact sheet" covering all possible elements of the intervention is used for prospective registration. Members of the specialized palliative care team fill in the sheet after each contact with a patient or caregiver. Medical records are also kept for further details.

The control group

The control group receives standard care at the Department of Oncology. In addition to anticancer treatment all patients have access to a number of paramedical services available through referral (Table 4). These services are not open for caregivers.

Table 4 Standard hospital based paramedical care

Nutritional support	• All cancer patients are screened for weight loss at the beginning of each treatment. In case of significant weight loss the patient is referred to a dietician
Physical support	• The patient can be referred to the hospital physiotherapist. The main reason is significant lymphedema • In cooperation between clinical oncology nurses and hospital physiotherapists patients having a high performance level are offered an extensive group based training program 4 times a week for 6 weeks
Phsycosocial support	• The outpatient clinic employs psychologists and social workers, and the hospital has a priest. The mean waiting time for a patient referred to a psychologist is currently 3 weeks

Outcome measures

Study objectives

The primary objective of the study is to assess the impact of the intervention on the symptom/problem prioritized by the patient. Secondary objectives are 1) to assess the impact on the symptoms/problems represented in the questionnaires, including QoL and symptoms of depression and anxiety, 2) to assess the impact on survival, and 3) to analyze economic consequences measured as health service utilization from enrollment until three months after final data collection.

Measurement instruments

All participants complete a questionnaire at baseline and six and 12 weeks after randomization. The questionnaire consists of EORTC QLQ-C30, which is a validated and widely used questionnaire for assessing symptoms and QoL in cancer patients [23], and Hospital Anxiety and Depression Scale (HADS), which is also validated and often used for screening and assessment of symptoms of anxiety and depression in palliative care, oncology, and other fields of research [24].

The EORTC QLQ-C30 consists of 30 items in 15 scales. In the present study additional items measuring role functioning, cognitive functioning, social functioning, dyspnea, pain, fatigue, insomnia, appetite loss, nausea/vomiting and constipation were added to the questionnaire to expand these scales to at least four items in each scale. The extra items were taken from the item banks developed for computer-adaptive testing of the EORTC QLQ-C30 dimensions [25–28]. The international clinical validation of the item banks is ongoing.

At baseline the patient prioritizes one "primary problem" from a list of 12 categories of "primary problems" corresponding to 12 of the 15 scales of EORTC QLQ-C30, or "none of the above" (Table 5). At six and 12-weeks follow-up the patient is asked whether he/she has received help with the "primary problem" (yes/no) and if yes, whether the help was "insufficient", "partly sufficient" or "sufficient".

The primary outcome measure is the difference between the intervention and control groups in the change from baseline to the weighted average at the six and 12-week follow-up measured as area under the curve

Table 5 List of possible "primary problems" the study participants to choose from

"Primary problem"	Corresponding outcome measure in EORTC QLQ-C30
Limitations in physical functioning	Physical function scale
Limitations in work and daily activities	Role function scale
Limitations in social life	Social function scale
Problems with memory and concentration	Cognitive function scale
Emotional problems (worry, irritation, depression, tension)	Emotional function scale
Fatigue (tiredness and weakness)	Fatigue scale
Pain	Pain scale
Breathlessness	Dyspnea item
Loss of appetite	Loss of appetite item
Nausea	Nausea and vomiting scale
Constipation	Constipation scale
Trouble sleeping	Insomnia item
None of the above	

(AUC) of the EORTC QLQ-C30 scale/category chosen by the patient (e.g., if pain was designated as 'primary problem', the primary outcome is based on the EORTC QLQ-C30 pain scale). If a patient has ticked the box "none of the above" and hence has not chosen any of the 12 scales/categories, the primary outcome measure for this patient will be change in health related QoL corresponding to the "Global health status/QoL"-scale in EORTC QLQ-C30. This way of devising and analyzing an individualized trial outcome has previously been motivated and elaborated, although in the previous study the patients did not select the outcome measure [29, 30]. The expanded EORTC scales (see above) will be used in the primary outcome; the traditional EORTC QLQ-C30 scales will be used in a secondary analysis.

Statistical analysis and sample size calculation

Sample size estimation

Data from other studies using EORTC QLQ-C30 suggest a standard deviation of less than 25 for a difference between the repeated measurements, and a group difference of 10 for clinical relevance [31].

With a risk of type I error of 0.05 and type II error of 0.10, 133 patients are required in each arm. In order to allow for a dropout rate of approximately 10% each arm will enroll 150 patients for a total of 300 patients.

Plan of analysis

Questionnaire data

Analyses will be made using the statistical package STATA, latest version (StataCorp, Texas, USA). The primary analysis will be based on the intention-to-treat principle. If the proportion of lacking answers is higher than 5%, we will use multiple imputations in the primary analysis with the following variables: age, gender, diagnosis, cancer stage, and WHO performance score. The questionnaire data will be transformed according to their respective scoring manuals [32, 24].

Multiple regressions will be applied, since despite the randomized design there may be imbalance between the two arms. We will adjust for "the primary problem" and WHO performance score.

Wilcoxon and Chi2 will be used to investigate whether there are differences between the two groups in relation to the following variables that may be of prognostic importance: gender, age, cancer stage, primary diagnosis, marital status, and educational background. If a significant group difference is found, the respective variable will be included in a sensitivity analysis.

In the analyses we combine the data from the three questionnaires by constructing an AUC using a weighted average of the change from baseline to the 6 and 12-week follow-up. A model for longitudinal data and repeated measurements in the multivariate analysis is applied as a subsequent sensitivity analysis.

Since the primary outcome measure "the primary problem" consists of 13 possible choices, we will also perform separate analyses of patients with the same primary problem.

Survival

Survival will be described by Kaplan-Meier plots. Patients still alive three months after final data collection will be censored as of that date. A Cox regression model will also be applied controlling for the same variables as in the questionnaire data analysis.

Economic consequences

Data on the number and length of hospital admissions and treatments, visits to outpatient clinics, emergency rooms, and general practitioners are applied in the evaluation of economic consequences of the intervention. The calculation includes the period from enrolment until three months after final data collection. The data are available from the Danish National Patient Registry [33] and the costs of the different services are obtainable through the Danish Health Authority.

Multivariate analysis is used to compare the two groups controlling for the same variables as in the questionnaire data analysis.

Other statistical and methodological considerations

A certain degree of cross over and loss to follow-up is expected in this study and will be registered.

The baseline characteristics of responders and non-responders will be compared to elucidate any differences. Likewise, the difference in baseline characteristics of patients who were invited to participate but declined and the study participants will be investigated.

Blinding of study participants and health professionals is not possible. However, the primary data analysis will be conducted in a blinded manner using coded numbers not referring to allocation or identifying patient characteristics.

Patient and caregiver involvement in the study

Before recruitment was initiated the main intervention of the study (the group program) went through a pilot period where alterations were made based on feedback by patients and caregivers to ensure feasibility and relevance.

The intervention is individually tailored during the 12-week study period. Only the initial and midway consultations are mandatory, which leaves room for a great deal of patient and caregiver involvement in the design of the intervention. The individual primary outcome is also chosen by the patient.

The trial is conducted in close collaboration with the Patient and Relatives Council at Vejle Hospital. The protocol was discussed with and finally approved by the Council, which also has a consulting role during the research process. Dissemination of the study result will also take place in collaboration with the Patient and Relatives Council.

Ethical considerations

In the study period no effort will be made to prevent patients in the control arm from being referred to specialized palliative care according to the referral criteria of the specialized palliative care team. The Helsinki II declaration is followed unconditionally.

Time plan

The study is actively recruiting and 68% of the intended study population has been enrolled so far. The analyses are expected to be finalized in 2018.

Discussion

The Pal-Rehab study is a randomized, controlled, single center, phase III trial evaluating palliative rehabilitation as a supplement to standard oncology care in the hospital setting for patients with newly diagnosed advanced cancer. After baseline assessment the patients will be randomized to either the intervention group receiving palliative rehabilitation involving systematic and tailored elements or to the control group receiving standard care alone. Follow-up measurements allow the detection of group differences in symptom control, mood and QoL. Health service utilization and survival will also be investigated.

To our knowledge this is the first time an individually tailored palliative rehabilitation program including a group offer is being evaluated in a randomized controlled setting where the patient group is not selected by cancer type or performance level. Also, this study seems to be the first to assess whether or not early palliative care is helpful in relation to the primary problem specified by the patient.

Reflections on the intervention of the study

We want to reach the patients and caregivers soon after time of diagnosis in order to focus on early recognition of symptoms and problems affecting QoL and on empowerment of the patients and caregivers with tailored advice by health professionals.

Patients with advanced cancer have many visits to the hospital, especially during standard oncologic treatment. The rehabilitation program takes place at the hospital where the patient is undergoing oncology care. The hospital setting ensures close collaboration between the specialized palliative care team and other healthcare professionals. Everybody involved in the treatment has access to the same patient record. For instance the physiotherapist can access the patient's diagnostic imaging reports which is helpful in the individual counselling, e.g. about restrictions due to bone metastases.

The group program is the main intervention. In addition to saving time and resources a group intervention enables patients and caregivers to meet with other people in a similar situation.

With the eligibility criteria of this study the traditional distinction between treatment with palliative and curative intent is avoided. Instead, the target group is defined as patients (and caregivers) living with advanced cancer at the time of initiating oncologic treatment. This definition seems relevant as to the future selection of patients for palliative rehabilitation based on the findings of this study.

Potential weaknesses and strengths of the study

It is a general problem that the voluntariness of research participation and potential gate keeping may lead to the selection of the most resourceful patients, who may not be the ones most in need of palliative support [34]. This is also true for the present study. Furthermore, patients with severe cognitive impairments are excluded from participation for ethical reasons. The prognostic factors of all patients invited to participate will be registered along with the reasons stated by patients who do not wish to participate. In this way we hope to be able to discuss our findings in the light of the characteristics of the group we have investigated and knowledge about the patients not included.

