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Exploratory analyses of the Danish Palliative Care Trial (DanPaCT): a randomised trial of early specialised palliative care plus standard care versus standard care in advanced cancer patients

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Abstract

Background: Early and integrated specialized palliative care is often recommended but has still only been investigated in relatively few randomized clinical trials.

Objective: To investigate the effect of early specialized palliative care plus standard care versus standard care on the explorative outcomes in the Danish Palliative Care Trial (DanPaCT).

Methods: We conducted a randomized multicentre, parallel-group clinical trial. Consecutive patients with metastatic cancer were included if they had symptoms or problems that exceeded a predefined threshold according to the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30). Outcomes were estimated as the differences between the intervention and the control group in the change from baseline to the weighted mean of the 3- and 8-week follow-up measured as areas under the curve. www.clinicaltrials.gov (NCT01348048)

Results: In total, 145 patients were randomized to early specialized palliative care plus standard care versus 152 to standard care only. Early specialized palliative care had no significant effect on any of the symptoms or problems. Of the 21 items addressing satisfaction, specialized palliative care improved the item 'overall satisfaction with the help received from the health care system' with 9 points (95% confidence interval 3.8 to 14.2, $p=0.0006$) and three other items (all $p<0.05$).

Conclusion: In line with the analyses of the primary and secondary outcomes in DanPaCT, we did not find that specialized palliative care, as provided in DanPaCT, affected symptoms and problems. However, patients in the intervention group seemed more satisfied with the health care received than those in the standard care group.

Introduction

The primary goal of palliative care is to improve quality of life (QOL) for patients with a life-threatening disease [1, 2]. Specialized palliative care is provided by health care professionals specializing in this. In most countries specialized palliative care is mainly provided to patients in the terminal phases of disease, if at all [3]. In Denmark, 53% of patients dying from cancer have contact with a specialized palliative care before they die [4] and the median survival time of patients from referral is six weeks [4]. Many patients with advanced cancer have complex symptoms or problems long before reaching the terminal phase [5-7]. It is therefore likely that these patients could benefit from specialized palliative care at an earlier time in their disease trajectory as recognized by WHO [1] and is recommended by the American Society of Clinical Oncology (ASCO) [8,9].

There is not one simple definition of early specialized palliative care. According to a recent Cochrane review [10], the term is used to differentiate palliative care treatments applied early in the course of a life-threatening disease from those delivered mainly in the terminal phase of the disease. Trials of early specialized palliative care differ on inclusion criteria and definitions, however, they all asses the effect of offering the intervention earlier in the course of disease than what would normally occur [2, 11-21]. In all trials except one [17], it was an inclusion criterion that the patients had advanced or metastatic cancer.

In 2009, we initiated the Danish Palliative Care Trial (DanPaCT) to evaluate the effect of early specialized palliative care [19-21]. Since then, another nine randomized clinical trials have evaluated the effect of early specialized palliative care in advanced cancer in RCT designs [2,11-19]. Of these eight trials, six were from North America, one Australian, and two were European. The recent Cochrane review [10] including seven of these trials, concluded that early palliative care interventions may have beneficial effects on quality of life and symptom intensity compared with usual/standard cancer care alone. A European trial integrating early palliative care for patients with advanced disease and refractory breathlessness also showed improved mastery of breathlessness [20]. No firm conclusions, however, can presently be reached about the effects on depression or survival, or on satisfaction with care [10].

We have already reported on the results of the primary and eight secondary outcomes which led to the conclusion that in DanPaCT we found no effect of early specialized palliative care maybe except for the secondary outcome nausea/vomiting where the intervention might have had a beneficial effect [21].

The aim of the current paper is to investigate the exploratory outcomes of DanPaCT, i.e. anxiety, depression, health-related quality of life, and satisfaction with care received from the health care system. In the DanPaCT protocol paper [22], these outcomes were referred to as secondary outcomes. However, in the subsequent DanPaCT statistical analysis paper we re-classified some of the secondary outcomes as explorative outcomes to reduce the number of secondary outcomes [23]. However, they are still important outcomes and could be affected by specialized palliative care.

Methods

Study design

The trial was a clinical, multicentre, parallel-group superiority trial with central randomisation (1:1) conducted at six Danish specialized palliative care centres. Patients were randomized to either the intervention group receiving referral to a multi-disciplinary specialized palliative care team plus standard care versus standard care [21-23]. The intervention period was eight weeks.

