



Standardizing Integrated Oncology and Palliative Care Across Service Levels: Challenges in Demonstrating Effects in a Prospective Controlled Intervention Trial

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ABSTRACT

Introduction: Patients with cancer often want to spend their final days at home. In Norway, most patients with cancer die in institutions. We hypothesized that full integration of oncology and palliative care services would result in more time spent at home during end-of-life.

Anne Kari Knudsen's affiliations have changed since the time of this study.

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Methods: A prospective non-randomized intervention trial was conducted in two rural regions of Mid-Norway. The hospitals' oncology and palliative care outpatient clinics and surrounding communities participated. An intervention including information, education, and a standardized care pathway was developed and implemented. Adult non-curative patients with cancer were eligible. Proportion of last 90 days of life spent at home was the primary outcome.

Results: We included 129 patients in the intervention group (I) and 76 patients in the comparison group (C), of whom 82% of patients in I and 78% of patients in C died during follow-up. The mean proportion of last 90 days of life spent at home was 0.62 in I and 0.72 in C ($p=0.044$),

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with 23% and 36% ($p=0.073$), respectively, dying at home. A higher proportion died at home in both groups compared to pre-study level (12%). During the observation period the comparison region developed and implemented an alternative intervention to the study intervention, with the former more focused on end-of-life care.

Conclusion: A higher proportion of patients with cancer died at home in both groups compared to pre-study level. Patients with cancer in I did not spend more time at home during end-of-life compared to those in C. The study intervention focused on the whole disease trajectory, while the alternative intervention was more directed towards end-of-life care. “Simpler” and more focused interventions on end-of-life care may be relevant for future studies on integration of palliative care into oncology.

Trial Registration: ClinicalTrials.gov Identifier: NCT02170168.

PLAIN LANGUAGE SUMMARY

Palliative care is an important part of cancer care to improve patients’ quality of life. To be cared for and die in the preferred place are quality markers in palliative care. Patients with cancer often want to spend their final days at home. In Norway, most patients with cancer die in institutions. We hypothesized that full integration of cancer and palliative care would result in more time spent at home during end-of-life. An intervention that included information, education,

and a standardized care pathway was developed and implemented in a region of Mid-Norway (the intervention region, I). A similar region served as comparison region (C). Adult patients with cancer treated with non-curative intent were eligible. Altogether, 129 patients in I and 76 patients in C were included in the study, of whom 82% in I and 78% in C died during follow-up. The mean proportion of time spent at home last 90 days of life was 0.62 in I and 0.72 in C ($p=0.044$), and 22.6% and 35.6% ($p=0.073$) died at home, respectively. A higher proportion died at home in both groups compared to pre-study national levels (12%). During the study period, C developed and implemented an alternative intervention to the study intervention, with the former placing more focus on end-of-life care compared to the she study intervention that focused on the whole disease trajectory. This may explain why the intervention did not result in more time spent at home during end-of-life as compared to C. “Simpler” interventions directed towards the study’s primary outcome may be relevant for future studies on integration of palliative care into oncology.

Keywords: End-of-life; Integration; Oncology; Palliative care; Regional model; Time at home

Key Summary Points

Why carry out this study?

Patients with cancer often want to spend their final days at home.

Integration of oncology and palliative care services early in the disease trajectory may contribute to more time at home at the end-of-life.

What was learned from the study?

Compared to the control group, the study intervention did not result in patients with cancer spending more time at home at the end-of-life.

The study intervention was complex and not solely focused on end-of-life care.

Future studies on integration of oncology and palliative care services should have “simpler” and more focused interventions on end-of-life care.

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INTRODUCTION

Modern palliative care (PC) is an important part of oncology, and early introduction is recommended in conjunction with anticancer therapy [1–3]. PC can be delivered in a variety of settings, including inpatient units, outpatient clinics, nursing homes, and the home (home-based care) [4, 5]. The increasing incidence and prevalence of cancer warrant rethinking the care delivery models [3]. In scattered populated areas, decentralized PC services are useful [6].

PC interventions are often complex [7, 8]. The use of scientifically recommended methods, such as randomized controlled trials (RCTs) to study their effects may be difficult due to poor recruitment, high attrition rates, bias, confounding, and small sample sizes [7]. However, well-founded study objectives evaluated by sound and time-responsive outcome measures are recommended [7]. Time spent at home is recognized as a valid outcome to assess the quality of end-of-life (EOL) care and is in line with patients' preferences [9–11]. In Norway, the majority of patients with cancer die in institutions, and this represents a pattern strengthened over the past decades [12]. Compared to other European countries, Norway is at bottom of the list of patients with cancer dying at home [13]. Prior to the Covid-19 pandemic, only 10–12% of patients with cancer died at home in Norway [14]; this had increased to 16% in 2021. Being able to spend the last phase of life at home and die at home if preferred depends on several factors, such as family support and easy access to healthcare services [15, 16].