The complexity of rehabilitation as a process poses great challenges in research and it is difficult to separate the specific features of an intervention from non-specific aspects that nonetheless may have powerful effects [21]. For instance it cannot be ruled out that preexisting beliefs about the effectiveness of the intervention plays a role when patients report their outcome. We have chosen two approaches to this methodological problem; firstly, patients are informed in a neutral manner, where few details about the content of the intervention are revealed before randomization. Secondly, patients are asked to choose a "primary problem" before randomization and are asked at follow-up, whether or not they have been helped with this problem. However, they are not informed that the "primary problem" they have chosen correlates to a scale in the EORTC QLQ-C30 questionnaire and they do not have their baseline questionnaire for comparison when answering the follow-up questionnaires. The primary outcome measurements are based on the scores in EORTC QLQ-C30.

Where the word "rehabilitation" may raise positive expectations, "palliative care" sometimes carries a stigma of death or dying, which will expectedly be a challenge when recruiting patients with newly diagnosed advanced cancer. As part of the oral information the patient and caregivers are specifically asked, if they have any experience with "palliative care" and the meaning of the word. If relevant, they are informed that the aim of the intervention is not "end-of-life support". Patients are also informed that they can participate in the study regardless of whether they initially feel a need for an intervention or not.

Pal-Rehab is a single center study, which may limit generalization of the results. On the other hand the study only includes healthcare professionals conventionally present at any hospital offering systemic cancer treatment in our country. The physical requirements are one group room and physical exercise facilities. We therefore believe the intervention is transmissible to other departments of oncology.

This study does not specifically evaluate the impact on the caregivers although the intervention does aim to cover the needs of the caregivers if invited by the patient. When evaluating economic consequences, the patient's utilization of health services is calculated, but expenses such as additional transportation and time off from work in connection with study participation are not considered.

There may be a certain amount of cross-over, since the group offer of palliative rehabilitation for people living with cancer is open through referral outside the protocol. However, according to our experience from the first two years of practice, patients are not referred until rather late in their disease trajectory and substantially later than the patients we are recruiting for this trial.

Conclusion

The Pal-Rehab study is a randomized controlled trial investigating whether an individually tailored, palliative rehabilitation program initiated shortly after diagnosis of advanced cancer improves the QoL of the patients. To our knowledge this has never been done before. The results will contribute to the evidence on early palliative care in standard oncology treatment and hopefully offer new knowledge and future directions about palliative rehabilitation programs.

Abbreviations

ADL: Activities of Daily Living; AUC: Area Under the Curve; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Core Questionnaire, version 3; HADS: Hospital Anxiety and Depression Scale; QoL: Quality of Life; WHO: The World Health Organization

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Availability of data and materials

Data collection is not complete. The trial is approved by The Danish Data Protection Agency.

Authors' contributions

LN conducts the trial as described in the protocol and drafted this manuscript. MG and TV conceived the study and its design and have revised the manuscript with substantial contributions. MAP participated in the design of the analyses plan and contributed to the draft of the manuscript. LHJ participated in the design and coordination of the study and helped to draft the manuscript. All authors read and approved the final manuscript.

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Ethics approval and consent to participate

All study participants are enrolled following verbal and written informed consent. The study protocol including the written material intended for potential study participants and the informed content sheet was approved by The Regional Committees on Health Research Ethics for Southern Denmark on April 2nd, 2014 (Project ID S-20140038).

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Publisher's Note

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Appendix 5

Paper II

Supportive Care in Cancer
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ORIGINAL ARTICLE

A new model of early, integrated palliative care: palliative rehabilitation for newly diagnosed patients with non-resectable cancer

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Abstract

Purpose The aim of this paper is to describe a model of palliative rehabilitation for newly diagnosed advanced cancer patients and present data on how it was utilised during a randomised controlled trial (RCT).

Methods We designed a highly flexible, multidisciplinary model of palliative rehabilitation consisting of a "basic offer" and tailored elements. The model was evaluated in the setting on an RCT investigating the effect of systematic referral to a palliative rehabilitation clinic concurrently with standard oncology treatment or standard treatment alone. The basic offer of palliative rehabilitation was two consultations and a 12-week possibility of contacting a palliative rehabilitation team, if needed. In addition, patients and family caregivers could be offered participation in a 12-week patient/caregiver school combined with individually tailored physical exercise in groups, individual consultations, or both. Contacts with the palliative rehabilitation team and participant evaluation were registered prospectively.

Results Between December 2014 and December 2017, 132 adults with newly diagnosed advanced cancer were seen in the palliative rehabilitation outpatient clinic. Twenty percent of the participants received the basic offer only ($n = 26$), 45% additionally participated in the group program ($n = 59$), and 35% received supplementary individual consultations without participating in the group program ($n = 47$). The intervention was primarily led by nurses, and the main themes of the individual consultations were coping, pain, and nutrition. When asked if they would recommend the intervention to others in the same situation, 93% of the respondents agreed, 7% partly agreed, and no one disagreed.

Conclusion The new model of palliative rehabilitation presented here had a flexibility to meet the needs of the participants and led to a very high degree of patient satisfaction. It could serve as an inspiration to other cancer centres wanting to integrate palliative care into standard oncology services.

Keywords Palliative care · Rehabilitation · Quality of life · Neoplasms · Models of care · Patient satisfaction

Introduction

A new clinic offering palliative rehabilitation was opened as a branch under the existing specialised palliative care (SPC) team at Vejle Hospital, Denmark, in 2013. The goal was to offer early palliative care in an outpatient setting to patients with advanced cancer undergoing active anticancer treatment and include elements of rehabilitation. It was

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decided to test the new service in a randomised clinical trial (RCT).

Early palliative care

Palliative care is often misconstrued as end-of-life care only [1].

In 2012, the American Society of Clinical Oncology published the first provisional clinical opinion (PCO) [1] about the integration of palliative care services into standard oncology practice at the time a person is diagnosed with metastatic or advanced cancer. Seven published randomised, controlled trials formed the evidence base, three of which were in the outpatient setting [2–4]. The PCO stated that early palliative care leads to better patient and caregiver outcomes including but not limited to improvement in symptoms, quality of life, patient satisfaction, and a reduced caregiver burden. Although integration of palliative care early in the cancer care continuum is now supported by health and cancer organisations worldwide [5–7], it has still not been widely implemented [8].

Palliative rehabilitation

Palliative care and rehabilitation professionals are trained to diagnose and treat complex problems through multidisciplinary interventions with the goal of improving quality of life. Rehabilitation services are underutilised among people with advanced cancer [9] even though maintenance of functional independence is central to quality of life and rehabilitation services tend to be most effective when initiated before the cancer-related functional loss is too severe [10].

In 2017, Cheville et al. described the integration of function-directed treatments into palliative care and suggested the following definition of palliative rehabilitation: "*A function-directed care delivered in partnership with other disciplines and aligned with the values of patients who have serious and often incurable illnesses in context marked by intense and dynamic symptoms, psychological stress, and medical morbidity, to realize potentially time-limited goals*" [10].

Only few studies have investigated multidisciplinary, individually tailored and quality of life-directed interventions integrated in standard oncology care for advanced cancer patients, and to the best of our knowledge, no models of palliative rehabilitation for patients with newly diagnosed advanced cancers have yet been published. One of the reasons behind the underutilisation of early palliative care and rehabilitation in these patients could be the lack of well described and tested models of delivery.

Aim

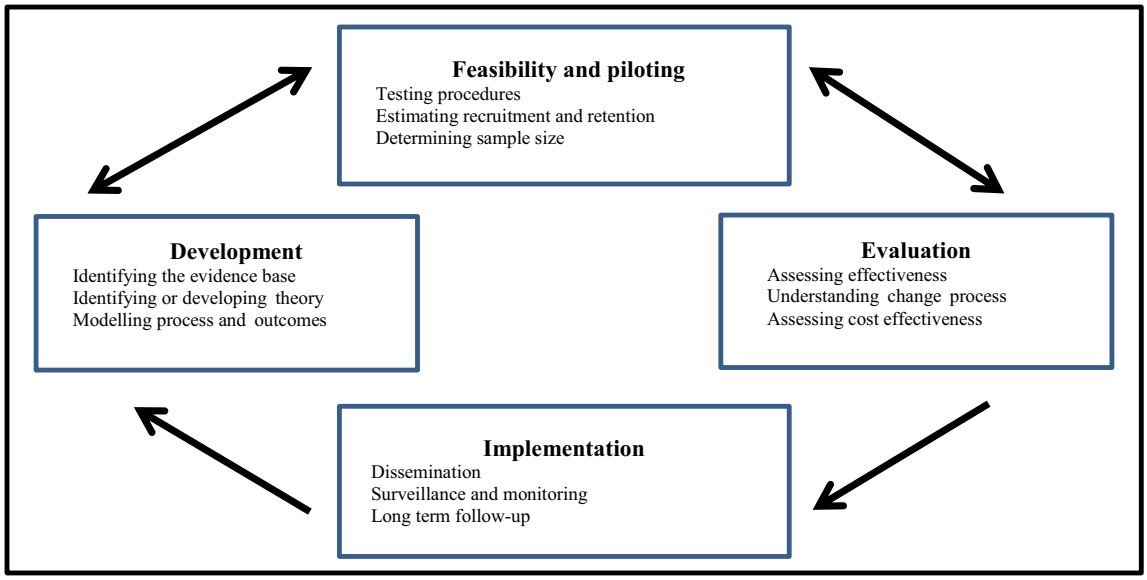
The aim of this paper is to describe a model of palliative rehabilitation for newly diagnosed, advanced cancer patients and present data on how it was utilised during an RCT.

Methods

Preparation and test phase

The development and testing of the model were based on the British Medical Research Council Guidance for the Development and Evaluation of Complex Interventions [11] (Fig. 1).

