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Randomised clinical trial of early specialist palliative care plus standard care versus standard care alone in patients with advanced cancer: The Danish Palliative Care Trial

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Abstract

Background: Beneficial effects of early palliative care have been found in advanced cancer, but the evidence is not unequivocal.
Aim: To investigate the effect of early specialist palliative care among advanced cancer patients identified in oncology departments.
Setting/participants: The Danish Palliative Care Trial (DanPaCT) (ClinicalTrials.gov NCT01348048) is a multicentre randomised clinical trial comparing early referral to a specialist palliative care team plus standard care versus standard care alone. The planned sample size was 300. At five oncology departments, consecutive patients with advanced cancer were screened for palliative needs. Patients with scores exceeding a predefined threshold for problems with physical, emotional or role function, or nausea/vomiting, pain, dyspnoea or lack of appetite according to the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) were eligible. The primary outcome was the change in each patient's primary need (the most severe of the seven QLQ-C30 scales) at 3- and 8-week follow-up (0–100 scale). Five sensitivity analyses were conducted. Secondary outcomes were change in the seven QLQ-C30 scales and survival.
Results: Totally 145 patients were randomised to early specialist palliative care versus 152 to standard care. Early specialist palliative care showed no effect on the primary outcome of change in primary need (−4.9 points (95% confidence interval −11.3 to +1.5 points); $p = 0.14$). The sensitivity analyses showed similar results. Analyses of the secondary outcomes, including survival, also showed no differences, maybe with the exception of nausea/vomiting where early specialist palliative care might have had a beneficial effect.
Conclusion: We did not observe beneficial or harmful effects of early specialist palliative care, but important beneficial effects cannot be excluded.

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Keywords
Palliative care, advanced cancer, randomised clinical trial, quality of life, needs assessment, patient satisfaction, EORTC QLQ-C30

What is already known about the topic?

- We searched PubMed using the terms 'palliative care' and 'randomized controlled trial' and 'quality of life' and 'cancer'. Studies investigating palliative care at the end of life were excluded.
- Three individual-patient randomised controlled trials (RCT) and one cluster RCT investigating early multidisciplinary specialist palliative care (SPC) and three RCTs of advanced practice nurses (one with an initial SPC assessment) providing or coordinating early palliative care were identified.
- Taken together, these trials indicate that early SPC may improve the patients' quality of life, symptoms, survival and caregiver outcomes, but in several cases no effect of the interventions could be found.

What this paper adds?

- Following an Italian trial restricted to pancreatic cancer patients, this is the first European RCT investigating early SPC in patients with a range of diagnoses. The trial recruited advanced cancer patients from oncology departments in Denmark.
- Patients with palliative care needs according to a screening instrument were randomised between SPC (i.e. referral to a palliative care team) plus standard care versus standard care alone.
- We found no effect of SPC on the primary outcome or the secondary outcomes, including survival, maybe with the exception of nausea/vomiting where early SPC might have a beneficial effect.
- Possible explanations of the lack of positive effect are suggested: The intensity of early SPC provided in this trial may have been insufficient because the SPC teams had not developed a model for the new target group, other patients with more acute needs may have been prioritised, and there may have been compensation in the control group. Alternatively, previous observations may have been biased due to random errors.

Implications for practice, theory or policy

- Integration of SPC with oncology care has the potential to improve quality of life during the treatment of advanced cancer, leads to more patient-centred care and potentially even increases survival. The American Society of Clinical Oncology (ASCO) has recommended implementation of early SPC.
- The present RCT highlights the importance of carefully testing promising new health-care interventions in new settings.
- Future research is needed to clarify how to design effective early SPC in various health-care systems: which components of early SPC are effective for which patient groups at which points in the trajectory, and what is the best distribution of roles and responsibilities between SPC teams and other health-care professionals?

Background

Palliative care aims to improve quality of life (QoL) by alleviating symptoms and problems.[1] Specialist palliative care (SPC) is provided by health-care professionals whose main task is to provide palliative care.

In Denmark, referral to SPC is late: the median survival from first contact with SPC is only 6 weeks (96% of these patients had cancer).[2] Many patients with advanced cancer have complex symptoms or problems long before being in their terminal phase,[3–6] and the World Health Organization (WHO) recognises that SPC is applicable early in the disease trajectory.[7]

A recent systematic review with meta-analysis identified 43 randomised controlled trials (RCTs) investigating palliative care interventions in adults with life-limiting illness and found improvements in QoL and symptom burden.[8] Six North American trials have investigated the effect of early SPC in advanced cancer.[1,9–13] Three trials tested access to an integrated palliative care service versus no access to this service.[1,9,13] Temel et al.[9] found improved QoL and mood after 12 weeks and prolonged survival in 151 newly diagnosed lung cancer patients. A subsequent study from the same group found no effect of early SPC on QoL at 12 weeks but a positive effect at 24 weeks in 350 patients with lung or gastrointestinal cancer.[13] Zimmermann et al.'s[1] cluster-randomised trial included 461 advanced cancer patients and found no effect on the primary outcome (QoL at 3 months), but positive effects on some secondary outcomes including QoL and patient satisfaction mainly after 4 months.