Implementing PC interventions into existing healthcare structures is challenging [17, 18]. Albeit the benefits of early integration of PC in oncology having been known for more than a decade, precise knowledge on which 'active components' in PC improve outcomes is still lacking [8]. Published research mainly addresses physical, psychological, social, and EOL care aspects [1, 2, 19–22], but few studies have addressed the coordination of care.

In previously publications, we described the development and implementation of a regional oncology and PC program [17, 23]. The program consisted of a complex intervention and represented full integration of oncology and PC throughout the entire disease trajectory, including improved care coordination within and between services at different levels of healthcare [23]. The development of the program was based on results from earlier studies in the areas of oncology and PC care and focused on increasing time spent at home at the EOL for patients with cancer [2, 17, 23–25]. From this studies, we concluded that development of the program was feasible, and healthcare providers reported that it improved cancer care. However, the program was only used to a limited extent in clinical practice. To evaluate its effectiveness on clinical outcomes, we conducted a prospective controlled non-randomized intervention trial in two health regions in Mid-Norway. This paper presents the clinical outcomes of this intervention trial. We hypothesized that the measurable effects of the complex intervention would increase during the project period, and that a major part of this change would be caused by the complex intervention and not only by general work to improve healthcare services. Time spent at home during the last 90 days of life was chosen as primary clinical outcome.

METHODS

Design and Participants

This prospective controlled non-randomized intervention trial was conducted in two regions of Mid-Norway, the Orkdal Region [23] and the Romsdal Region. Two hospitals in these regions, Orkdal Hospital and Molde Hospital, respectively, coordinated the trial. Characteristics of the two regions are given in Table 1.

Patients in the intervention group (I) resided in 13 municipalities neighboring Orkdal Hospital. Patients in the comparison group (C) were recruited from Molde Hospital and nine adjacent municipalities.

Inclusion and Exclusion

Eligibility criteria were: advanced loco-regional and/or metastatic cancer; adult residents (> 18 years of age) of the participating municipalities; and capability to comply with study procedures and read and write Norwegian.

Patients receiving anticancer therapy with a curative intent were excluded.

The Intervention Group

A complex intervention focusing on introducing PC along the entire disease trajectory was introduced in the intervention group. The intervention was based on previous studies and complied with national standards for palliative cancer care [24–29]. The activities and strategies included in the intervention are summarized in Table 2, and

Table 1 Characteristics of the regions

Characteristics of the regions	Intervention region (I)	Comparison region (C)
No. of inhabitants	56,000	66,000
No. of municipalities	13	9
No. of driving hours from the most remote municipality to the hospital	2	2
No. of healthcare workers identified as working with cancer and palliative care	1320	817
No. of nurses at the outpatient clinic	3.0	6.5
No. of oncologists at the outpatient clinic	2.0 ^c	1.0
No. of palliative care physicians at the outpatient clinic	0 ^c	0.5
Referral to palliative care team based on needs and symptom burden (yes/no)	No ^c	Yes
No. of consultations in 2016 at the outpatient clinic	3800	3600
Cancer incidence 2015 (<i>N</i>) ^a	382	484
Cancer prevalence 31 December 2019 (<i>N</i>) ^a	3443	4217
No. of deaths from cancer in 2013 ^b (<i>N</i>)	147	167
<i>Place of death patients with cancer 2013^b</i>		
Hospital (<i>N</i> (%))	59 (40%)	65 (39%)
Nursing home (<i>N</i> (%))	69 (46%)	78 (47%)
Home (<i>N</i> (%))	17 (12%)	20 (12%)
Not known (<i>N</i> (%))	2 (1.4%)	4 (2.4%)

^aData from Cancer registry of Norway, 2019. The interpretation and reporting of these data are the sole responsibility of the authors, and no endorsement by the Cancer Registry of Norway is intended nor should be inferred

^bData from the Norwegian Cause of Death Registry, 2013

^cIntegrated oncology and palliative care

details on implementation have been described elsewhere [17, 23]. The main components were:

1. A standardized care pathway (SCP) with integrated and coordinated oncology and PC services throughout the disease trajectory and across healthcare levels.
2. An educational program intended to improve healthcare professionals' (HCPs') knowledge and skills in oncology and PC.
3. An information program on oncology and PC aimed at the public, patients, and carers.