We identified the evidence base by reviewing the literature on early palliative care, palliative day-care services, and rehabilitation services for advanced cancer patients in November of 2013. The literature and the clinical experience in the specialised palliative care team from working with advanced cancer patients and their families formed the basis of the new outpatient service to be tested in the setting of an RCT. The aim of the RCT was to investigate the effect of systematic referral to a palliative rehabilitation clinic concurrently with standard oncology treatment versus standard care alone for newly diagnosed advanced cancer patients. During the first year of service, while the RCT was under preparation, procedures in the palliative rehabilitation outpatient clinic were tested with patients receiving chemotherapy who were referred to the specialised palliative care team. They were offered palliative rehabilitation in the outpatient clinic, and the model was subject to ongoing adjustments based on feedback by patients, caregivers, and staff before enrolment in the study began. The new offer was designed as a group program based on two components: a patient/caregiver school and individually tailored physical exercise in groups. Feedback from patients and caregivers was collected through semi-structured interviews performed approximately 12 weeks after the initial consultation or when the patient was discharged from the palliative rehabilitation clinic, whichever came first (data not presented). A topic guide for the semi-structured interviews included the patients' and caregivers' thoughts on being referred to and participating in a palliative rehabilitation program and their suggestions for future alterations to the offer. If they had participated in the group program, they were further asked about the frequency and duration of the group program, the relevance of the topics in the school sessions, and the elements of the exercise program, as well as the strengths and limitations of a group setting. The contents and organisation of the offer were discussed at monthly staff meetings. The study protocol was thoroughly discussed with the hospital's Patient and Relatives Council.



Source: The Medical Research Council 'Developing and evaluating complex interventions: new guidance', 2008. Reprinted with permission.

Fig. 1 Key elements of the development and evaluation process. Source: The Medical Research Council "Developing and evaluating complex interventions: new guidance", 2008. Reprinted with permission

The palliative rehabilitation outpatient model

The final and highly flexible model consisted of a "basic offer" and tailored elements (Fig. 2).

The basic offer was two mandatory consultations and the option of contacting a palliative rehabilitation team directly during the participation period of 12 weeks, if needed. The two consultations were an initial 1-h consultation with a physician and nurse specialised in palliative care and a 40-min follow-up consultation with a nurse after 6–7 weeks. In addition, patients and family caregivers could be offered participation in a 12-week patient/caregiver school combined with individually tailored physical exercise in groups, individual consultations with members of the palliative rehabilitation

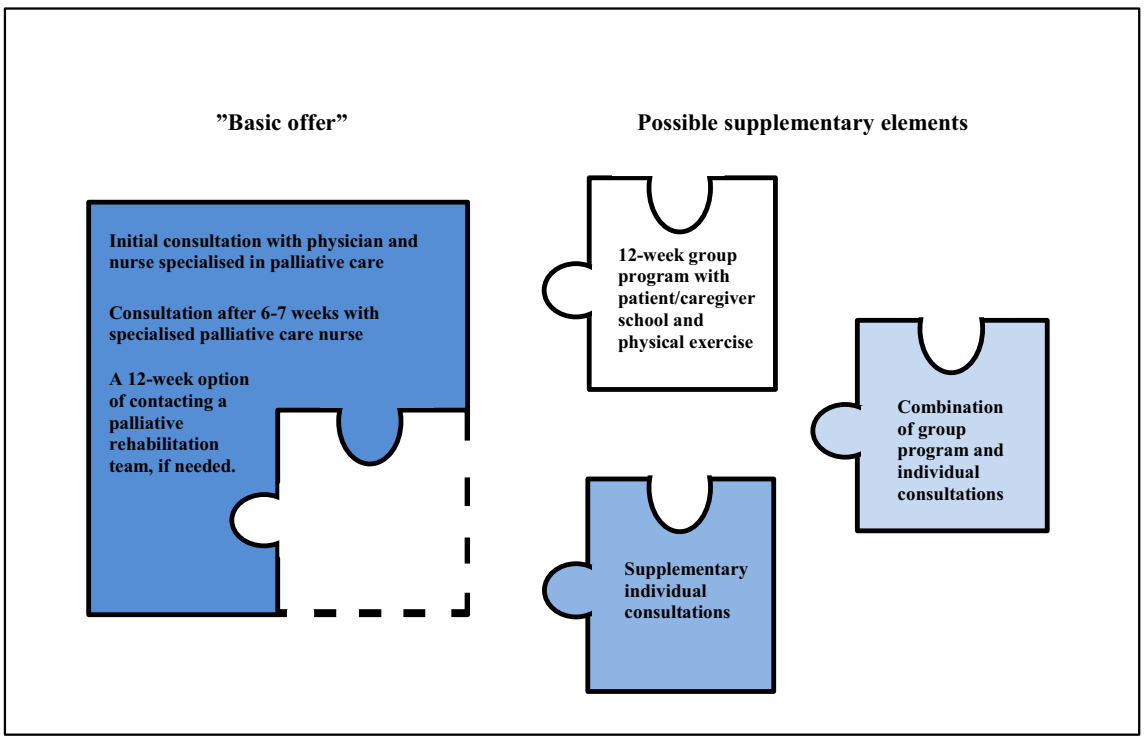


Fig. 2 The palliative rehabilitation offer

team, or both. At the end of the first consultation, the patient and family caregivers were given the team's contact information and the name of a contact nurse and physician.

The palliative rehabilitation team

The usual specialised palliative care team counting physicians, nurses, physiotherapists, and psychologists was enhanced by engaging a part time social worker, dietician, occupational therapist, and chaplain from other clinical departments at the hospital, all experienced in dealing with cancer patients. Except for the chaplain, all team members offered individual consultations to patients and family caregivers in the palliative rehabilitation clinic or over the telephone. The team assembled for weekly multidisciplinary conferences discussing each patient at least once.

The initial consultation

A template was developed for the initial consultation with a specialised palliative care physician and nurse drawing on inspiration from the template used during an earlier trial on the early integration of palliative care by Temel et al. [4]. The consultation would address symptoms, mood, barriers to activities of daily living (ADL), illness and prognostic understanding, thoughts and goals for the future, a map of the patient's family and network, coping mechanisms, and individual needs of the family caregiver(s). If found relevant based on specific symptoms, a focused physical examination was performed. A plan was made for the next approximately 12 weeks in collaboration with the patient and family caregivers, documented in the electronic patient record, and a copy sent to the patient's general practitioner.

The group program

If patients and family caregivers were eligible for the group intervention, they were offered participation in a 12-week group program with weekly meetings. Groups were formed by consecutive patients and family caregivers. Main exclusion criteria were statements of discomfort from the patients about participating in a group setting or indications of personal crisis, where an individually tailored intervention was deemed more appropriate. The program consisted of a patient/caregiver school with educational sessions followed by individually tailored physical exercise in groups for patients only. The educational sessions lasted approximately 1 h initiating with a 20-min lecture and 40 min for questions, debate, and exchange of personal experience. The topics of the educational program can be seen in Table 1.

Written material on the weekly topic was handed out after each session in a personal folder for the patient to take home. After the educational session, a 30-min break gave the participants the possibility to relate more informally to each other before the 1-h exercise program led by a physiotherapist. The exercise program would combine aerobic exercises on treadmills, steppers, and cross trainers with dynamic muscle strengthening exercises using weight-lifting machines, elastic bands, or the patients' own weight, as applicable. Two parallel groups were established, each with a maximum of 10 participants. A facilitating nurse attended the group each time and offered individual consultations immediately after the group session or arranged consultations with other members of the palliative rehabilitation team, if needed.

Before entering the group program, the patient met with a physiotherapist who introduced the program, tested the patient's performance level, set a shared and realistic goal for the 12-week intervention, and, if relevant, made instructions for supplementary home exercises. The performance tests applied were 6-min walk, hand grip strength measurement, and

Table 1 Contents of the group educational program for patients and family caregivers

Topic	Responsible healthcare professionals
Body and movement	Physiotherapist and facilitating nurse
Sleep and tiredness	Two nurses (one being the facilitating nurse)
Breathlessness	Physiotherapist and facilitating nurse
Fatigue	Occupational therapist and facilitating nurse
Nutrition	Dietician and facilitating nurse
Coping with the patient role	Psychologist and facilitating nurse
Open session	Physician and facilitating nurse
Coping with the caregiver role	Psychologist and facilitating nurse
When life hurts	Hospital chaplain and facilitating nurse
Financial and social issues	Social worker and facilitating nurse
Open session	Psychologist and facilitating nurse
Rest and relaxation	Physiotherapist and facilitating nurse

sit-to-stand ability [12–14]. At the end of the 12-week program, a final, individual evaluation with the facilitating nurse and physiotherapist was offered. The physical performance tests were repeated, and the patients advised individually on how to maintain the obtained results. A summary of the intervention and future directions was documented in the electronic patient record and sent to the patient's general practitioner.

Setting

The specialised palliative care team is organised under the Department of Oncology, Vejle Hospital. The team has 15 years of experience in treating patients with life-threatening illnesses and their caregivers, predominately as home-based specialised palliative care and in the late phases of the disease.

In connection with the establishment of the palliative rehabilitation outpatient clinic, the team moved to new facilities adjacent to the hospital with outpatient consultation rooms, group rooms, lounge areas, and physical exercise facilities. All members of the team received 3 days of formal training before the new clinic was established, a 1-day course by a Danish PhD in Health Education teaching about group dynamics and the facilitator role in health services and a 2-day visit from researchers and palliative rehabilitation clinicians Gail Eva and Cathy Payne from the British and Irish Health Systems, respectively. Two nurses were appointed to have a facilitating role in the group program.

Patients

Patients diagnosed with non-resectable solid cancer for the first time within 8 weeks of randomisation who were receiving standard oncology treatment were eligible for participation in the RCT. Details on study design and eligibility criteria have previously been reported [15].

Data collection

Before randomisation, baseline characteristics were registered and patients were asked to select the "primary problem" they needed help with from a list of 12 possible problems corresponding to scales in the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30). EORTC QLQ-C30 consists of 15 scales and is an extensively validated and widely used questionnaire for assessing symptoms and quality of life in cancer patients [16]. A 13th option on the list was "none of the above". Diarrhoea, financial difficulties, and global health status/quality of life were not included as possible primary problems.

All contacts with the palliative rehabilitation team, including individual consultations with family caregivers, were registered prospectively. The themes of the individual supplementary contacts were categorised by means of a retrospective review of the patient records. One main theme was chosen to represent each contact. Twelve weeks after enrolment, patients were given an evaluation form asking if they agreed, partly agreed, or disagreed with the statements "The intervention made a positive difference to me" and "I would recommend the intervention to others in a situation like mine". The evaluation form for participants in the group program also included the following statements: "It was a positive experience to spend time with others in the same situation" and "The physical exercise program improved my wellbeing".

Data analyses

Descriptive statistics were applied and included median and range of continuous variables, and number and percentage of categorical variables. All data analyses were performed using the statistical package, STATA, version 14 (StataCorp 2015, TX, USA).