The protocol was approved by the Ethics Committee for the Capital Region, Denmark (journal number H-3-2010-144), the Danish Data protection agency (journal number BBH-2011-05), and registered at www.clinicaltrials.gov (NCT01348048; https://clinicaltrials.gov/ct2/show/NCT01348048?term=01348048&rank=1; registered May 2011). The protocol and an update specifying in detail the planned statistical analysis was published before we analyzed the data [22,23].

Patients

Consecutive patients from five different departments of oncology were screened by research nurses if they had stage IV cancer according to the 'TNM' (Tumor, Node, Metastases) classification [24]

or cancer in the central nervous system grade three or four, aged at least 18 years, lived in the area of one of the participating specialized palliative care teams, and had not had contact with the team during the previous year. If, according to their answers in the questionnaire, they had a palliative need and four additional symptoms (see definition below) they were eligible for the trial unless excluded because they could not understand Danish well enough to fill in a questionnaire or were considered incapable of complying with the trial protocol. In addition, they had to give informed consent collected by a project nurse after being informed of the trial and been giving time to consider participation.

Patients were screened with the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) [25]. They were defined as having a palliative need (which was one of the inclusion criteria (see above)) if they:

a) scored at least 50% of the score corresponding to maximal symptom burden or maximally reduced functioning on at least one of the following scales in EORTC QLQ-C30: physical function, role function, emotional function, nausea and vomiting, pain, dyspnoea, or lack of appetite; and
b) had four additional symptoms (defined as EORTC QLQ-C30 scale scores of at least 33% of the score corresponding to maximal symptom burden or maximally reduced functioning) out of the 13 remaining EORTC QLQ-C30 scales (global health status/QOL and financial difficulties excluded).

The primary outcome of the trial was the change in the patient's primary need. The primary need was the EORTC QLQ-C30 scale among the seven scales listed above (a) having the highest score at baseline.

Intervention and control

Patients in the intervention group were referred to a specialized palliative care team in addition to standard care. The teams were instructed to receive the DanPaCT patients and treat these patients as they would have treated patients referred to the team by the usual procedures. This means that treatment and care plans were made according to the needs of the patients and following the European Association for Palliative Care white paper [26], the World Health Organization's guidelines [1], and national and local guidelines.

Specialized palliative care is a complex, multidisciplinary, and personalized intervention that is adapted to each patient. All six teams had at least four different disciplines working in the team, always including doctors and nurses [22]. Furthermore, all teams had a psychologist, most had a physiotherapist and some teams had a chaplain and a social worker [22]. It is a national target that all patients are discussed at a multi-disciplinary meeting [4]. No additional guidelines were developed for the intervention and the teams providing the intervention were expected to use the guidelines and expertise they already had, and therefore fidelity checks were not made.

Of the 145 patients randomized to specialized palliative care, 138 had at least one face-to-face contact with the team during the 8-week trial period and 74 patients had two or more face-to-face contacts. Most patients had additional telephone contacts with the team [21].

Patients in both groups received standard care. Standard care consisted of basic palliative care provided by the departments of oncology, general practitioners (GP) and home care nurses/services.

Randomisation and masking

Central randomisation via telephone was carried out by the Copenhagen Trial Unit (CTU). The allocations sequence was computer-generated with a varying block size and stratified by the variable ’primary need’ (see previous section). Due to the nature of the intervention, the participants and trial personnel could not be blinded. The statistician and researchers were blinded when conducting and concluding on the primary and secondary analyses, however, they were not blinded for the analyses presented here.

Patient reported outcomes

Patients received a questionnaire at baseline and at three and eight weeks follow up, including the EORTC QLQ-C30 [25], the Hospital Anxiety and Depression Scale (HAD Scale) [27], a questionnaire assessing the patients’ satisfaction with the health care system, the FAMCARE-P16 questionnaire [28], and additional items (see below).

The EORTC QLQ-C30 [25] assesses the patients’ health-related quality of life within the previous week. Scores for the 15 scales ranging from 0 to 100 were calculated according to the scoring manual

[29]. For the symptom scales in EORTC QLQ-C30, a high score represents high symptom load. For the function scales, a low score represents high impairment. Seven of the 15 scales constituted the primary and secondary outcomes of DanPaCT and were reported in the primary publication from this trial [21]. The remaining eight scales (social function, cognitive function, quality of life, fatigue, sleeplessness, constipation, diarrhoea and financial difficulties), are reported in this publication. In addition, a sum-scale score was calculated based on all scales in the EORTC QLQ-C30 except the global health/QOL and Financial difficulties scale as described by Giesinger et al. [30] and calculated according to the scoring algorithm provided by the EORTC Quality of Life Group [31].