The intervention hospital had an outpatient clinic providing integrated oncology and PC services at all stages of the disease, delivered by one team of HCPs consisting of an oncologist and oncology nurse, a physiotherapist, an occupational therapist, a chaplain, a dietitian, and a social worker [23]. The patients were thus not referred to PC when needed. Due to the lack of oncologists with formal training in palliative medicine in Norway, medical residents in oncology trained in palliative medicine in cancer during their oncology fellowship provided care and advice [23]. Home care nurses, nurses at nursing homes, and general practitioners (GPs) in the communities could contact the intervention hospital around the clock, where they had access to nurses and physicians trained in oncology and PC at the outpatient clinic Monday to Friday between 08 a.m. and 16 p.m [23]. Out of hours, the

internal medicine department at Orkdal Hospital or Cancer Clinic at Trondheim University Hospital could be contacted.

The Comparison Group

The comparison hospital had a cancer outpatient clinic and a PC team of whom 50% were physicians with formal training in palliative medicine (Table 1). Patients were referred to the PC team based on needs and symptom burden. The primary focus of the team was providing PC and included home visits upon request and providing support for the patients and their families. Nurses from the communities and the local hospital collaborated on education in a PC network at least once a year. PC physicians collaborated with GPs through visits to the GP offices, visits with the GP to patients at home or in nursing homes, and through bi-annual PC training courses. In addition, home care nurses, nursing home nurses, and GPs could contact a hospital PC physician around the clock. A project focusing on structured advance care planning (ACP) and a palliative plan in primary healthcare to all individuals with life-limiting illnesses, such as incurable cancer, was launched in the comparison region in 2015, and systematically implemented from January to June 2018 (Table 3) [30].

Table 2 Summary of the main components of the intervention in the intervention region

Standardized care pathway	Education	Information
Symptom assessments	Standardized care pathway	Public meetings
Symptom treatment	Nutrition, depression, delirium	Brochures
Multidisciplinary	Acute oncology	Web-site
Carers	Pain	Newspaper
Nurse checklists when change of place of care	Gastrointestinal conditions related to cancer	
Description of content of consultations	Dying patient	
Referral criteria	Carers	
Care and treatment plan when the patient is dying	Communication	

Table 3 Timeline

	2013	2014	2015	2016	2017	2018	2019
Intervention region							
Planning of intervention	■						
Implementation		■	■	■	■	■	
Inclusion of participants		■	■	■	■		
Follow-up		■	■	■	■	■	■
Comparison region							
Planning of ACP			■	■	■		
Implementation of ACP						■	
Inclusion of participants			■	■	■		
Follow-up			■	■	■	■	■

ACP advance care planning

Data Collection and Assessments

Data were managed by 29 community nurses and The Trial Office, Trondheim University Hospital. Paper-based forms were used. At inclusion, information on patient demographics, cancer diagnosis, disease stage and location of metastases, present anticancer treatment, medications, place of care, and performance status were registered. Updates on the patients' general condition, use of hospital services and admissions, and use of community healthcare services (days in rehabilitation and nursing homes included) were collected every 4 weeks. Date and place of death were recorded.

Patients received questionnaires at inclusion every 4 weeks for 2 years or until death. Patients included in the study for > 2 years received questionnaires every 6 months after 2 years to avoid loss of motivation to participate. Data on symptom intensity and quality of life (QoL) were collected using the European Association for Palliative Care (EAPC) basic dataset [31] and European Organization for Research and Treatment of Cancer "Quality of Life Questionnaire Core 15 palliative" (EORTC QLQ C15-PAL) [32]. Furthermore, every 12 weeks the patients stated preferred places of terminal care

and death. These questions formulated were introduced by: "We know from experience that you might change your mind over time. We would like to get your opinion about the next questions again, independently of what you have answered earlier." (1) "Many persons, sick and healthy, think of where they, once in time, prefer to die. When time comes, and you yourself could chose, where would you prefer to die?" (2) "If you could choose where to be cared for at the end of life, where would you prefer to receive treatment and care?" Response categories were "Home", "Nursing home", "Hospital," or "Others." The last recorded response was used for analysis.

Pre-study data on cancer deaths and place of death were obtained from the Norwegian Cause of Death Registry. The Norwegian Cancer Registry provided data on cancer incidence and prevalence (Table 1).