Results

Between December 2014 and December 2017, 132 adults with newly diagnosed advanced cancer were seen in the palliative rehabilitation outpatient clinic after enrolment in the RCT. Baseline characteristics and primary problems selected by the participants appear from Table 2.

After the initial consultation, participants were distributed as follows: 20% received the two mandatory consultations only ($n = 26$), 45% additionally participated in the group program ($n = 59$), and 35% received supplementary individual consultations without participating in the group program ($n = 47$).

The contents of the offer divided by primary problem as selected by the patient at baseline can be seen in Table 3.

Of the 59 patients who entered the group program, 83% ($n = 49$) had one or more supplementary individual consultations. Patients in the group program participated in an average of 10 of the 12 planned weekly sessions (median = 10, range 1–13) and had an average of five individual non-mandatory supplementary contacts (median = 5, range 0–21). Patients receiving supplementary individual consultations without participating in the group program had an average of three non-mandatory contacts (median = 2, range 1–18).

Apart from the planned individual elements (i.e. the two mandatory consultations in the basic offer and the introduction and test by a physiotherapist for participants in the group program), patients received 411 individual consultations. The distribution and themes of these consultations can be seen in Fig. 3.

Table 2 Baseline characteristics and "primary problem" chosen by patients

Characteristics	Patients ($N = 132$)
Mean age, years (SD)	66 (9)
Age group, *N* (%)	
18–59	27 (20)
60+	105 (80)
Sex, male, *N* (%)	77 (58)
Education, ≤ 13 years, *N* (%)	84 (65)
Married or partnered, *N* (%)	93 (70)
Cancer type, *N* (%)	
NSCLC	36 (27)
SCLC	16 (12)
Breast cancer	11 (8)
Colorectal cancer	35 (27)
Prostate cancer	24 (18)
Gynaecological cancer	4 (3)
Other	6 (5)
Intention of oncology treatment, *N* (%)	
Potentially curative	23 (17)
Non-curative	109 (83)
ECOG performance status, *N* (%)	
0	52 (39)
1	65 (49)
2	15 (11)
Primary problem chosen by patient, *N* (%)	
Physical function	10 (8)
Role function	11 (8)
Emotional function	15 (12)
Cognitive function	4 (3)
Social function	1 (1)
Fatigue	11 (8)
Nausea and vomiting	4 (3)
Pain	14 (11)
Dyspnoea	10 (8)
Insomnia	11 (8)
Appetite loss	5 (4)
Constipation	1 (1)
None of the above	33 (25)
Missing value	2 (–)

The sum of percentages may not reach 100 because of rounding

NSCLC non-small cell lung cancer, *SCLC* small cell lung cancer, *ECOG* Eastern Cooperative Oncology Group, *SD* standard deviation

Family caregivers

Half of the participants brought one or more family caregivers to the initial consultation ($n = 67$), and half of the participants in the group program brought a family caregiver to the weekly sessions ($n = 29$).

Individual consultations with family caregivers consisted of ambulatory solo consultations with a psychologist ($n = 18$), ambulatory consultations ($n = 3$) and telephone consultations ($n = 9$) with a nurse about coping, and telephone consultations with a social worker ($n = 9$).

Coordination of care

Part of the intervention was the coordination of care with other healthcare professionals and institutions. The specialised palliative care physicians referred a patient to another hospital department or to the general practitioner due to unmanaged comorbidity 16 times during the study. Other types of coordinated care were the establishment of community-based occupational therapy ($n = 8$), community-based home nursing ($n = 7$), community-based physiotherapy ($n = 5$), and social worker contact to the patient's municipal authorities ($n = 4$).

Participant evaluation

Twelve weeks after enrolment, 122 of the 132 participants were eligible for evaluation (four died before 12 weeks, one withdrew consent, and five were not given the evaluation form, because the staff considered it inappropriate in the situation). The evaluation form was completed by 80% of the eligible participants ($n = 97$) of which 80% ($n = 78$) agreed that the intervention had made a positive difference, 15% ($n = 15$) partly agreed, and 4% ($n = 4$) disagreed. When asked if they would recommend the intervention to others in the same situation, 93% ($n = 90$) agreed, 7% ($n = 7$) partly agreed, and no one disagreed.

For participants in the group program, 82% ($n = 46$) of the respondents agreed that it had been positive to spend time with others in the same situation, 17% ($n = 9$) partly agreed, and 1% ($n = 1$) disagreed. When asked if the physical exercise program had improved their well-being, 88% ($n = 49$) agreed, 9% ($n = 5$) partly agreed, no one disagreed, and two did not answer the question.

Termination or continuation of care

The intervention was designed to be time-limited, and ultimately 84% of the participants ($n = 111$) were discharged from the palliative rehabilitation clinic after having received the planned intervention. The average time from first to last contact with the team was 76 days (median 70, range 3–196).

On the other hand, 17 participants (13%) were evaluated to still need specialised palliative care and were either referred to the team's home-based palliative care function ($n = 11$), their local specialised palliative care team ($n = 4$), or admitted to a hospice ($n = 2$).

Table 3 The intervention received divided by "primary problems" chosen by patients at baseline

	Intervention received			Total
	"Basic offer" only *N*	Group program (with or without individual contacts) *N*	Supplementary individual contacts without group program *N*	*N*
A specific "primary problem" chosen*—total	12	51	34	97
Physical function	2	5	3	10
Role function	1	6	4	11
Emotional function	3	8	4	15
Fatigue	1	8	2	11
Digestive symptoms** (appetite loss, nausea and vomiting, and constipation)	0	5	5	10
Pain	1	6	7	14
Dyspnoea	2	5	3	10
Insomnia	1	7	3	11
Other** (social function and cognitive function)	1	1	3	5
"None of the above" chosen as primary problem	12	8	13	33
Missing value for primary problem	2	–	–	2
Total N (%)	26 (20)	59 (45)	47 (35)	132 (100)

*Primary problem chosen by patients from a list of 12 possible problems correlating to scales in EORTC QLQ-C30 or "none of the above". Two missing values

**"Primary problems" combined due to few observations

Discussion

This paper presents a flexible model of multidisciplinary, integrated palliative rehabilitation to patients and their family caregivers early in the course of advanced cancer treatment combining a group program and individual consultations. The model was designed to match the needs of individual patients and caregivers and is presented in detail together with an analysis of its utilisation during an RCT and how it was received by the patients.

In this cohort of newly diagnosed advanced cancer patients, 20% did not need palliative rehabilitation in excess of the basic offer of two mandatory consultations. The largest group of 45% additionally entered the group program with the majority receiving one or more supplementary individual consultations (83%). Finally, 35% of the participants received supplementary individual consultations without entering the group program.

The patients were expected to have conflicting schedules due to anticancer treatment, comorbidity, and possible deterioration potentially making weekly attendance in a group program difficult. At the same time, a group offer had obvious administrative benefits in addition to the possibility for the participants to form relationships with the staff and other people in a situation like their own. This was highlighted as the main outcome of a 2005 review of British specialist palliative day-care offers [17]. In the present study, the participants also found it beneficial to spend time with others in the same situation. During the test and preparation phase, it was a focal point of the participants that the educational session would not last too long allowing sufficient time for questions, debate, and the exchange of personal experiences. Thus, the initial 45 min of lecture was ultimately cut down by more than half to 20 min, leaving 40 min for the less formal part of the 1-h session. Ground rules for the debates were secured by information to all participants about discretion and absolute confidentiality.

The groups were mixed in terms of diagnoses, primary problems, and other potentially predictive variables. The first group program tested during the preparation phase assigned the patients to different groups depending on their main problem (e.g. fatigue group, cognitive impairment group, and dyspnoea group). However, the participants and staff found this division to be artificial and noted that the problems, symptoms, and worries presented by the patients and caregivers were more universal than first assumed. Also, the participants did not mind that not all subjects in the group educational program were of equal relevance in their present situation. On the contrary, it was evaluated as one of the strengths of the program that participants were given pieces of information that provided them with more knowledge of potential future complications and where to seek more information and help at a later stage in their disease trajectory, if relevant—thereby

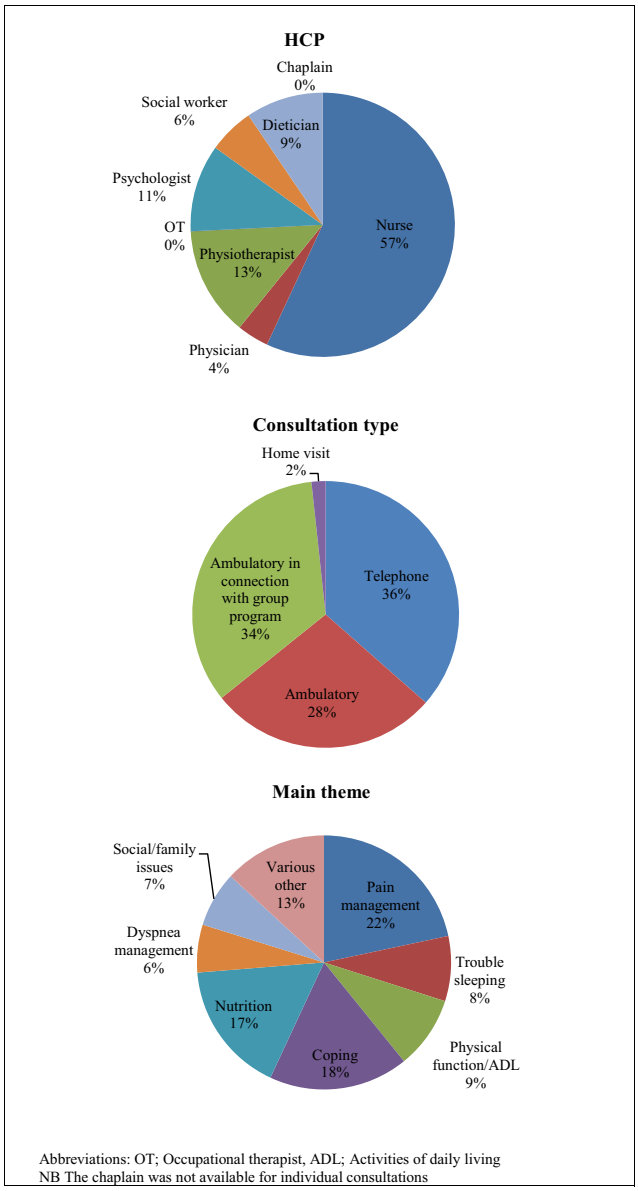


Fig. 3 Supplementary, individual patient consultations ($N = 411$) distributed by responsible healthcare professional (HCP), type of consultation, and main theme

enhancing the self-efficacy of patients and family caregivers. The attendance in the group program was high with a median of 10 out of the 12 planned weekly meetings.