Three trials were coordinated by advanced practice nurses. One trial ($N = 322$) investigated a psycho-educational palliative care intervention versus usual care in 322

patients and found positive effects on QoL and depressed mood during 1 year.[11,14] A subsequent trial ($N = 207$) used a fast-track design (30–60 days after diagnosis versus 3 months later) testing a slightly modified intervention including an initial SPC consultation and found no effects on patient-reported outcomes but better 1-year survival[10] and lower caregiver depression scores.[15] A third cluster-randomised trial ($N = 146$) compared a multidisciplinary intervention coordinated by an advanced care nurse to enhanced usual care (a manual on symptom management) and found no effect on patient-reported outcomes.[12] Recently, an Italian trial compared systematic versus on-demand early SPC in 207 pancreatic cancer patients and found improved QoL at 12 weeks.[16] Thus, overall, the findings about early SPC are mixed. The American Society of Clinical Oncology (ASCO) recommends early SPC.[17,18]

In Denmark, a large, nationally representative survey of patients with advanced cancer, who had not been in contact with SPC, showed a high prevalence of palliative care needs.[3,4] Based on these findings, the Danish Palliative Care Trial (DanPaCT) was designed to investigate the potential impact of early SPC in patients with advanced cancer and palliative care needs. The DanPaCT protocol and statistical analysis plan (SAP) have been published.[19,20] This article reports the primary and secondary outcomes of DanPaCT.

Methods

Setting

Palliative care in Denmark (5.7 million inhabitants) may take place in primary care, in hospital departments not specialised in palliative care (e.g. oncological), or in SPC centres. In 2011, SPC in Denmark consisted of 26 hospital-based palliative care teams/units and 17 hospices.[2] Almost all health care in relation to cancer and palliative care is publicly funded and free of charge for patients.

Trial design

This was a randomised clinical, multicentre, parallel-group superiority trial with balanced randomisation (1:1) conducted at six Danish SPC centres. The protocol was approved by the Ethics Committee for the Capital Region, Denmark (H-3-2010-144), the Danish Data protection agency (BBH-2011-05) and registered at www.clinicaltrials.gov (NCT01348048).

The protocol has been described in detail elsewhere.[19] Patients were randomised to the *intervention group* who were referred to a multidisciplinary SPC team (further information about the teams in a prior publication[19]) plus standard care versus the *control group* who received standard care. In both groups, standard care potentially included palliative care provided by the departments of oncology, general practitioners (GPs) or home care services. The trial period was eight weeks.

Assuming a difference of 7.5 point in the primary outcome, the planned sample size was 300 (alpha: 5%; beta: 10%; standard deviation (SD): 20).[19]

Intervention

The DanPaCT intervention consisted of 'early SPC' defined as 'usual SPC' initiated at an earlier time than would otherwise have been the case. Patients in the intervention group were referred to an SPC team, and the number and frequency of contacts with the SPC team and the treatments and other interventions were determined by the patient's needs, following the European Association for Palliative Care White Paper,[21] the WHO guidelines[7] and national and local guidelines. The common understanding was that SPC is a complex and multidisciplinary intervention that is adapted to each patient. No additional guidelines were developed for the intervention in DanPaCT since the SPC teams were expected to use the guidelines and expertise they already had. Likewise, procedures, activities and processes were those normally used by the SPC teams and the interventions were given by the staff normally providing the interventions. The same was true for the location and timing of the treatment. The number of contacts between the SPC units and the included patients, the type of contacts and the type of staff involved will be described in the 'Results' section. After the completion of the 8-week trial period, patients remained in contact with the SPC team if clinically relevant according to the same principles as for other patients. Future research will investigate the activities and interventions reported in medical records in more detail based on qualitative analysis. Intervention fidelity was not assessed since there was not a specific manual for the intervention. No known modifications to the intervention happened over time.

Patients

Consecutive patients who were in oncological treatment or follow-up at five different departments of oncology were screened for palliative care needs by research nurses if they

- Had cancer stage IV[22] or cancer in the central nervous system grade III/IV;
- Were $\geqslant$18 years;
- Lived in the area of one of the participating SPC centres;
- Had no contact with an SPC during the previous year.