Outcomes

The primary outcome was the proportion of the final 90 days of life spent at home. The secondary outcome was the number of home deaths. Death at preferred place and patients'

health-related QoL as measured by EORTC QLQ C15-PAL served as exploratory outcomes [32].

Data Analyses and Statistics

We calculated that 250 deaths would allow a power of 90% for the detection of at least a 20% difference in the mean proportions of time spent at home during the final 90 days of life between I and C, provided a C proportion of 45% and with a two-sided significance level of 5%.

The proportion of the final 90 days of life spent at home was calculated by subtracting the number of days spent in hospital, nursing homes, or rehabilitation institutions from the number of days at home. Residency in sheltered municipal housing was defined as “home,” while residency in a nursing home was not. Day of discharge was counted as inpatient-day and day of admission was not. For patients who died prior to 90 days after inclusion, the proportion of remaining lifespan spent at home was used. Home death was analyzed as dying at home compared to dying elsewhere. The global QoL item of the EORTC QLQ-C15-PAL was used for analysis of QoL at inclusion and before death.

Descriptive statistics were used to analyze population characteristics and calculate death at preferred place. Pearson’s Chi-square test was used for group comparisons, and the Welch *t*-test was used in case of unequal variances. The proportion of the final 90 days of life spent at home was approximately normally distributed. A two-sided independent *t*-test was used to compare means of proportions. Logistic regression was used to estimate odds ratio (OR) for dying at home in the compared groups. To compare deaths at preferred place between the two groups, Pearson’s Chi-square test was used. The global QoL item of EORTC QLQ-C15-PAL was scored from 1 (“very poor”) to 7 (“excellent”), and the result was calculated following the procedures of the EORTC QLQ-C15-PAL Scoring Manual: $\text{Score} = ([\text{Raw score} - 1]/6) \times 100$ [33].

Kaplan–Meier estimates were used to calculate time from inclusion to end of follow-up or death, and to calculate time from last reported preferred place of terminal care and preferred place of death to death. Linear and logistic

regression models were used to explore possible influences by demographic and clinical differences on the proportion of the final 90 days spent at home and home deaths, respectively. For both models, a univariate analysis with “region” as the independent variable was performed as the first step; this was followed by multivariate analyses that were performed to adjust for variables differing between the two compared groups.

P values ≤ 0.05 were considered to be statistically significant.

For all analyses, Stata Statistical Software Release 16.0 and 17.0 (StataCorp LP, College Station, TX, USA) were applied.

Ethics and Consent

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Regional Committee for Medical Research Ethics Central Norway, REK Central (2014/212). Written informed consent was obtained from all participants included in the study. In cases where the participant was competent to give oral informed consent but not able to write, an adult family member or HCP signed a proxy consent.

RESULTS

Protocol Deviations

Patients were entered in the study from November 2014 to December 2017; the follow-up period ended December 2019 (Table 3). Due to the inclusion rates and survival rates being different from assumed, the preplanned inclusion and follow-up periods were prolonged by 1 and 2 years, respectively. The study was closed before reaching the planned 250 analyzable deaths and, in addition, the C proportion was smaller (36%) than assumed in the study power calculations.

Patient Characteristics

Eligible patients were recruited from the outpatient clinics, with 130 patients included in I and

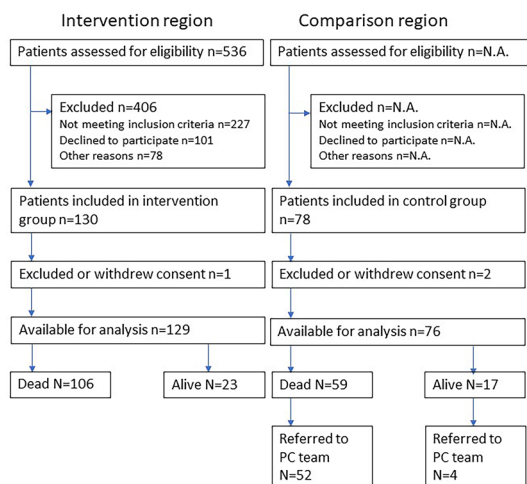


Fig. 1 Study flow diagram. *N.A.* not assessed, *PC* palliative care

78 patients included in C (Fig. 1). One patient in each group withdrew consent and one patient in the comparison group did not fulfill inclusion criteria.

Patient characteristics at inclusion are given in Table 4. Mean age was 70.7 (range 38–92) years in I and 68.1 (range 47–84) years in C. In I and C, 57% and 82% of patients, respectively, had a Karnofsky Performance Status (KPS) of at least 90% [34]. Compared to patients in C, fewer patients in I received medical anticancer therapy at inclusion, and they also lived farther away from the hospital.