Patients participating in the group program had more individual contacts than participants receiving supplementary consultations without participating in the group program. This finding does not necessarily reflect a greater need for individual consultations among the group program participants but maybe rather that the relationship building of patients and caregivers with healthcare professionals is an important mechanism in palliative care [18]. Hence, participation in the group program itself may have led to a higher identification of needs.

When patients were asked before randomisation what they needed help with the most, the largest group did not choose any of the 12 possible primary problems but instead the 13th option none of the above (25%) (Table 2). Other large groups were participants selecting emotional function (12%) and pain (11%) as their primary problem. However, 64% of the patients who indicated at baseline that they did not need help with any of the possible primary problems ultimately received more than the basic offer—either as part of the group program or as supplementary individual consultations (Table 3). Of the patients who selected a specific primary problem, 12% had no need for palliative rehabilitation other than the two mandatory consultations. This suggests that if the initiation of an intervention is based solely on a patient's perception of needs, an important point may be missed, namely that the true establishment of a need may occur in the meeting of patient values and preferences with healthcare professionals' assessments and knowledge of potentially beneficial and accessible interventions. Also, irrespective of the patient's perceived needs, many family caregivers have unmet needs and would like more information, preparation, and support to assist them in the caregiving role [19]. This supports the design of the study with highly individualised interventions only fully determined after the patient and caregivers had met the palliative rehabilitation team.

Unfortunately, in this cohort only, around half of the participants brought a family caregiver to the palliative rehabilitation clinic, which means that the full potential of the support offer to the caregivers was probably not met.

Nurses were the responsible healthcare professionals in the majority of individual consultations (55%), and 70% of the consultations were either conducted over the telephone or in connection with participation in the group program keeping the use of resources low (Fig. 3).

No individual consultations with an occupational therapist (OT) took place during the study. This is probably due to the fact that the team's physiotherapists manage many of the tasks that could be provided by OTs, e.g. guiding in ADL and instructing in the use of assistive devices. Additionally, the specialised palliative care physiotherapists refer the patients to community-based occupational therapy if a need for ongoing support is identified. This happened eight times during the study.

In this cohort, 13% of the patients were re-directed to hospice or home-based specialised palliative care. Early palliative care is not generally implemented in healthcare [8], and this is also true in a Danish context with the median survival time after referral to specialised palliative care in 2016 being 39 days [20]. The model presented here efficiently identified the patients in need of ongoing specialised palliative care already at the onset of their disease.

Some limitations of the investigation must be noted. The study population was based on participants of an RCT, and generalisation of the results should be considered in that light. The participants were relatively well educated, not living alone, and in good performance status, which may lead to "healthy volunteer bias", a well-known challenge in palliative care trials [21].

Themes of the individual contacts were established retrospectively by reviewing patient records. It might have been more accurate to give team members a checklist for registration immediately after the contact as was done in a newly published evaluation of the elements of an American early palliative care intervention by Hoerger et al. [22]. However, the finding in our study that pain management and coping (22% and 18%, respectively) were the main themes of the individual consultations is consistent with the findings of Hoerger et al.

A third major theme in this study was nutrition, which accounted for 17% of the individual consultations. This finding emphasises the relevance of including the expertise of dieticians in quality of life-directed interventions for newly diagnosed, advanced cancer patients.

Conclusion

In conclusion, the flexibility of the palliative rehabilitation model presented here allowed for consideration of the needs of individual patients and caregivers. In this cohort of newly diagnosed, advanced cancer patients, the use of resources was relatively low and the patient satisfaction was very high. The main themes of the individual consultations were pain management, coping, and nutrition. Patients who entered the group program had a high degree of adherence.

Long-term follow-up, comparison of clinical outcomes between patients enrolled in this model and patients in standard care as well as an economic evaluation will be reported later when mature data from the RCT are available.

This new model of palliative rehabilitation could serve as an inspiration to other cancer centres wanting to integrate palliative care into standard oncology services early in the disease trajectory of advanced cancer.

Acknowledgments The authors first and foremost wish to thank the patients and family caregivers participating in the study and the Patient and Relatives Council of Vejle Hospital for important input and inspiring discussions. We thank the Danish Cancer Society for conducting by invitation-only workshops during the trial period with valuable exchange of knowledge with other researchers working with patient and caregiver involvement. We thank the employees in the palliative rehabilitation team, especially facilitating nurses Birgitte Skov Zellweger and Grethe Misser Hansen for their important contribution to the study. We thank Karin Larsen for linguistic editing of the manuscript.

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Compliance with ethical standards

All procedures performed in this study were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments. Informed consent was obtained from all individual participants included in the study.

The study protocol, including all written material intended for study participants, was approved by The Regional Committees on Health Research Ethics for Southern Denmark on April 2, 2014 (Project ID S-20140038).

Conflict of interest The authors declare that they have no conflict of interest.

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Appendix 6

Paper III (draft)

Title page

The effect of individually tailored, multidisciplinary, palliative rehabilitation for patients with newly diagnosed advanced cancer: the Pal-Rehab randomized controlled trial

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Running head

Palliative rehabilitation in advanced cancer.

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List of presentations

The abstract was presented at the ASCO Palliative & Supportive Care in Oncology Symposium on November 16th, 2018.

Abstract

Purpose The aim of the trial was to test the effect of systematic palliative rehabilitation on the quality of life of newly diagnosed advanced cancer patients.

Methods At Vejle Hospital, Denmark, adults diagnosed with advanced cancer within the last eight weeks were randomized 1:1 to standard oncology care or standard care plus palliative rehabilitation. The intervention consisted of two mandatory consultations and a 12-week opportunity of contacting a specialized palliative care team, if needed. The team additionally offered a multidisciplinary group program, supplementary individual consultations, or both.

Assessments at baseline and after six and 12 weeks were based on short forms representing the scales of EORTC QLQ-C30. At baseline participants were asked to choose a "primary problem" from a list of 12 possible symptoms/problems corresponding to 12 of the 15 QLQ-C30 scales. The primary endpoint was the change in that "primary problem" measured as area under the curve (AUC) across the 12 weeks. Scales were scored using T-scores (European mean value =50, SD=10). Blinding was applied during allocation, data management, and statistical analysis.

Results Between Dec 3, 2014, and Dec 22, 2017, 1303 patients were screened of whom 288 were randomized. Ultimately, 279 patients were included in the modified intention-to-treat analysis (146 in the standard care group and 133 in the palliative rehabilitation group).

The absolute between-group difference for the primary outcome (AUC) was 3.0 (95% CI 0.0-6.0; p=0.047) favouring the intervention group. A sensitivity analysis of the change from baseline to 12 weeks later showed an absolute difference of 3.3 (95% CI 1.0-5.6; p=0.005).

Conclusion A palliative rehabilitation intervention initiated soon after diagnosis and integrated into standard oncology treatment improved quality of life.

The trial is registered with ClinicalTrials.gov, number NCT02332317.

INTRODUCTION

Palliative care is defined as an approach aiming to improve the quality of life (QoL) of patients and their families facing the problems associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual.[1] Early palliative care is provided alongside active disease treatment such as chemotherapy or radiotherapy and is recommended by international cancer and health organisations.[1–3]

Rehabilitation and palliative care share the goal of improving QoL, emphasize patient and family centred care, and focus on achieving patient goals through a multidisciplinary approach.[4]

Palliative rehabilitation can be defined as function-directed care delivered in partnership with other disciplines and aligned with the values of patients who have serious and often incurable illnesses in contexts marked by intense and dynamic symptoms, psychological stress, and medical morbidity, to realize potentially time-limited goals.[5]

Early palliative care and rehabilitation services for advanced cancer patients are both underutilized [6, 7] and research on palliative rehabilitation is sparse. [8]

We designed this study to investigate whether QoL is improved by systematic use of palliative rehabilitation in the form of a 12-week individually tailored, multidisciplinary program initiated shortly after an advanced cancer diagnosis and integrated into standard oncology care.

METHODS

Study design and participants

In this randomized, parallel-group controlled trial patients with newly diagnosed non-resectable cancer were recruited from the Department of Oncology, Vejle Hospital. Eligible patients were 18

years or older and diagnosed with a solid tumour for the first time within the last eight weeks, where the first choice of treatment was systemic. Complete surgical removal of the malignant tissue was either ruled out or depended on the success of the systemic treatment. Patients with advanced prostate cancer were eligible if referred to the Department of Oncology for systemic treatment for the first time within the last eight weeks. Patients were excluded from participation if they were not eligible for or refused standard oncology treatment, could not comply with study procedures due to cognitive or other impairments or language barriers, or if they had received specialised palliative care (SPC) within a year prior to enrolment.

Study participants were enrolled following written and verbally informed consent. The study protocol, including the written material intended for potential study participants and the informed content sheet, was approved by The Regional Committee on Health Research Ethics for Southern Denmark on April 2nd, 2014 (Project ID S-20140038). The study design and set-up was discussed thoroughly and approved by the hospital's Patient and Relatives Council.

Details of the study protocol appear in a previous publication.[9]

Randomisation and masking

Patients were randomly assigned (1:1) to standard oncology care or standard oncology care plus an offer of palliative rehabilitation. The randomization list was made at randomizer.org without stratification.[10] The allocation sequence was available to an independent research nurse only and was unknown to the investigators and all personnel involved in recruitment. Study documents were labelled with unique identification numbers. After the allocation of study participants blinding of the personnel directly involved in patient care was not possible.

In the analysis phase, all study documents for outcome measures were double-entered manually by blinded personnel and merged afterwards using the Research Electronic Data Capture -software (REDCap). [11] The statistician carrying out the analyses was blinded to intervention allocation.