The Hospital Anxiety and Depression (HAD) questionnaire [27] assesses anxiety and depression with two scales each ranging from 0 to 21 where 21 represents maximum distress. Analyses were made for the full score distributions for the anxiety and depression scales. When calculating scale scores, patients received a score if they had answered at least six of the seven items in the scale.

FAMCARE-P16 [28] assesses advanced cancer patients' satisfaction with the health care system and the questionnaire includes several items that address key areas of palliative care [28, 32]. It uses 5-point Likert scales where 1='very satisfied', 2='satisfied', 3='undecided', 4='dissatisfied' and 5='very dissatisfied'. The patients were asked to rate the care they received within the previous month. The analysis was made on single-item level [28] and as a sum-scale [2, 32] and both item and sum-scores were converted to 0-100 scales. When calculating the scale score, patients who had answered at least half of the items received a score.

We also included five additional items measuring aspects of satisfaction that we considered relevant for a trial of early specialised palliative care (see Table 3 for abbreviated item texts). By mistake, one of these items were not included in the protocol paper. One item ('Have you been satisfied with the overall care received from the health care system?') had the same response categories as FAMCARE P-16. The remaining items had the response categories: Yes, to a large extent/Yes, to some degree/No, only to a little extent/No, not at all/Do not know or not applicable. Item scores were converted to 0-100 scales.

Statistical analyses

All analyses were made with SAS statistical software version 9.4 [33]. For sample size calculation, see [22]. Each outcome was estimated as the difference between the intervention and the control group in the change from baseline to the weighted mean of the 3- and 8-week follow-up measured as area under the curve (AUC). If an outcome was approximately normally distributed, the analysis was conducted as multiple linear regression adjusted for the primary need. If not, it was transformed to follow a normal distribution when possible. If this was not possible, we would use the nonparametric van Elteren test [34].

As written in the DanPaCT statistical analysis plan [23], the analysis of the exploratory outcomes was made as complete case analysis. Thus, only patients answering the baseline, three- and eight-weeks questionnaires were included. The level of significance was 0.05. However, due to multiple tests, any significant difference should be confirmed in other studies before any final conclusions are drawn.

Results

Patients

Patients were included in the trial from May 2011 to December 2013, and the last follow-up questionnaire was sent out in March 2014. A flowchart of randomized patients can be seen in Figure 1. In total, 306 patients were randomized. However, nine withdrew consent or were ineligible for the trial according to our inclusion criteria and were therefore excluded from analyses. Of the remaining 297 participants, 145 were randomized to the experimental intervention group versus 152 to the standard care control group. Before the eight-week follow-up, 15 patients died in each intervention group (10% of the sample), leaving 267 potential respondents. In total, 248 (84%) answered the three-week follow-up and 226 answered the eight-week follow-up (76%). The characteristics of participants can be seen in Table 1. Patients had different cancer diagnoses, about 60% were females, and the majority had a WHO performance score between 0-2, meaning that they were ambulatory and capable of selfcare.

(Figure 1 and Table 1 about here)

Outcomes

Early specialized palliative care had no significant effects on any of the symptoms or problems measured with EORTC QLQ-C30 (Table 2). Neither did it have any effect when analyzed with the EORTC QLQ-C30 total score (the sum of 13 of the scales in EORTC QLQ-C30, see section on patient reported outcomes). The intervention did not have any effect on anxiety and depression measured with the HAD scales either (Table 2).

Of the 16 FAMCARE P-16 items addressing satisfaction with care, three items had $p<0.05$ (all favoring the intervention group) (Table 3). These were doctors' attention to the description of symptoms, information given about how to manage pain, and the way the family was included in decisions. FAMCARE is often analyzed on scale-level [33] and Cronbach's alpha of the scale was 0.93 (not shown in table). Analyzing FAMCARE P-16 on scale-level showed insignificant results.

Of the five additional items investigating satisfaction, the item 'overall satisfaction with the help received from the health care system' had the largest difference seen in the trial favoring early specialized palliative care of 9.0 points (95% confidence interval 3.8 to 14.2, $p=0.0006$). For the remaining four items, there were no significant differences.