Patients were screened with the European Organisation for Research and Treatment of Cancer Quality of Life

Questionnaire (EORTC QLQ-C30)[23,24] and were eligible for the trial if they

1. Scored at least 50% of the score representing maximal symptom or maximally reduced functioning on at least one of the following seven scales: physical function, role function, emotional function, nausea/vomiting, pain, dyspnoea or lack of appetite;
2. Had at least four additional symptoms (defined as a score of at least 33% of the score corresponding to maximal symptom burden or maximally reduced functioning) as measured by any of the 13 remaining scales (global health status/QoL excluded).

Among the seven EORTC QLQ-C30 scales listed in (1), the scale having the highest score at baseline was named as the patient's '*primary need*'.

Patients were excluded from the trial if they did not understand Danish well enough to fill in a questionnaire or were considered incapable of complying with the trial protocol.

Randomisation and masking

Central randomisation via telephone was carried out by the Copenhagen Trial Unit (CTU), which was independent of the trial administration office. The allocation sequence was computer-generated 1:1 with varying block size of 8 and 12 per strata and was kept unknown for all investigators. Randomisation was stratified by 'primary need'.

All statistical analyses of the primary and secondary outcomes were carried out blinded to intervention allocation. Based on blinded results, two conclusions concerning results for the primary and secondary outcomes were written down and agreed upon among authors before de-blinding.[25,26]

Patient-reported outcomes

Patients received a questionnaire at baseline and at 3- and 8-week follow-up including the EORTC QLQ-C30[23] and additional instruments.[19]

The EORTC QLQ-C30 assesses health-related QoL within the previous week. Scores ranging from 0 to 100 were estimated according to the scoring manual.[24] A total of 7 of the 15 scales (physical function, role function, emotional function, nausea/vomiting, pain, dyspnoea and lack of appetite) were selected as key targets of palliative care by the palliative care physicians involved in the trial and constituted the primary and secondary outcomes of DanPaCT.[20] For the analyses of the primary outcome, the function scores were reversed (100 representing maximal impairment).

The *primary outcome* of DanPaCT was the change in the patient's primary need. The primary outcome was thus a patient-individualised outcome, that is, for a patient having the highest score for pain, the change in pain represented the primary outcome. The *secondary outcomes* were the changes in the seven QLQ-C30 scales; the analysis of each scale included all participants.

Statistical analyses of the primary outcome

All analyses were two-sided and were made with SAS statistical software version 9.3.[27] According to the SAP,[20] each outcome was estimated as the change from baseline to the weighted mean of the 3- and 8-week follow-up measured as area under the curve (AUC). The analyses were adjusted for the stratification variable (primary need). All outcomes were normally distributed and multiple linear regressions were used.

For the analysis of the primary outcome, the significance level was 0.05, and a *modified intention-to-treat (ITT) analysis* was conducted: patients who withdrew consent after randomisation, were randomised but did not fulfil inclusion criteria or died before 8 weeks were excluded (Figure 1). Missing answers were replaced using multiple imputations as described elsewhere.[20]

Five sensitivity analyses were made as follows:

1. A *fully adjusted analysis* conducted as the primary analysis but additionally adjusted for the following covariates if they were significantly associated ($p < 0.10$) with the outcome: centre, WHO Performance Status, time since the patient was diagnosed with advanced disease, treatment status, sex, age, diagnosis and education.
2. A *complete case analysis* conducted as the primary analysis, but only including patients who had completed all three assessments (no imputation).
3. *Analysis of repeated measurements* to investigate whether there was a difference in the intervention effect at the 3- and 8-week follow-up.
4. A *per protocol analysis* where patients in the intervention group who had not had contact with SPC were included in the control group, and patients in the control group who had contact with an SPC were included in the intervention group.
5. A *full ITT analysis* including all randomised patients except those who withdrew consent or did not fulfil inclusion criteria.

Multiple imputations were conducted except in analysis (2). All analyses were adjusted for the primary need.

Statistical analyses of the secondary outcomes

The analyses of the seven scales from the EORTC QLQ-C30 were carried out as described for the primary outcome. Additionally, the same five sensitivity analyses were conducted.