Median time from inclusion to end of follow-up or death was 425 (95% CI 272–557) days in I and 403 (95% CI 268–635) days in C. In C, 56 patients (74%) were referred to the PC team. By the end of the study period, 106 (82%) patients in I and 59 (78%) patients in C died (Fig. 1); of these, 16 in I and nine in C died before reaching 90 days of observation.

Primary Outcome

Patients who died before study closure were analyzed for the primary outcome. The mean number of days of inclusion was 81 (range 1–90) in I and 85 (range 20–90) in C. The mean proportion of time spent at home during the last 90 days of

life was 0.62 (95% CI 0.56–0.68) in I and 0.72 (95% CI 0.64–0.80) in C (Fig. 2a; Electronic Supplementary Material [ESM] Table S1), with a statistical difference of 0.10 (95% CI 0.00–0.20, $p=0.044$) in favor of C. When adjusting for education level, performance score, symptom score (<4 or ≥ 4), anticancer therapy (yes/no), and distance from home to hospital, the difference was 0.15 (95% CI 0.03–0.27, $p=0.018$) in favor of C.

Secondary and Exploratory Outcomes

Twenty-four (22.6%) and 21 (35.6%) patients died at home in I and C, respectively (Fig. 2b; ESM Table S2; $p=0.73$). Univariate logistic regression analysis showed an OR of 1.9 (95% CI 0.94–3.8; $p=0.075$) in favor of dying at home in C. When adjusting for education level, performance score, symptom score (<4 or ≥ 4), anticancer therapy (yes/no), and distance from home to hospital, the OR was 2.6 (95% CI 0.97–6.7, $p=0.059$) in favor of C. Forty-one (38.7%) patients in I and 18 (30.5%) patients in C died in hospital; the corresponding numbers for deaths in nursing homes were 41 (38.7%) and 20 (34.0%), respectively (Fig. 2b; ESM Table S2).

Of the patients who had died, 90 patients (response rate=85%) in I and 45 patients (response rate=76%) in C had stated a preferred place of death. In both groups, approximately one third of the responses were collected fewer than 90 days prior to death. In their response to the question on preferred place of death, 57 (63.3%) patients in I and 25 (55.6%) patients in C preferred home death (Fig. 2c; ESM Table S3), while 55 (64.7%) and 32 (69.6%) patients in I and C, respectively, preferred terminal home care. Thirty-four (37.8%) patients in I and 14 (31.1%) patients in C died at the preferred place (Pearson $\chi^2 p=0.45$).

QoL, as scored by EORTC QLQ C15-PAL item 15, revealed no mean group differences at inclusion: 66.2 ($n=99$, 95% CI 61.3–71.0) in I versus 65.2 ($n=46$, 95% CI 58.0–72.4) in C ($p=0.82$) (Fig. 2d). Comparison of the mean decline in scores from inclusion to last measurement revealed a significant difference in favor of C: -18.3 ($n=73$, 95% CI -24.5 to -12.1) in I versus -7.2 ($n=44$, 95% CI -16.3 to 1.9) in C ($p=0.04$) (Fig. 2d).

Table 4 Characteristics of patients at inclusion

	All patients				Patients who died				
	Intervention group		Comparison group		Intervention group		Comparison group		P
	N	Values	N		N		N		
<i>Age, mean years (min-max)</i>	129	70.7 (38-92)	76	68.1 (47-84)	106	70.3 (38-92)	59	68.4 (47-84)	0.22
<i>Sex</i>	129		76		106		59		0.56
Female, n (%)	48	(37%)	34	(45%)	40	(38%)	25	(42%)	
Male, n (%)	81	(63%)	42	(55%)	66	(62%)	34	(58%)	
<i>Civil status</i>	125		58		103		46		0.62
Married/cohabitant, n (%)	84	(67%)	41	(71%)	71	(69%)	31	(67%)	
Divorced, n (%)	6	(4.8%)	5	(8.6%)	6	(5.8%)	5	(11%)	
Widowed, n (%)	17	(14%)	8	(14%)	12	(12%)	6	(13%)	
Single, n (%)	18	(14%)	4	(6.9%)	14	(14%)	4	(8.7%)	
<i>Residence</i>	124		58		102		46		0.37
Villa or semi-attached house, n (%)	108	(87%)	51	(88%)	90	(88%)	39	(85%)	
Apartment, n (%)	11	(8.9%)	6	(10%)	7	(6.9%)	6	(13%)	
Sheltered municipal housing, n (%)	5	(4.0%)	1	(1.7%)	5	(4.9%)	1	(2.2%)	
Nursing home, n (%)	0		0		0		0		
<i>Living situation</i>	125		57		103		45		0.71
Alone, n (%)	38	(30%)	17	(30%)	29	(28%)	15	(33%)	
With spouse/partner, n (%)	77	(62%)	35	(61%)	64	(62%)	28	(62%)	
With children, n (%)	2	(1.6%)	0		2	(1.9%)	0		
With spouse/partner and children, n (%)	6	(4.8%)	5	(8.8%)	6	(5.8%)	2	(4.4%)	
With others	2	(1.6%)	0		2	(1.9%)	0		
<i>Educational level</i>	123		56		101		44		0.042