(Tables 2 and 3 around here)

Discussion

Main findings/results of the DanPaCT study

Based on the analyses of the primary and secondary outcomes of DanPaCT we concluded that early specialized palliative care plus standard care did not show any beneficial or harmful effects in advanced cancer patients when compared with our standard care control group [21]. Similarly, the present paper found no effect on the patients' symptoms, function, anxiety, or depression.

Importantly, we found some indication that patients in the intervention group were more satisfied than patients in the control group when looking at individual items of the FAMCARE scale. This is an important outcome of specialized palliative care and increased satisfaction was seen in relation to some core areas of palliative care such as doctors' attention to symptoms, information given about how to manage pain, and the way the family was included in decisions. However, there were also individual items addressing core areas of palliative care showing no differences between groups.

Moreover, we cannot exclude that the beneficial effects in satisfaction may be due to bias, as the participants were not blinded to the intervention [36-37].

Strengths and weaknesses/limitations of the DanPaCT trial

For the primary and secondary outcomes reported elsewhere [21] we performed five types of sensitivity analysis for all outcomes, including a per protocol analysis where patients were analysed in their 'correct' group (thus, if they were in the control group, but had crossed over to the intervention group, they were analysed as such). This did not change any conclusions, and therefore – and because the current paper reported explorative data - we did not include sensitivity analysis in the present paper.

The lack of effect on symptoms and psychosocial problems in the DanPaCT trial may be due to the time frame of the intervention [21]. Psychosocial interventions, which could have had an impact on patients' emotional or social function, may often take longer time than eight weeks. We could see in the medical records that some of the interventions were planned in the intervention period, but not implemented before the end of follow-up. This was especially true for interventions that needed a referral, a test or some form of application before being initiated (such as receiving assistive technology at home). This also meant that, in the intervention period, most patients did not get the full benefits of being referred to a SPC, e.g. it was only few who were seen by the psychologist in the intervention period. Newer trials of early specialized palliative care that found a beneficial effect generally had longer follow-up periods [2,16,18]. Based on this trial, we would also recommend a longer follow-up time for trials of early SPC, although this must be balanced with the higher rates of attrition that must be expected due to death and deterioration.

It is also possible that the patients in the intervention group of DanPaCT received too little attention from the specialized palliative care teams. Since the SPC teams are used to see patients who have very complex symptoms [38], they may have considered that many of the patients they received through the DanPaCT trial did not need interventions, since they were not severely burdened by symptoms and problems. The majority of patients referred in DanPaCT had WHO performance score 0-2 meaning that they were all ambulatory and capable of selfcare. Furthermore, they had rather low levels of symptoms and problems compared to a more traditional sample of patients in

SPC [38]. This interpretation is supported by the fact that only slightly more than half of the patients who were referred to specialized palliative care in DanPaCT were seen by the team more than once during the trial period [21]. Based on the low number of contacts that the intervention group received from the team one may consider if early specialized palliative care needs a more structured approach where a number of visits are planned regardless of the patients' health status and needs; this has been done in several of the other trials of early SPC [11,12,20]. In addition, one should consider the content of early SPC. In DanPaCT, the teams were not instructed to do anything specifically. However, it might have been advantageous if it had been estimated which types of interventions would have been beneficial for patients at this stage of their disease. This could for example be advance care planning [39], which could help patients and their families prioritize what is important to them, and which was also a concept included in the Temel and coworkers' studies [11]. About 10% of the sample died in the intervention period (see flow-chart) and 66% had died three months after the end of the eight-week trial period [21].
Finally, a reason for the lack of effect in the trial, as discussed in our paper on the primary and secondary outcomes [21], may be that patients in the control arm received high levels of relevant palliative care from the departments of oncology.

It is still debated whether QOL scores should be analyzed as total scores having a very high reliability or rather as profiles (where differences in sub-domains can be detected). In our previous paper we added a layer to this complexity by suggesting a patient-individualized score [21] and in this paper we added an analysis using the EORTC QLQ-C30 total score [30]. We can now compare the results of the analyses at various levels. When using the patient-individualized outcome, a non-significant effect of -4.9 points in favor of the intervention group was observed (0-100 scale). When analyzing the 15 scales individually, only one of the scales showed a slightly larger difference of -5.8 points in favor of the intervention group. The total score showed only a difference of 0.9 points. The patient-individualized outcome may be a relevant approach, and this could be tested in future research.