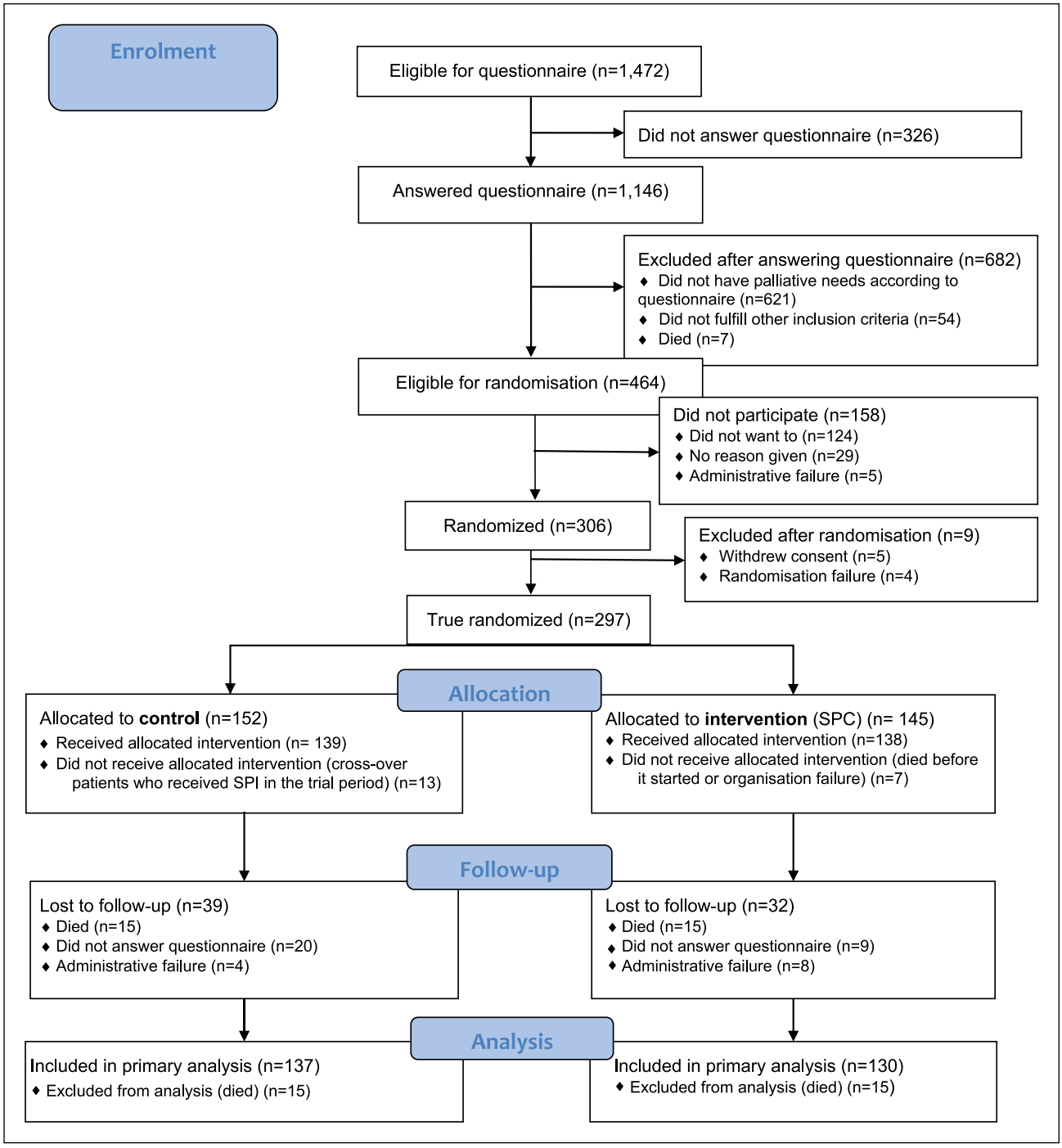

Figure 1. CONSORT 2010 flow diagram for DanPaCT.

Survival was analysed using a Kaplan–Meier plot. Patients who were alive 3 months after the end of data collection (20 June 2014) were censored at this date. A Cox regression analysis was conducted adjusting for the primary need. One sensitivity analysis was made additionally adjusting for the covariates in the fully adjusted sensitivity analysis for the primary outcome. For the secondary outcomes, a significance level of 0.01 was chosen.[28,29]

Results

Patients

Patients were included from May 2011 to December 2013, and the last follow-up questionnaire was mailed in March 2014. A flow-chart of randomised patients can be seen in Figure 1. After screening for palliative care needs, 464 were considered eligible, and 306 patients

were randomised; however, nine of them withdrew consent or were ineligible for the trial according to inclusion criteria and were therefore excluded from the analyses. Of the remaining 297 patients, 145 were allocated to the intervention group and 152 to the control group. Before the 8-week follow-up, 15 patients died in each group (10% versus 10%), leaving 267 patients for the primary outcome analysis. The numbers of patients answering the 3- and 8-week follow-up questionnaires were 247 and 226, respectively.

The characteristics of participants can be seen in Table 1. The majority of patients were 60–79 years old, more were females and about one-third had lung cancer. The majority were receiving chemotherapy when entering the trial, and almost two-thirds had been diagnosed with advanced cancer within the previous year. The most frequent primary outcomes were role function (36%), dyspnoea (17%) and lack of appetite (16%).