Procedures

Standard care was provided at the discretion of the medical oncologist. In Denmark standard oncology care entails the possibility of initiating supportive, palliative, and rehabilitative services alongside the disease specific treatment. The SPC team at Vejle Hospital is organized under the Department of Oncology and all local communities in the region of the hospital offer cancer rehabilitation. The department collaborates with the hospital's dieticians and physiotherapists. For psychosocial support the department occupies chaplains, psychologists, and social workers. Health care in relation to cancer, palliative care, and rehabilitation is publicly funded in Denmark and almost entirely free of charge for patients.

For this study a new function of palliative rehabilitation was developed in an out-patient clinic under the SPC team. The usual members of the SPC team counting physicians, nurses, physiotherapists, and psychologists were supplemented by part time engagement of an occupational therapist, a dietician, a social worker, and a chaplain to form the palliative rehabilitation team.

Patients allocated to the intervention arm were systematically offered palliative rehabilitation concurrently with the standard oncology treatment. The "basic offer" of palliative rehabilitation was 1) a one-hour consultation with a physician and a nurse specialized in palliative care as soon as possible and preferably within one week after enrolment, 2) a 40-minute consultation with an SPC nurse six to seven weeks after enrolment, and 3) a 12-week possibility of contacting the palliative rehabilitation out-patient clinic. The intervention was designed to be tailored to individual patient and caregiver needs. Thus, in addition to the two individual consultations in the "basic offer",

patients and family caregivers could be offered participation in a 12-week patient/caregiver school combined with individually tailored physical exercise in groups (Fig. 1), individual consultations with members of the palliative rehabilitation team, or both.

A template was made for the initial consultation that would address symptoms, mood, barriers to activities of daily living (ADL), illness and prognostic understanding, thoughts and goals for the future, a map of the patient's family and network, coping mechanisms, and individual needs of the family caregiver(s). A summary and plan was registered in the electronic patient file shared by the Department of Oncology. Patients were discussed at least once at a multidisciplinary, palliative rehabilitation team conference.

Potential study participants were approached by a nurse or a physician in the oncology clinic if deemed eligible by a research assistant. When patients gave their consent to participate the clinician filled in a sheet of baseline characteristics. If the patient declined participation, anonymised demographic characteristics were registered, possibly together with a reason for declining. Before randomization and at six and 12 weeks after enrolment all study participants were asked to complete a questionnaire consisting of short forms measuring the domains (symptoms and functions) of the European Organisation for Research and Treatment of Cancer Quality of Life Core Questionnaire (EORTC QLQ-C30). The questionnaire consists of 30 items forming 15 scales and is validated and widely used for assessing QoL in cancer patients.[12] Recently, the EORTC Quality of Life Group has developed computerized adaptive testing (CAT) versions of all EORTC QLQ-C30 domains except the Global health status/QoL.[13] The paper version of the short forms designed for this study included all the original items from EORTC QLQ-C30. Additionally, members of the palliative rehabilitation team chose extra items from the CAT item banks (calibrated collection of items) available at the time of designing the study for more precise measurements within the existing scales (see details in supplemental material).

Participants were asked at baseline to choose a "primary problem" that they needed help with the most from a list of 12 possible symptoms/ problems and a 13th option of "none of the above" (Table 1). The 12 possible symptoms/problems each corresponded to an EORTC QLQ scale/ -short form. After six and 12 weeks the patients were asked on a separate form if they had received help with the primary problem chosen at baseline (yes/no).

Outcomes

The primary outcome was the change since baseline in the score representing the problem prioritized by the patient. If the patient chose "none of the above" the global health status/QoL scale was used for measurements.

Group comparisons of whether or not the patients felt they had been helped with their "primary problem" six and 12 weeks after baseline are also reported (secondary outcome).

Information on adverse events can be found in the supplemental material.

Statistical analysis

Scales based on the EORTC CAT item banks are scored using item response theory (IRT) based T-scores without a fixed upper and lower limit but centred so that the European general population has mean=50 and standard deviation (SD)=10. At the time of trial design no data were available for sample size calculation based on the IRT-based scoring system and hence, the sample size was estimated based on studies using the original EORTC QLQ-C30 and a chosen SD of 25. To obtain a power of 90% to detect a group difference of 10 points for the primary outcome, the required sample size was calculated as 266 (133 in each study arm). We decided to aim for a sample size of 300 to allow for a drop-out of approximately 10%.

The significance level was set at 0.05 and a modified intention-to-treat (ITT) analysis was conducted meaning that screen failures, patients who withdrew their consent to participate, died

before 12 weeks, or did not have a baseline assessment were excluded from the primary outcome analysis.

Analyses were made with SAS® statistical software version 9.4.[14] Multiple imputations were based on the same potentially predictive baseline variables as mentioned below. [15]

Each outcome was estimated as the change from baseline to the weighted mean of the six and 12-week follow-up measured as area under the curve (AUC) for the EORTC-QLQ short form scale representing the "primary problem" chosen by the patient. The analyses were performed as multiple regressions adjusted for the variables believed to be of predictive importance, i.e. ECOG performance status, sex, age, intention of the oncology treatment (potentially curative or non-curative), primary diagnosis, living status, educational background, and primary problem. The decision to adjust for potentially predictive variables in the main analysis was made before any analyses were conducted but is a change from the previously published statistical analysis plan. [9] The decision was based on recommendations from Kahan et al. stating that covariate adjustments should be routinely incorporated into the analysis of randomized trials. [16]

As a sensitivity analysis, the primary analysis was repeated for the change from baseline to the six and 12-week follow-up, respectively.

An explorative analysis was performed as a test for interactions between the intervention variable and the predictive variables used in the primary analysis. We used the observed data and a linear regression model.

Group comparisons of whether or not the patients felt that they had been helped with their "primary problem" six and 12 weeks after baseline were made with Chi squared tests on observed data.

RESULTS

Between Dec 3, 2014 and Dec 22, 2017, 1,303 patients were screened of which 804 were eligible. A total of 288 patients with newly diagnosed advanced cancer were randomly assigned to receive standard oncology care (n=149) or the same care supplemented with palliative rehabilitation (n=139) (Fig. 2). Ultimately, 279 patients were included in the modified intention-to-treat analysis with 146 patients in the standard care group and 133 patients in the palliative rehabilitation group. Baseline characteristics and "primary problems" chosen at baseline appear from Table 1. Differences in baseline characteristics between participants and non-participants can be seen in Table 2. The analyses were repeated comparing the 279 included in the primary analysis with the non-participants without altering the results.

The score of the "primary problem" significantly improved during the 12-week participation period in patients receiving palliative rehabilitation compared to those receiving standard oncology care alone with an absolute group difference of 3.0 (95% CI 0.0-6.0; p=0.047) (Table 3). The results of the sensitivity analyses also appear from Table 3.

At six weeks, 60% in the palliative rehabilitation group agreed that they had received help with their primary problem vs. 48% in the standard care group, p=0.133. At 12 weeks significantly more patients in the group receiving palliative rehabilitation agreed that they had received help (75%) compared to the standard care group (51%), p=0.002.

Explorative analysis of interactions showed no correlation between the effect of the intervention and the predictive variables included in the multiple linear regression model except for a borderline significant effect for sex (better effect for females) and a significant effect for "intention of oncology treatment" (better effect for patients receiving treatment with non-curative intent than those treated with potentially curative intent).

Eighteen patients dropped out of the study based on withdrawn consent (n=10) or other types of non-random withdrawal (n=8). All were in the palliative rehabilitation arm. One patient withdrew the consent after the initial SPC consultation and similarly, one patient did not want to complete further study procedures after the initial consultation. The remaining 16 patients dropped out before any consultation had taken place. Reasons for dropping out were "feeling no need" (n=3) and "feeling too overwhelmed by the idea of paying extra visits to the hospital in the current situation" (n=15).

The median time from randomization to the initial consultation with an SPC physician and a nurse for 132 of the 139 (95%) patients allocated to the palliative rehabilitation group was 11 days (IQR 7-16). The distribution of participants in the palliative rehabilitation arm after the initial consultation appear from Figure 3.

Patients in the group program participated in an average of 10 of the 12 planned weekly sessions (median=10, IQR 9-11) and had an average of five individual supplementary contacts (median=5, IQR 3-8). Patients who received supplementary individual consultations without participating in the group program had an average of three additional contacts (median=2, IQR 1-3).

While the intended intervention period was 12 weeks, 26% of group sessions and 18% of individual consultations took place after 12 weeks.

DISCUSSION

In this study an early integration of palliative rehabilitation into standard oncology care significantly improved QoL among patients diagnosed with advanced cancer. A patient-individualised outcome was used to measure the effect of the intervention on the main symptom/problem prioritized by the patient, thus emphasising the relevance of the intervention across the heterogeneous nature of individual QoL.

The result was obtained by combining six and 12-week follow-up data. When the analysis was repeated for the change from baseline to 12 weeks, the result was highly significant. This finding was mirrored in the fact that significantly more patients in the palliative rehabilitation group agreed that they had been helped with their "primary problem" after 12 weeks compared to the standard care group.

To our knowledge this is the first time a randomized controlled study has combined elements of cancer rehabilitation and palliative care and tested the effect of integrating this combination into standard oncology care early in the disease trajectory of advanced cancer. We also believe it is the first time a study of early palliative care has been conducted with the aim of improving a domain of QoL prioritized by the patient.

The overall result of the study adds to the evidence presented in a 2017 review and meta-analysis by the Cochrane group concluding that early palliative care interventions may have more beneficial effects on quality of life and symptom intensity than usual/standard cancer care alone among patients with advanced cancer. [17] The studies were performed in North America, Europe, and Australia and included a total of 1614 participants. [18–24]

We designed the present study to measure the effect of the intervention over 12 weeks. Three previous trials on the integration of early palliative care into standard oncology care showed a significant improvement in QoL at 12 weeks [18, 19, 25] whereas another three found improvements at later time points.[20, 24, 26]

Our findings suggest that the effect of palliative rehabilitation increases with time, and we might have been able to show an even stronger effect if we had included a later follow-up assessment, e.g. after 18 weeks enabling us to assess the effect of the total intervention.