In this DanPaCT trial, the sample size was carefully planned, allocation was concealed to investigators and project nurses, and the primary analyses were conducted by a blinded statistician. However, as trials of specialized palliative care cannot be blinded to participants, their assessment may be biased [36-37]. In addition, although we believe attrition was low considering the

target population, there was still a proportion of patients who dropped out which may also cause bias [39].

What this study adds

This study adds to the increasing knowledge base of early specialized palliative care and it is the second European study. A recent Cochrane review concludes that early specialized palliative care may have beneficial effects on symptom intensity and quality of life, that effects on depression and anxiety are uncertain, and that more research is required for this newly emergent field [10]. This trial found no effect on symptoms and psychosocial problems. However, the trial indicates that the intervention group may have been more satisfied with the health care received, which is an important outcome for patients and families during serious and advanced illness. Furthermore, based on the low number of contacts the intervention group had with the specialized palliative care team one may consider if early specialized palliative care needs a more structured approach, where a number of visits are planned regardless of the patients' health status and needs and focused referral or screening criteria are developed. Further, one may consider the what are the focus and main outcomes of early specialized palliative care as well as the time-frame of the intervention.

Conclusion

The exploratory analyses reported here confirm the findings from our main DanPaCT publication. We did not find any effects of early specialized palliative care as provided in this trial on symptoms or psychosocial problems in the eight -week trial period. The analyses of patient satisfaction indicate that patients receiving early specialized palliative care may have felt that they received more support from the health care system.

Declarations

Authors' contribution

ATJ, MAP, CG, JL, PF, PS, LP, MAN, TBV, AD, IJH, MG took part in designing the trial and ATJ drafted the protocol. MAP, CG, JL, PF contributed with special competence in randomized clinical trials and/or statistical analysis, and ATJ, PS, LP, MAN, TBV, AD, IJH, MG with special competence in palliative care. PS, LP, MAN, TBV, AD, JBN, MG were clinical investigators and in

charge of the data collection, and ASS helped collect data. ATJ was postdoc on the study, project coordinator, did the data-management and made the analysis for this study in collaboration with MAP. MG was principal investigator and received the funding for the trial. ATJ drafted the paper and all authors read, amended, and approved the final manuscript.

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Declaration of interests
The authors declare that they have no competing interests.

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Table 1. Baseline characteristics of 297 DanPaCT participants.

		Intervention group (N=145) N (%)	Control group (N=152) N (%)
Age (years)	<50 years	10 (7)	15 (10)
	50 - 59 years	27 (19)	25 (16)
	60 - 69 years	65 (45)	58 (38)
	70 - 79 years	36 (24)	45 (29)
	≥80 years	7 (5)	9 (6)
Sex	Male	63 (43)	62 (41)
	Female	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)
	- Ovarian	6 (4)	9 (6)
	- Prostate	11(8)	8 (5)
	- Brain	8 (6)	2 (1)
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)
	4	0 (0)	0 (0)
	Missing	16 (11)	17 (11)
Education	None after mandatory school	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)

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.

Table 2. Exploratory outcomes measured with EORTC QLQ-C30, HAD scales and FAMCARE-P16 using multiple linear regression.