Table 4 continued

Patients' characteristics at baseline	All patients				Patients who died				
	Intervention group		Comparison group		Intervention group		Comparison group		P
	N	Values	N		N		N		
Lower than high school	54	(44%)	14	(25%)	45	(45%)	10	(23%)	
High school	41	(33%)	26	(46%)	31	(31%)	20	(45%)	
University	28	(23%)	16	(29%)	25	(25%)	14	(32%)	
Distance from home to hospital, mean km (min-max) ^a	44.6	(0-130)	27.1	(0-87)	45.9	(0-130)	23.5	(0-87)	0.000
Karnofsky performance status [34]	127		76		104		59		0.005
90-100%, n (%)	73	(57%)	62	(82%)	55	(53%)	46	(78%)	
60-80%, n (%)	45	(35%)	131	(17%)	41	(39%)	12	(20%)	
≤ 50%, n (%)	9	(7.1%)	1	(1.3%)	8	(7.7%)	1	(1.7%)	
Cancer diagnosis	129		76		106		59		0.31
Upper gastrointestinal except pancreas, n (%)	13	(10%)	7	(9.2%)	11	(10%)	6	(10%)	
Colorectal, n (%)	17	(13%)	9	(12%)	17	(16%)	9	(15%)	
Pancreas, n (%)	12	(9.3%)	4	(5.3%)	12	(11%)	3	(5.1%)	
Lung, n (%)	8	(6.2%)	13	(17%)	8	(7.6%)	11	(19%)	
Breast, n (%)	11	(8.5%)	11	(14%)	9	(8.5%)	6	(10%)	
Female genital organs, n (%)	4	(3.1%)	4	(5.3%)	3	(2.8%)	4	(6.8%)	
Prostate	30	(23%)	14	(18%)	19	(18%)	10	(17%)	
Urinary organs except prostate, n (%)	14	(11%)	3	(4.0%)	12	(11%)	2	(3.4%)	
Lymphoid, hematopoietic and related tissue, n (%)	11	(8.5%)	6	(7.9%)	7	(6.6%)	5	(8.5%)	

Table 4 continued

Patients' characteristics at baseline	All patients				Patients who died									
	Intervention group		Comparison group		Intervention group		Comparison group		P					
	N	Values	N		N		N							
Other sites, n (%)	9	(7.2%)	5	(6.6%)	8	(7.6%)	3	(5.1%)						
<i>E.APC symptom score^b, n (median [25, 75 percentile]) [31]</i>														
Pain	122	0	(0, 3)	54	1	(0, 3)	0.046	100	0	(0, 2)	44	1	(0, 3)	0.14
Tiredness	122	2	(0, 4)	56	5	(2, 6)	0.000	100	2	(0, 4)	46	5	(2, 6.25)	0.003
Drowsiness	121	1	(0, 3)	56	3	(2, 5)	0.000	99	1	(0, 3)	46	3.5	(2, 5.25)	0.000
Nausea	120	0	(0, 0)	56	1	(0, 2)	0.000	98	0	(0, 0)	46	1	(0, 3)	0.000
Lack of appetite	120	0	(0, 3)	57	2	(0, 4)	0.022	98	0	(0, 3.25)	46	2	(0, 5)	0.021
Shortness of breath	121	0	(0, 2)	56	2	(0, 4)	0.002	99	0	(0, 3)	46	2	(0, 4)	0.003
Depression	120	0	(0, 1)	57	1	(0, 3)	0.02	98	0	(0, 1)	46	1	(0, 3)	0.009
Anxiety	122	0	(0, 1)	57	1	(0, 2)	0.17	100	0	(0, 1)	46	1	(0, 2)	0.17
Wellbeing	120	1	(0, 3)	57	2	(1, 4)	0.046	98	2	(0, 3)	46	2	(1, 4)	0.21
Sleep	121	1	(0, 3)	57	2	(1, 4)	0.010	99	1	(0, 3)	46	3	(1, 5)	0.012
Constipation	121	0	(0, 1)	58	0	(0, 2.25)	0.019	99	0	(0, 1)	46	1	(0, 3.25)	0.007
Vomiting	121	0	(0, 0)	57	0	(0, 1)	0.001	99	0	(0, 0)	45	0	(0, 1)	0.000
At least on symptom score $\geq 4^b$	123	64	52%	58	45	78%	0.001	101	54	53%	46	37	80%	0.002
Years from diagnosis to inclusion, mean years (min-max)	129	3.1	(0.03-34.0)	76	3.0	(0.06-15.4)	0.77	106	2.9	(0.03-34.0)	59	2.8	(0.06-15.4)	0.79
Tumor burden	129			76			0.22	106			59			0.16
Locally or locally advanced disease, n (%)	16		(12%)	5		(6.7%)		12		(11%)	2		(3.5%)	
Distant metastatic disease, n (%)	111		(86%)	71		(93%)		93		(88%)	57		(97%)	
Remission, n (%)	2		(1.6%)	0		0		1		(0.9%)	0			