Explorative analysis of the primary outcome suggested the intervention to be most effective in women and in patients receiving oncology treatment with non-curative intent. These associations should be explored further in future research. Importantly, we found no interaction between the diagnosis or the primary problem chosen by the patient and the effect of the intervention.

The study has several methodological strengths. Blinding was used in all possible steps during allocation, data management, and analysis to reduce the risk of bias. The risk of confounding factors was reduced by using a multivariate regression analysis for the primary outcome.

Some limitations of the study must be noted. Firstly, the study was performed at a single centre due to the novelty of the intervention design, which may limit generalizability. Secondly, blinding of the treating personnel was not possible. Thirdly, attrition and gatekeeping are well known challenges in palliative care research and can lead to selection bias.[27] We found that participants were significantly younger and better educated than non-participants (Table 2). It is noteworthy that almost half of the patients invited to join the study declined participation and 18 patients allocated to the intervention either withdrew consent or did not want to stay in the study resulting in skewed attrition. The majority of this type of attrition happened before any intervention procedures had taken place, which questions the timing of the intervention. On the other hand, we know from a previous study of early versus delayed initiation of palliative care that the effect may be higher when the intervention is introduced closely after diagnosis as compared to three months later.[21] Also, inactivity may play a critical role in the interaction between symptom burden and functional decline and maintaining the motivation and desire to be mobile from the onset of the diagnosis may contribute to prolonged and improved QoL.[4, 7] More research is needed in order to establish the best timing of a palliative rehabilitation intervention.

It is not possible based on our findings to isolate the effective components. However, we mainly attribute the positive outcome to the flexibility of the intervention model to meet individual patient and family caregiver needs.

In conclusion, the quality of life of this mixed cohort of newly diagnosed advanced cancer patients was significantly improved in the group that received palliative rehabilitation concurrently with anticancer treatment as opposed to the group receiving standard oncology care alone. The study adds to the evidence on the effect of early integrated palliative care and offers additional and new knowledge of a highly flexible and multidisciplinary model of delivery based on the combination of elements of palliative care and cancer rehabilitation.

Contributors

MG and TV conceived the study and its design and have revised the manuscript with substantial contributions. MAP did the statistical analysis of the primary outcome and contributed with revision of the manuscript. LN did the literature search, data collection, remaining statistical analyses, and the first draft of this manuscript. LHJ sponsored the trial and revised the manuscript with a substantial contribution. All authors were involved in the data interpretation and read and approved the final manuscript.

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Table 1. Baseline characteristics and "primary problems" of 288 patients with newly diagnosed advanced cancer randomly assigned to receive standard oncology care or an additional offer of palliative rehabilitation. SD= standard deviation, NSCLC= non-small cell lung cancer, SCLC= small cell lung cancer, ECOG= Eastern Cooperative Oncology Group, EORTC= European Organisation for Research and Treatment of Cancer.

	Palliative rehabilitation group (N=139)	Standard care group (N=149)
Time from diagnosis to enrolment (days), mean ±SD	35±16	36±16
Age (years), mean ±SD	66±9	66±10
Age groups (years), N (%)		
18-59	28 (20)	34 (23)
≥60	111 (80)	115 (77)
Male sex, N (%)	80 (58)	89 (60)
Cancer site, N (%)		
NSCLC	37 (27)	45 (30)
SCLC	17 (12)	16 (11)
Breast cancer	11 (8)	8 (5)
Colorectal cancer	38 (27)	39 (26)
Prostate cancer	25 (18)	28 (19)
Gynaecological cancer	5 (4)	5 (3)
Other	6 (4)	8 (5)
ECOG performance score [a)], N (%)		
0	53 (38)	65 (44)
1	69 (50)	66 (44)
2	17 (12)	18 (12)
Education (years), N (%)		
≤10	15 (11)	23 (15)
11-12	32 (23)	35 (23)
≥13, not university	79 (57)	73 (49)
Academic	10 (7)	15 (10)
Missing	3 (2)	3 (2)
Living status, N (%)		
Married or partnered	96 (69)	114 (77)
Living alone	43 (31)	35 (23)
Intention of oncological treatment, N (%)		
Potentially curative	26 (19)	25 (17)
Non-curative	113 (81)	124 (83)
Status of disease, N (%)		
Locally advanced	23 (17)	20 (13)

Distant metastases present	116 (83)	129 (87)
Brain metastases present, N (%)	8 (6)	7 (5)
Bones the only metastatic site, N (%)	11 (8)	14 (9)
Primary problem chosen by patients, N (%)		
Physical function	10 (7)	22 (15)
Role function	11 (8)	11 (7)
Emotional function	15 (11)	19 (13)
Cognitive function	4 (3)	4 (3)
Social function	1 (1)	3 (2)
Fatigue	11 (8)	18 (12)
Nausea and vomiting	4 (3)	4 (3)
Pain	16 (12)	9 (6)
Dyspnoea	11 (8)	3 (2)
Insomnia	12 (9)	11 (7)
Appetite loss	5 (4)	4 (3)
Constipation	1 (1)	1 (1)
None of the above	35 (25)	40 (27)
Missing	3 (2)	-
Baseline values for EORTC short form scales [b)], mean ±SD		
Physical function	45±10	46±10
Role function	41±10	44±10
Emotional function	51±8	53±8
Cognitive function	50±8	49±9
Social function	49±7	50±7
Fatigue	54±9	53±8
Nausea and vomiting	55±11	54±9
Pain	51±9	48±8
Dyspnoea	54±11	52±10
Insomnia	51±9	49±8
Appetite loss	56±12	55±11
Constipation	52±9	50±9
Diarrhoea	53±10	52±9
Financial difficulties	49±5	50±7
Global health status/Quality of life	50±11	50±10

The sum of percentages may not total 100 because of rounding.
a) ECOG Performance status ranges from 0 to 4, 0=able to carry out all normal activity without restrictions, 4=completely disabled; totally confined to bed or chair.
b) Baseline values for EORTC short form scales for 279 patients included in the modified intention-to-treat analysis. T-scores centred with European mean value=50 (SD=10)

Table 2. Baseline characteristics of 288 participants and 290 non-participants. Non-participants declined participation (n=281) or regretted giving consent to participate (withdrew consent shortly after randomization (n=9)). Differences in categorical variables were tested with Chi-squared test. Difference in age was tested with Wilcoxon rank sum test. SD, standard deviation; ECOG, Eastern Cooperative Oncology Group.

	Participants (N=288)	Non-participants (N=290)	P-value
Age (years), mean ±SD	66±10	70±8	0.000
Male sex, N(%)	169 (59)	163 (56)	0.580
Cancer site, N(%)			0.001
Lung cancer	115 (40)	158 (55)	
Breast cancer	19 (7)	8 (3)	
Colorectal cancer	77 (27)	46 (16)	
Prostate cancer	53 (18)	46 (16)	
Gynaecological cancer	10 (3)	15 (5)	
Other	14 (5)	16 (6)	
ECOG performance status [a)], N (%)			0.506
0	118 (41)	104 (36)	
1	135 (47)	145 (51)	
2	35 (12)	38 (13)	
Education (years), N (%)			0.000
≤10	38 (13)	48 (25)	
11-12	67 (24)	77 (40)	
≥13, not university	152 (54)	61 (31)	
Academic	25 (9)	9 (5)	
Living status, N (%)			0.325
Married or partnered	210 (73)	200 (69)	
Living alone	78 (27)	89 (31)	

The sum of percentages may not total 100 because of rounding.
a) ECOG Performance status ranges from 0 to 4, 0=able to carry out all normal activity without restriction, 4=completely disabled; totally confined to bed or chair.

Table 3. Effect of the intervention on the "primary problem" chosen by the patient at baseline. An absolute between group difference >0 means the group receiving palliative rehabilitation had a greater improvement over the study period than the group receiving standard care alone. Measurements were made with short forms representing the scales in EORTC QLQ-C30 with extra items added from the EORTC Quality of Life group item banks for computer-adaptive testing to obtain more precise measurements. Scales were scored using T-scores centred so the European general population has a mean value of 50 (SD=10). Analyses were performed as multiple regressions adjusted for ECOG performance status, sex, age, intention of the oncology treatment (potentially curative or non-curative), primary diagnosis, living status, educational background, and primary problem. Imputed values were based on the same variables. AUC= area under the curve, CI= confidence interval, EORTC QLQ C-30= European Organisation for Research and Treatment of Cancer Quality of Life Core Questionnaire, SD= standard deviation.

Effect of the intervention	Absolute between group difference	95% CI	P-value
Overall effect over 12 weeks [a)]	3.0	0.0 to 6.0	0.047
Change from baseline to 6 weeks	1.3	-0.9 to 3.6	0.234
Change from baseline to 12 weeks	3.3	1.0 to 5.6	0.005

a) Primary outcome measure. AUC of the six and 12-week measurements combined.

Fig. 1. Model of one of the optional elements of the intervention: the palliative rehabilitation group program containing patient/caregiver school and individually tailored physical exercise in groups.