	Intervention			Control				
	Baseline mean[1] (SD)	3 weeks mean[1] (SD)	8 weeks mean[1] (SD)	Baseline mean[1] (SD)	3 weeks mean[1] (SD)	8 weeks mean[1] (SD)	Mean weighted change[2] (95% CI)	p-value [3]
The EORTC QLQ-C30								
Function scales (range 0-100, worst score 0)								
Cognitive function	67.1 (23.6)	71.0 (24.1)	70.5 (25.0)	71.9 (25.6)	73.7 (26.0)	72.6 (26.9)	-0.8 (-6.0;4.4)	0.766
Social function	70.5 (25.1)	66.9 (28.7)	68.2 (27.9)	66.4 (24.7)	66.7 (25.0)	66.5 (25.2)	0.2 (-6.0;6.5)	0.944
Global Health/Quality of Life (QOL)	49.1 (19.4)	48.8 (20.1)	53.9 (20.7)	48.0 (17.7)	48.8 (18.3)	49.7 (19.0)	-0.3 (-5.1;4.5)	0.895
Symptom scales (range 0-100, worst score 100)								
Fatigue	59.6 (22.8)	54.1 (25.5)	53.0 (25.6)	61.4 (20.8)	59.3 (23.9)	58.8 (24.0)	-2.8 (-7.2;1.8)	0.232
Sleeplessness	35.4 (32.4)	30.9 (29.2)	26.4 (27.7)	33.3 (31.0)	29.9 (32.2)	29.5 (30.5)	-1.8 (-9.0;5.5)	0.630
Constipation	20.8 (28.1)	20.0 (27.9)	17.6 (27.1)	24.7 (30.4)	19.5 (30.8)	17.9 (25.5)	-1.1 (-8.4;6.1)	0.757
Diarrhoea	23.4 (29.8)	20.8 (27.1)	14.8 (23.8)	22.7 (31.8)	20.9 (27.1)	18.5 (28.2)	-1.0 (-8.8;7.0)	0.812
Financial difficulties	13.8 (26.7)	12.7 (25.7)	12.0 (23.0)	9.0 (20.0)	10.0 (22.6)	9.4 (21.9)	-0.3 (-5.2;4.6)	0.910
Sum-scale score[4] (range 0-100, worst score 0)								
QLQ-C30 sum score	63.7 (13.4)	66.5 (16.4)	68.1 (16.7)	63.2 (12.8)	66.2 (15.9)	65.9 (16.6)	0.9 (-2.0;3.8)	0.541
The HAD scale								
Anxiety and depression (range 0-21, worst score 21)								
Anxiety	6.9 (4.1)	7.3 (4.5)	6.6 (4.2)	6.8 (3.9)	6.6 (4.3)	6.5 (4.4)	0.69 (-0.0;1.4)	0.058
Depression	6.3 (3.9)	7.3 (4.5)	6.6 (4.2)	6.3 (3.7)	6.6 (4.3)	6.5 (4.4)	0.54 (-0.5;1.6)	0.328
FAMACARE P-16								
FAMCARE total score (range 0-100, worst score 0)								
	76.7 (16.1)	78.2 (14.4)	76.2 (18.7)	75.4 (17.9)	73.7 (19.3)	74.6 (14.4)	2.6 (-1.5;6.6)	0.210

1) Mean scores provided for all patients answering the item.

2) Mean weighted change: the difference in the area under the curve (AUC) converted to the original 0-100 scale for QLQ-C30 and FAMCARE P-16 and the original 0-21 scale for HAD. For the QLQ-C30 function scales and the sum-scale score a positive mean weighted change value indicates a larger improvement in function in the intervention group than in the control group. For the symptom scales a negative mean weighted change value indicates a larger symptom reduction in the intervention group than in the control group. For the HAD scale, a negative mean weighted change value in anxiety and depression indicates (more) reduction in anxiety and depression in the intervention group compared to

the control group. For the FAMCARE P-16 scale a positive mean weighted change value indicates (more) improvement in satisfaction in the intervention group compared to the control group.

[3] P-value provided for differences in mean changes between groups for complete cases.

[4] The EORTC QLQ-C30 Summary Score is calculated from the mean of 13 of the 15 QLQ-C30 scales (the quality of life and financial impact scale are not included). Prior to calculating the mean, the symptom scales were reversed to obtain a uniform direction of all scales [28, 29].

Table 3. Satisfaction with the health care system measured with the FAMCARE p-16 scale and five additional items using multiple linear regression.