Table 4 continued

Patients' characteristics at baseline	All patients				
	Intervention group		Comparison group		P
	N	Values	N	Values	
<i>Ongoing medical anticancer therapy^c</i>	129		76		0.000
Yes, n (%)	106	(82%)	75	(99%)	
No, n (%)	23	(18%)	1	(1.3%)	
<i>Ongoing pain treatment</i>	129		76		0.41
Yes, n (%)	62	(48%)	32	(42%)	
No, n (%)	67	(52%)	44	(58%)	
					0.52

^aDistances calculated by using <http://no.avstander.himmera.com>

^bSymptom intensity score was rated on a numerical rating scale from 0 (best situation) to 10 (worst situation)

^cMedical anticancer therapy, including hormone therapy

EAPC European Association for Palliative Care

DISCUSSION

Statement of Principal Findings

In both groups, the proportion of home deaths among patients with cancer increased from the pre-study period of 12% to 22.6% (I) and 35.6% (C). It also increased more than in the general population of Norway during the same period (12% in 2019) [14].

We assumed that C represented the general situation for PC in Norway. However, during the study period, an intervention directed towards EOL care was initiated in C [30]. Consequently, the study consisted of two different interventions, both of which were having a positive effect on the proportion of home deaths in both groups, as compared to pre-study levels. Patients in C spent more time at home compared to patients receiving the intervention measures in I during the final 90 days of life. Hence, measurable effects of the complex intervention did not increase during the project period as we hypothesized. The difference between the groups in proportion of home deaths did not reach statistical significance. There were no group differences in deaths at preferred place. The decline in QoL during the study period for the patients who died was larger in I.

Appraisal of Methods

We chose a study design consisting of an intervention group and a control group. The rationale for a control group was to better be able to measure a potential intervention effect. An RCT or a cluster-randomized trial was not feasible due to small-scale conditions and the system-level nature of the intervention. Given the complex nature of the intervention, a study design with baseline observations before implementation of the complex intervention may also be an appropriate design.