Contact with the SPC team

Of the 145 patients randomised to SPC, 138 had at least one face-to-face contact with the SPC team during the 8-week trial period, but only 74 patients had two or more face-to-face contacts (Table 2). Most patients had additional telephone contacts, and 27 had more than five calls. In the control group, 13 patients had at least one face-to-face contact with the SPC team within the 8 weeks.

The primary outcome

Early SPC had no significant effect on the primary outcome over 8 weeks (defined as AUC difference in symptoms equivalent to −4.9 points (0–100 scale); $p = 0.14$; Table 3). The 95% confidence interval was −11.3 to +1.5 points. The five sensitivity analyses showed similar results (Table 4).

Both groups had relatively high baseline scores (SPC group mean (SD): 75.5 (17.6), control group: 74.3 (17.3)) and experienced large improvements of −21.7 and −17.8 points, respectively, to 3 weeks and minor additional improvements to 8 weeks.

Secondary outcomes

The separate analyses of each of the seven EORTC QLQ-C30 scales also showed no differences between SPC and control groups, maybe with the exception of nausea/vomiting for which the largest change was seen (−5.8 points; −10.3 to −1.2) favouring the SPC group (Table 3). This was also the lowest p-value (0.013), close to the selected threshold (0.01). The five sensitivity analyses showed similar results (Table 4).

Of the 297 patients, 197 (66%) had died 3 months after the end of data collection. Survival time did not differ

Table 1. Baseline characteristics of 297 DanPaCT participants.

	Intervention group (*N* = 145), *N* (%)	Control group (*N* = 152), *N* (%)
Age (years)		
<50	10 (7)	15 (10)
50–59	27 (19)	25 (16)
60–69	65 (45)	58 (38)
70–79	36 (24)	45 (29)
⩾80	7 (5)	9 (6)
Sex		
Men	63 (43)	62 (41)
Women	82 (57)	90 (59)
Cancer		
Lung	57 (39)	46 (30)
Digestive system	20 (14)	38 (25)
Breast	31 (21)	35 (23)
Other	37 (26)	33 (22)
Receiving chemotherapy		
Yes	120 (83)	122 (80)
No	25 (17)	29 (19)
Missing	0 (0)	1 (1)
WHO performance score[a]		
0	23 (18)	36 (24)
1	78 (54)	79 (52)
2	27 (19)	16 (11)
3	1 (1)	4 (3)
Missing	16 (11)	17 (11)
Time since diagnosed with stage IV (months)		
<12	83 (57)	94 (62)
12–24	27 (19)	20 (13)
>24	32 (22)	36 (24)
Missing	3 (2)	2 (1)
Education		
None	26 (18)	18 (12)
Semi-skilled worker/short education (<1 year)	19 (13)	19 (13)
Skilled worker	23 (16)	31 (20)
Short theoretical (1–3 years)	21 (14)	24 (16)
Long theoretical (>3 years)	39 (27)	44 (29)
Academic	9 (6)	11 (7)
Missing	8 (6)	5 (3)
Centre		
Bispebjerg University Hospital[b]	25 (17)	25 (16)
Copenhagen University Hospital Rigshospitalet[b]	28 (19)	23 (15)
Odense University Hospital	20 (14)	28 (18)
Vejle Hospital	29 (20)	20 (13)
Aarhus University Hospital	19 (13)	29 (19)
Herning Hospital	24 (17)	27 (18)
Primary need[c]		
Physical function	12 (8)	11 (7)
Role function	52 (36)	54 (36)
Emotional function	9 (6)	13 (9)
Pain	19 (13)	18 (12)
Nausea/vomiting	5 (3)	6 (4)
Dyspnoea	25 (17)	26 (17)
Lack of appetite	23 (16)	24 (16)

DanPaCT: Danish Palliative Care Trial; WHO: World Health Organization.
[a]WHO Performance Score ranges from 0 to 4, where 0 = able to carry out all normal activity without restriction and 4 = completely disabled; cannot carry on any self-care; totally confined to bed or chair.
[b]Patients for the palliative care teams at Bispebjerg and Rigshospitalet were recruited from the Department of Oncology, Copenhagen University Hospital Rigshospitalet.
[c]The number of patients having each primary need. The primary need was the symptom or problem out of seven that had the highest intensity at baseline according to the EORTC QLQ-C30.

Table 2. Face-to-face and telephone contacts with specialist palliative care during the 8-week trial period in DanPaCT.