	Intervention			Control				
	Baseline mean[1] (SD)	3 weeks mean[1] (SD)	8 weeks mean[1] (SD)	Baseline mean[1] (SD)	3 weeks mean[1] (SD)	8 weeks mean[1] (SD)	Mean weighted change[2] (95% CI)	p-value[3]
FAMACRE P-16 (range 0-100, worst score 0)								
Information provided about prognosis	70.0 (20.9)	69.8 (22.4)	68.5 (22.8)	67.9 (23.4)	66.0 (24.7)	67.8 (22.2)	3.3 (-2.5;9.2)	0.264
Answers from health professionals	82.2 (16.8)	80.7 (17.1)	79.6 (19.4)	78.8 (20.6)	77.7 (20.8)	77.9 (20.2)	1.9 (-3.4;7.1)	0.485
Information about side effects	80.0 (20.3)	77.7 (18.4)	76.4 (21.6)	78.6 (20.5)	76.4 (22.6)	76.3 (18.0)	0.3 (-4.8;5.5)	0.900
Referrals to specialists	69.5 (21.7)	72.0 (23.4)	77.1 (21.4)	70.1 (25.5)	69.3 (25.6)	66.0 (22.4)	6.7 (-0.3;13.8)	0.063
Speed with which symptoms are treated	77.9 (28.1)	80.1 (21.2)	78.8 (24.1)	75.2 (27.4)	74.6 (25.4)	73.4 (23.4)	5.5 (-0.9;11.8)	0.096
Doctor's attention to symptoms	77.5 (25.8)	80.3 (20.6)	81.3 (20.6)	78.9 (22.0)	75.4 (25.1)	77.2 (20.5)	7.4 (1.4;13.4)	0.016
The way tests and treatments are performed	84.0 (19.2)	84.0 (17.1)	84.5 (17.5)	81.6 (22.5)	79.6 (20.8)	80.5 (18.5)	0.0 (-5.0;5.1)	0.992
Availability of doctors to answer questions	81.7 (20.5)	83.4 (18.2)	81.8 (20.0)	79.2 (22.7)	77.4 (22.2)	77.6 (17.8)	2.7 (-2.7:8.0)	0.333
Availability of nurses to answer questions	87.2 (17.3)	89.8 (13.2)	86.7 (16.5)	85.8 (20.0)	84.5 (18.4)	83.6 (15.2)	2.6 (-2.3;7.59)	0.299
Coordination of care	86.0 (17.3)	84.4 (16.0)	81.3 (18.4)	80.1 (21.8)	78.0 (23.3)	78.8 (21.1)	0.3 (-5.4;6.0)	0.920
The way family is included in decisions	78.3 (20.3)	78.4 (18.9)	78.5 (19.8)	78.9 (18.7)	74.0 (22.8)	73.2 (22.3)	6.4 (0.75;12.0)	0.027
Information about how to manage pain	76.3 (21.1)	77.8 (20.5)	75.9 (21.2)	76.1 (20.9)	72.0 (25.1)	73.4 (18.9)	7.3 (1.7;12.8)	0.011
Information about tests	81.6 (17.4)	82.1 (15.9)	79.1 (18.9)	80.1 (20.0)	78.4 (21.5)	80.4 (15.9)	1.3 (-3.6;6.4)	0.592

How thoroughly the doctor assesses symptoms	75.9 (23.2)	79.4 (17.2)	76.4 (21.9)	75.5 (20.9)	74.4 (24.0)	75.8 (19.3)	3.6 (-2.1;9.3)	0.221
The way tests and treatments are followed up	80.2 (21.4)	80.3 (19.3)	78.0 (21.2)	78.1 (21.9)	76.2 (22.2)	75.7 (19.7)	1.2 (-4.3;6.8)	0.666
Availability of doctor to the family	75.7 (21.0)	76.5 (19.9)	75.5 (21.7)	75.5 (19.8)	74.4 (22.6)	72.9 (20.1)	1.4 (-4.2;7.1)	0.610
Additional satisfaction scores (range 0-100, worst score 0)								
Overall support and help	79.8 (19.4)	83.9 (18.9)	82.5 (19.9)	78.9 (19.2)	76.8 (22.6)	77.2 (20.3)	9.0 (3.8;14.2)	<0.001
Felt safe in the health care system	87.9 (20.0)	90.2 (16.9)	89.3 (19.2)	88.8 (17.1)	86.1 (21.6)	85.2 (21.6)	3.2 (-2.0;8.5)	0.230
Received Answers to difficult questions	82.1 (24.5)	83.4 (23.1)	84.9 (21.4)	78.2 (26.5)	79.8 (27.3)	79.9 (25.7)	0.5 (-5.9;7.0)	0.870
Respectful and dignifying care	90.1 (18.1)	90.5 (18.4)	86.0 (25.2)	87.2 (20.8)	85.9 (22.9)	86.7 (22.3)	0.2 (-5.2;5.5)	0.954
Health care staff not being intimidating	92.4 (22.3)	92.9 (22.8)	85.3 (31.0)	91.4 (22.8)	88.5 (25.0)	89.3 (24.1)	-1.1. (-7.7;5.6)	0.756

1) Mean scores provided for all patients answering the items
2) Mean weighted change: the difference in the area under the curve (AUC) converted to a 0-100 scale. A positive mean weighted change value indicates (more) improvement in satisfaction in the intervention group compared to the control group.
3) P-value provided for differences in mean changes between groups for complete cases.