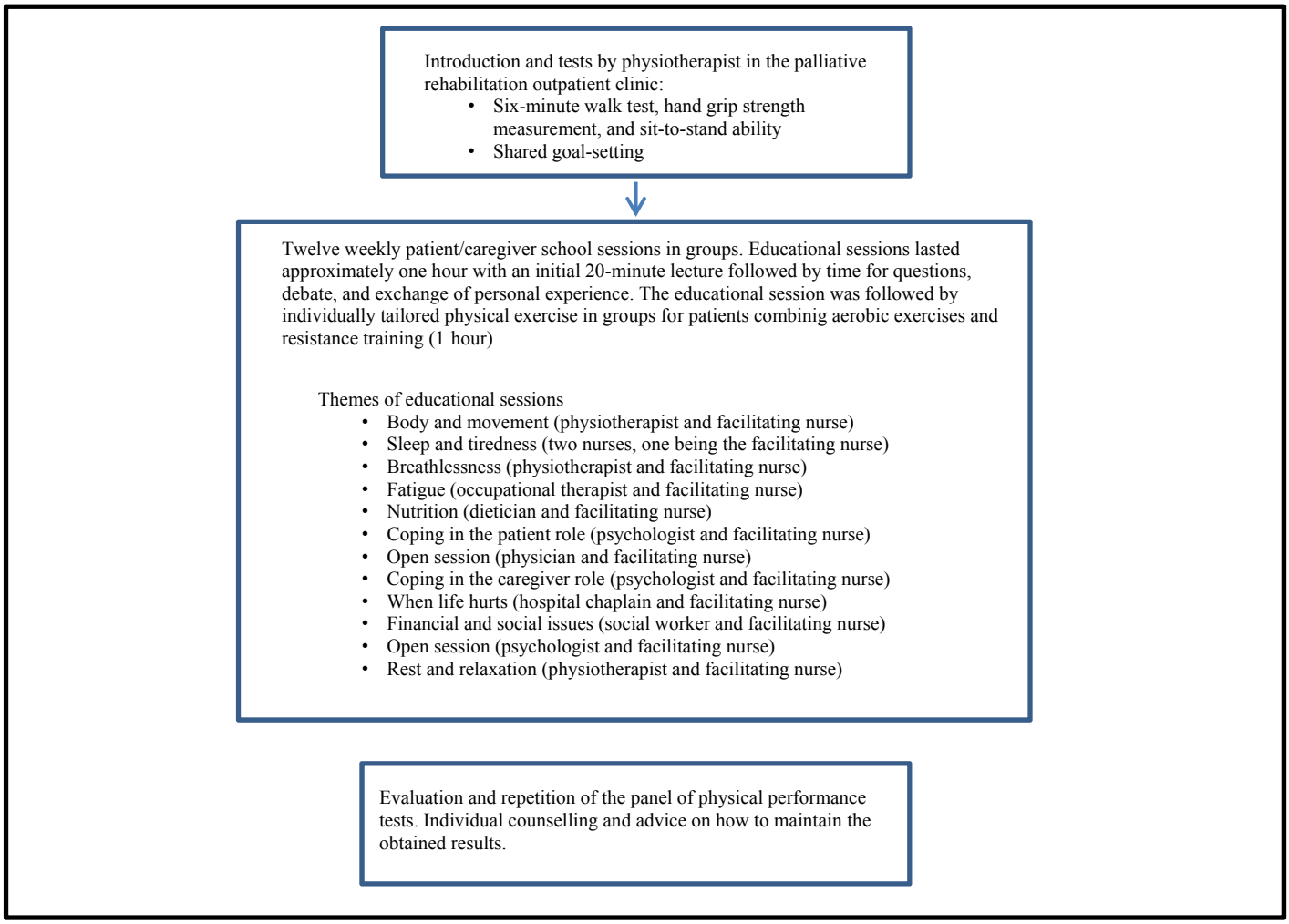


Fig. 2. Trial profile.

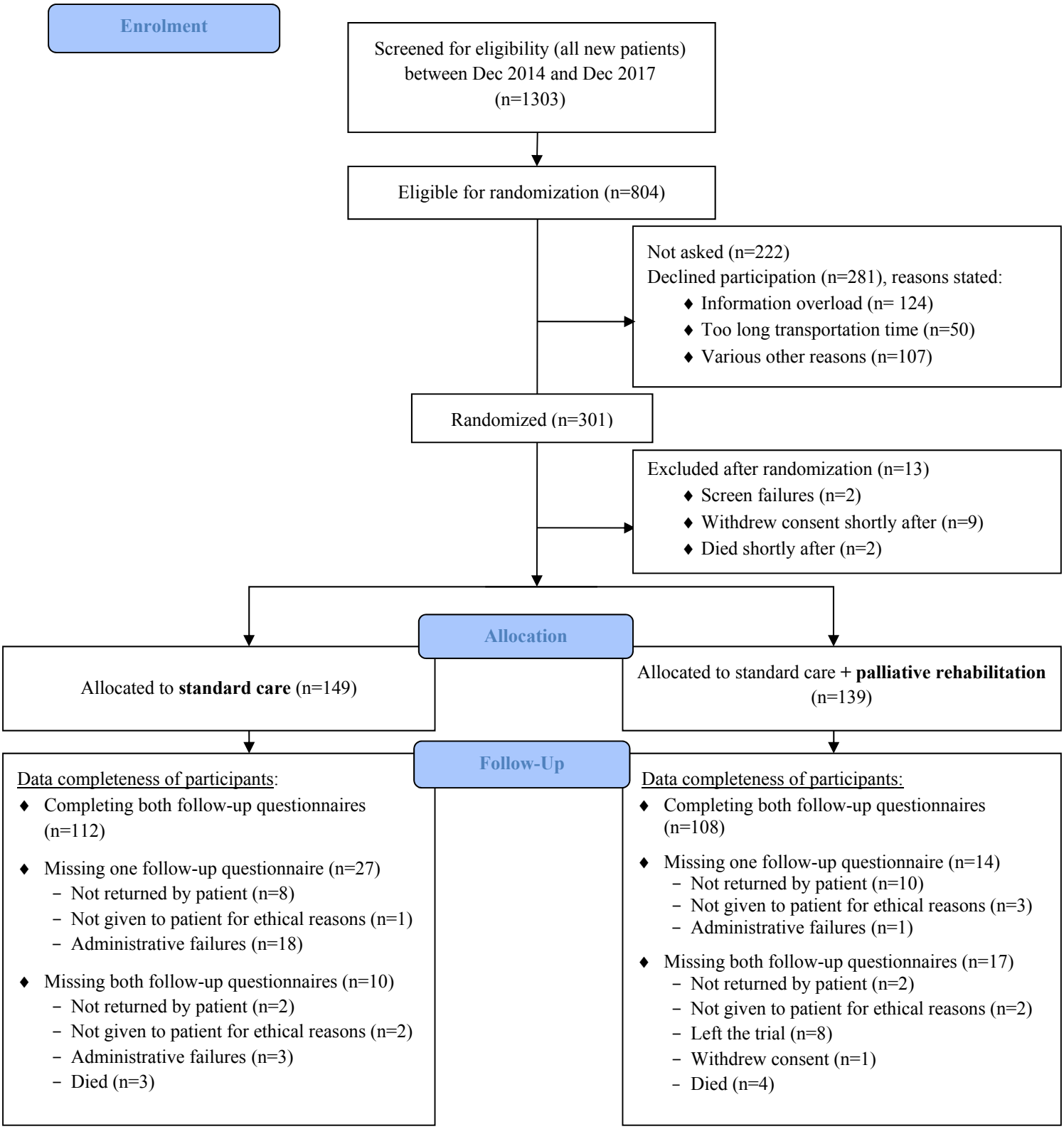
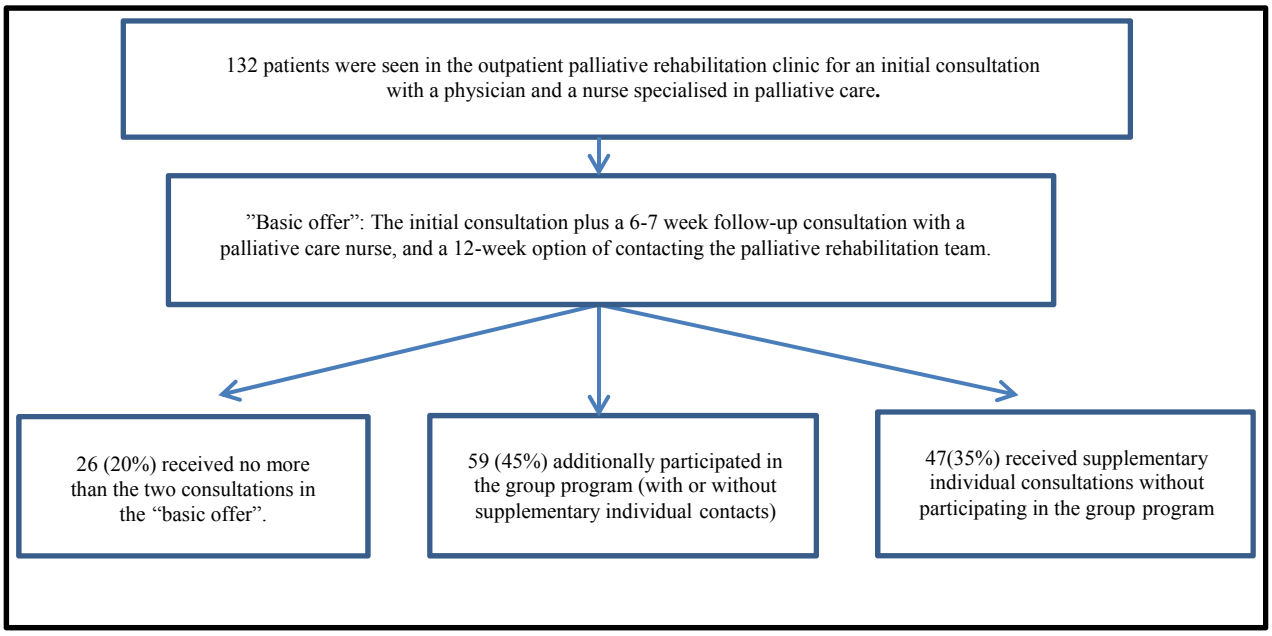


Fig. 3 Use of the palliative rehabilitation intervention during the study.



Supplemental material

Table A1. Overview of the number of items in the QLQ-C30 short form scales.

Short form scales	Original items (EORTC QLQ-C30 ver. 3.0)	Extra items added	Total number of items
Potential "primary problem"			
Physical function - PF2	5	0	5
Role function – RF2	2	2	4
Emotional function - EF	4	0	4
Cognitive function - CF	2	2	4
Social function - SF	2	2	4
Fatigue - FA	3	2	5
Nausea and vomiting - NV	2	2	4
Pain - PA	2	2	4
Dyspnoea - DY	1	3	4
Insomnia -SL	1	3	4
Appetite loss - AP	1	3	4
Constipation - CO	1	3	4
Others			
Diarrhoea - DI	1	0	1
Financial difficulties - FI	1	0	1
Global health status/QoL – QL2	2	0	2
Total	**30**	**24**	**54**

Table A2. Overview of adverse events.

	Adverse events	Comments
Control group	0	-
Palliative rehabilitation group	2	One participant felt the physical exercise worsened his nausea, and one participant said the questions asked in the initial consultation in the palliative rehabilitation outpatient clinic added to her emotional distress.