Number of contacts	Intervention group ($N = 145$)		Control group ($N = 152$)	
	Face-to-face	Telephone	Face-to-face	Telephone
None	7[a]	29	139	143
1	64	27	9	4
2	32	22	3	2
3–4	25	40	0	2
5 or more	17	27	1	1

[a]Two died before contact, two administrative failures and three participants did not want the intervention.

Table 3. Results of the main analysis of the primary[a] and secondary outcomes measured by the EORTC QLQ-C30.

	Intervention			Control			Mean weighted change[b] (95% CI)	p
	Baseline, mean (SD)	3 weeks, mean (SD)	8 weeks, mean (SD)	Baseline, mean (SD)	3 weeks, mean (SD)	8 weeks, mean (SD)		
Primary outcome[a] (range: 0–100; worst score 100)	75.5 (22.7)	53.8 (29.7)	50.7 (29.6)	74.3 (17.3)	56.5 (27.5)	55.4 (29.9)	−4.9 (−11.3; 1.6)	0.14
Secondary outcomes								
Function scales (range: 0–100; worst score 0)								
Physical function	57.5 (19.6)	59.1 (22.8)	57.6 (22.3)	58.8 (19.3)	60.2 (21.0)	59.9 (22.5)	−0.4 (−4.0; 3.2)	0.84
Role function	36.8 (25.0)	42.7 (29.7)	46.9 (30.4)	41.8 (27.0)	47.0 (27.9)	45.7 (30.4)	2.1 (−3.9; 8.1)	0.48
Emotional function	67.8 (22.4)	69.6 (23.1)	73.0 (21.4)	66.7 (22.1)	72.2 (22.4)	70.1 (22.7)	−1.6 (−5.7; 2.5)	0.45
Symptom scales (range 0–100, worst score 100)								
Pain	35.5 (30.2)	29.4 (28.7)	31.4 (30.0)	34.2 (26.0)	30.5 (27.3)	35.0 (30.8)	−3.4 (−9.5; 2.6)	0.27
Dyspnoea	41.6 (33.8)	35.4 (35.2)	36.5 (32.5)	39.8 (33.4)	38.0 (32.7)	38.7 (31.0)	−4.2 (−10.6; 2.3)	0.20
Nausea/vomiting	17.1 (24.1)	9.5 (15.4)	8.9 (15.6)	17.6 (18.1)	15.2 (18.8)	14.8 (22.6)	−5.8 (−10.3; −1.2)	0.013
Lack of appetite	30.5 (34.7)	24.8 (30.6)	22.6 (29.3)	38.0 (33.5)	33.8 (32.0)	31.7 (35.4)	−2.0 (−8.9; 4.9)	0.57

EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; SD: standard deviation; CI: confidence interval.
Multiple linear regression was used. A negative mean weighted change value in the primary outcome and in symptom scales indicates a larger symptom reduction in the intervention group than in the control group. The opposite is the case for the function scales.
[a]The primary outcome was patient-individualised (for each patient, the scale, out of the seven listed here, with the score representing the highest symptomatology was chosen as primary outcome). It was scored with 100 as the worst possible score.
[b]Mean weighted change: the difference in the area under the curve (AUC) converted to the original QLQ-C30 scale (0–100).

between the two groups (SPC group median 323 days versus control group 364 days, $p = 0.16$, fully adjusted analysis $p = 0.39$; Figure 2).

Discussion

This first European randomised clinical trial of early SPC plus standard care versus standard care alone in advanced cancer patients with a range of diagnoses showed no clear beneficial or harmful effects. There was no difference in the primary outcome ($p = 0.14$). The 95% confidence interval (−11.3 to +1.6 points) does not exclude the possibility of the hypothesised difference of −7.5 points favouring early SPC. The five sensitivity analyses showed similar results.

Whereas our primary outcome was an unusual, patient-individualised outcome, the secondary outcomes were analysed 'traditionally' and examined each of the seven EORTC QLQ-C30 scales selected for the trial. Again, no significant differences ($p < 0.01$) between groups were found, maybe with the exception of the outcome nausea/vomiting where the early SPC might have a beneficial effect. Survival time was not significantly affected.

Compared to the other trials of early SPC, DanPaCT is among the larger trials, was based on individual randomisation and was conducted with high completeness of data at follow-up. Although we recruited patients with advanced cancer throughout the disease course, the median survival was about 12 months, which was similar to Temel et al.'s[9] trial.

Our trial has several strengths. The randomisation was conducted through central, stratified allocation by a computer-generated sequence unknown to the investigators. We stratified for primary need, our intervention groups seemed well randomised, and we considered stratification in our analyses. We conducted our analyses blinded, and

Table 4. Results from the five sensitivity analyses in DanPaCT, compared to the results of the primary analysis.

	Primary analysis		Sensitivity analyses									
	MWC	p	Fully adjusted[a]		Complete case (no imputation)		Repeated measures		Per protocol		Including dead	
			MWC	p	MWC	p	NA	p	MWC	p	MWC	p
Primary outcome	−4.9	0.14			−3.8	0.28		0.12	−3.2	0.34	−4.3	0.20
Function scales (range: 0–100, worst score 0)												
Physical function	−0.4	0.84			−1.0	0.59		0.79	−1.4	0.42	−0.9	0.61
Role function	2.1	0.48	1.9	0.53	−0.2	0.95		0.37	−0.2	0.94	2.3	0.45
Emotional function	−1.6	0.45			−1.9	0.34		0.71	−0.7	0.72	−1.7	0.37
Symptom scales (range 0–100, worst score 100)												
Pain	−3.4	0.27			−2.2	0.50		0.18	−1.5	0.65	−1.2	0.70
Dyspnoea	−4.2	0.20	−4.7	0.16	−3.5	0.31		0.17	−4.1	0.21	−4.1	0.20
Nausea/vomiting	−5.8	0.013			−6.3	0.0075		0.0115	−5.4	0.0178	−4.7	0.044
Lack of appetite	−2.0	0.57			−3.6	0.30		0.52	−1.9	0.59	−2.4	0.49

DanPaCT; Danish Palliative Care Trial; MWC: mean weighted change.
The sensitivity analyses are described in the text. The MWC and the p values are shown except for the repeated measures analysis, where MWC is not applicable. A negative MWC value in the primary outcome and in symptom scales indicates a larger symptom reduction in the intervention group than in the control group. The opposite is the case for the function scales.
[a]Additional covariates were included in the fully adjusted analysis *if* they were significantly associated with the outcome; however, this was not always the case, and therefore, the results are only shown when they differ from the primary analysis.

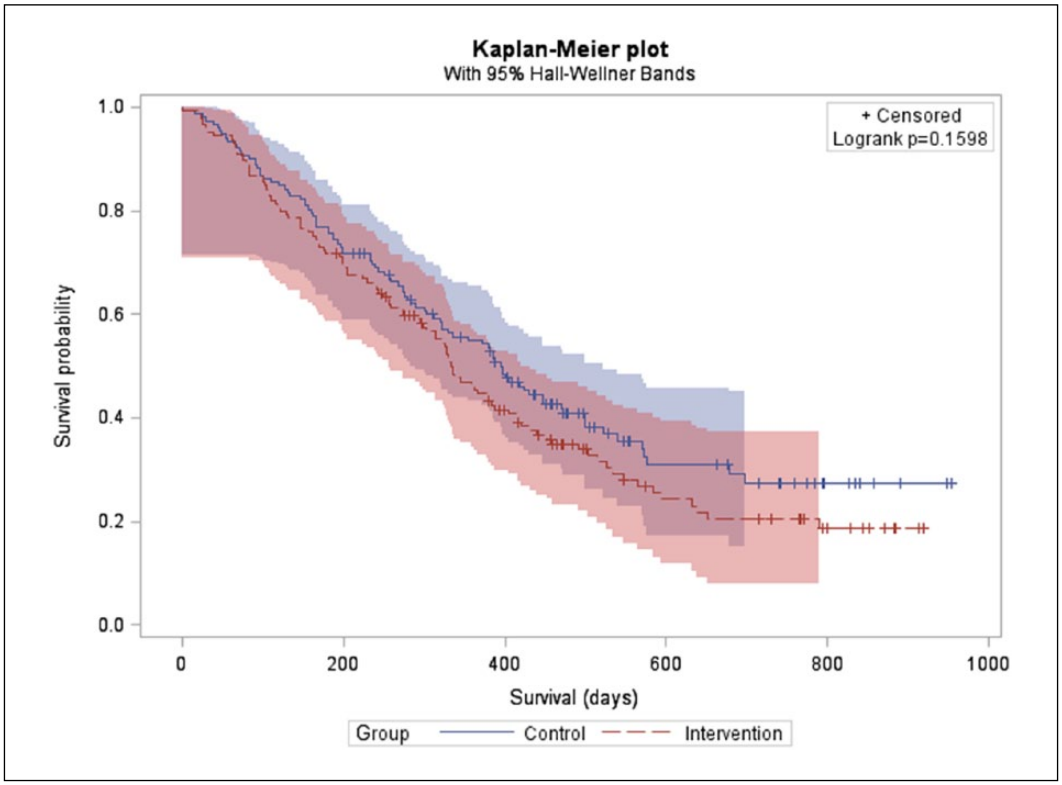

Figure 2. Survival time in the two groups in DanPaCT.

missing data were handled by multiple imputation and sensitivity analyses. We also drew our conclusions blinded to intervention group.[25,26]

How should we interpret the lack of a clear effect of early SPC in DanPaCT? One obvious reason could be that early SPC does not work. However, we find it premature to draw

such a conclusion. First, although our trial reached its planned size ($N = 300$), it is still a relatively small trial and may have overlooked therapeutic benefits. Second, as discussed below, there are several aspects of our trial that may explain the neutral findings even if early SPC is beneficial.

Possible under-treatment of the intervention group?

Our intention was to study the effect of what seemed to us as a clinically relevant future scenario for improvement of palliative care, that is, that patients with advanced cancer in oncology departments were regularly screened for palliative needs, and if such needs were identified, patients were referred to SPC. We did not request that any specific treatment guidelines or any frequency of visits were used in the SPC teams, as we wanted to investigate 'usual SPC' as offered by six of the most experienced teams in Denmark.

The number of face-to-face contacts in the intervention group was low: only 51% (74/145) were seen by SPC teams more than once during the 8-week trial period, although there were more frequent telephone contacts. The SPC teams in Denmark have relatively low capacity and usually receive patients with very complex symptoms and a short survival;[2] the SPC teams may have perceived some DanPaCT patients as having no urgent need compared to their other patients.

Should some of the patients identified via the DanPaCT screening procedure be regarded as false positive? Maybe 'early SPC needs' require a different type of intervention, for example, a more structured approach with planned visits even when there are no alarming symptoms and where the content is structured around patient-education,[10,15] coping, communication and prognostic awareness.[30] Each of our six SPC teams received only about 25 intervention patients, and they may not have had the time and attention to build up a specific approach. Temel et al.[9] and Zimmerman et al.[1] conducted single centre trials, which may involve stronger and more focussed interventions. However, such single centre trials may have less external validity.

Formalised collaboration between SPC team and oncology departments, for example, via multidisciplinary conferences, may improve the impact of SPC, but this was not routinely practised in Denmark while this trial was conducted.

Finally, our intervention period of 8 weeks was relatively short, and, as we had hoped, this resulted in high completeness of data at follow-up. When designing our trial, we had the belief that an effect of SPC would be observed within few weeks and we were keen to limit attrition in order to maximise the power of the trial. Our 3-week assessment was chosen to secure information from patients who dropped out early. Temel et al.'s[9] initial trial was 12 weeks, and Zimmerman et al.'s[1] trial found most effect after 4 months. Temel et al.'s[13] second trial found no impact on QoL at 12 weeks but at 24 weeks. We may have overlooked a benefit beyond 8 weeks.

Crossover/compensation in control group?

The proportion of crossover from the control group to SPC was limited (13/152; 8.6%), but may have reduced the difference between groups.

May some of the experienced study nurses at the oncology departments have felt a moral obligation to compensate for the lack of SPC? They may have encouraged patients in the control group to contact their oncology doctor or GP. The nurses may also have taken a good, long talk with distressed patients or may have suggested contacting a psychologist or counselling. The oncology department staff may have made an extra effort to help disappointed patients. If such extra activity took place in the control group, it is a bias weakening our ability to detect an effect of the intervention.

A related possibility is that, as this was not a cluster RCT, the oncologists may have learned from the palliative care consultations done with patients in the intervention group and may thus have provided better primary palliative care to the control group.

Outcomes

Of all oncology patients screened, about 43% were above our threshold for having a need. We used the EORTC QLQ-C30, which is one of the most widely used and validated measures in oncology trials.[31,32] Our choice of seven QLQ-C30 scales for screening may of course be disputed, but still one would expect a better effect in patients with documented needs than if all patients were offered treatment.

The scores for the remaining symptoms/problems were relatively low, indicating that the number of problems per patient was limited. This was the motivation for our unusual outcome: we devised the patient-individualised outcome in order to address the methodological problems arising from the heterogeneous nature of palliative care needs: if, for example, only 20% of the patients need additional treatment for pain, then even with excellent effect among these 20%, the overall effect measured on the pain scale is diluted by the lack of change in the 80% not treated for pain (and there might be insufficient power to detect a difference among the 20%). The average change on the seven QLQ-C30 scales was −2.2 points, while the change on the primary outcome was −4.9 points. Thus, there is very preliminary evidence supporting the assumption that the new approach is more sensitive. Our combination of a new outcome with a traditional analysis of seven symptom scales selected to cover important targets of palliative care secures that we do not draw conclusions from the new approach only.

Conclusion

This RCT could not show beneficial or harmful effects of early SPC in advanced cancer patients with palliative care needs. These findings and their interpretations should be studied carefully by others working with implementation of early SPC in advanced cancer.

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