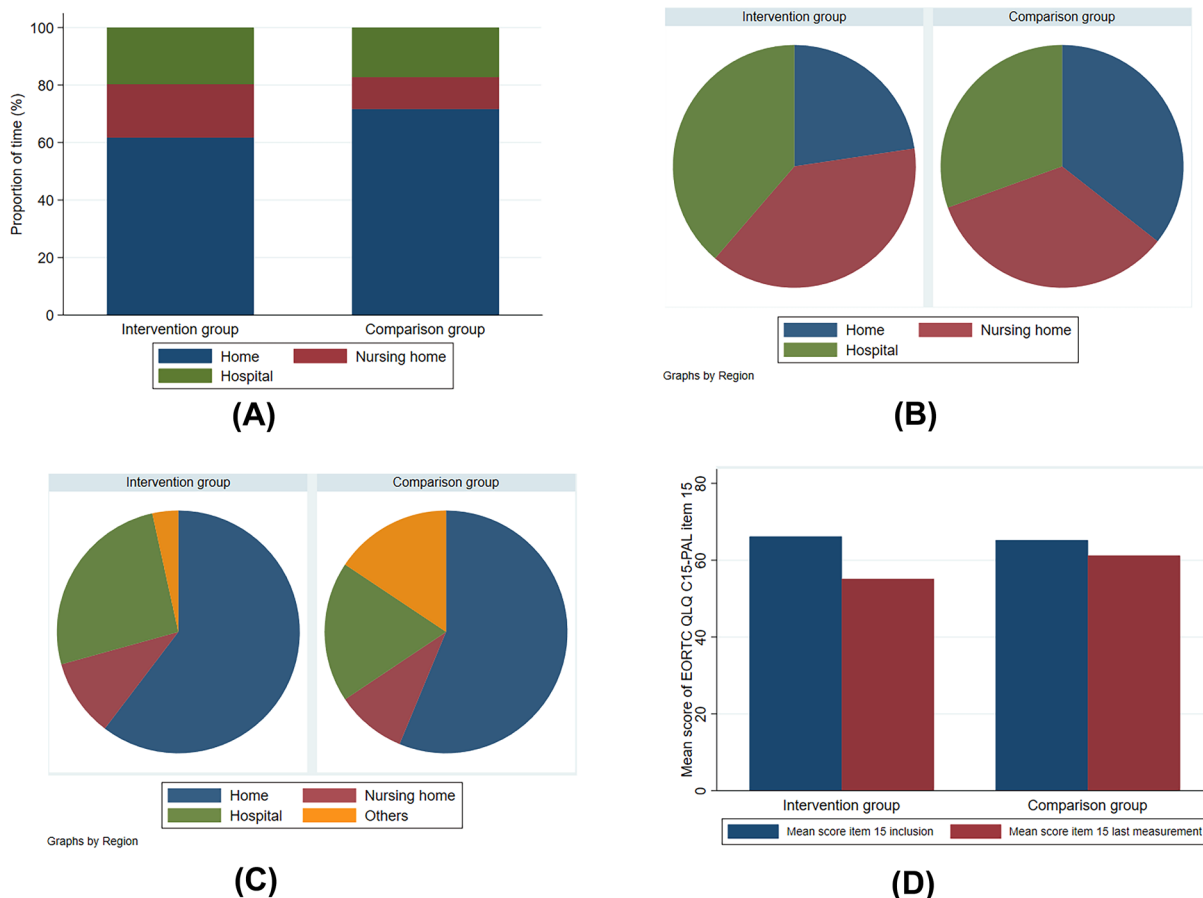


Fig. 2 Primary, secondary, and exploratory outcomes. **a** Mean proportion of time spent in different care settings during the last 90 days of life. **b** Actual place of death. **c** Preferred place of death. **d** Mean score of EORTC QLQ

C15-PAL item 15 at inclusion and last measurement before death. *EORTC QLQ C15-PAL* European Organization for Research and Treatment of Cancer “Quality of Life Questionnaire Core 15 palliative”

Since the effect of the intervention in C was larger than anticipated, we compared the content of the interventions related specifically towards EOL care. The interventions in both groups included those that focused on EOL care and, in particular, home care. The actual study intervention had a broader aim and included the entire disease trajectory. Patients were exposed to the intervention for a mean of 14 months prior to death. In C, the applied intervention was more directed towards EOL, with ACP introduced in primary care to the patients at a mean of 114 days prior to death [30]. The comparison region (C) had a PC specialist who worked 50%, and the nurses and GPs had special training in PC. Consequently, an unintended intervention

with focus on EOL was implemented in the comparison region during the study period. The intervention region lacked a physician with formal competence in PC, which may also had a negative influence on the results.

Patients with advanced cancer were recruited regardless of life expectancy and PC needs. A median follow-up of > 1 year is unusual in PC trials [35]. The long follow-up in the present study was in line with our aim to provide the patients with the intervention over a substantial period before they reached the final phase of their life. One may argue whether study endpoints focusing on the entire disease trajectory, such as regular measurement of symptom burden, quality of life, and satisfaction with care,

would have been more appropriate in this case than study endpoints directed towards EOL, and whether the study design at all allowed for assumptions on causality [36, 37].

Previously published results revealed that the SCP was used to a limited extent [17]. Hence, insufficient implementation of the intervention and lack of adherence may also have affected the results. Potential effects of the intervention were measured as early as at the initiation of the implementation process, possibly before effects were evident. Furthermore, no pilot study on intervention acceptance and uptake in clinical practice was conducted.

The study was conducted with protocol deviations. The preplanned inclusion and follow-up periods were prolonged, and the study was closed before reaching the number of patients and group proportions used for power calculations [38]. Temporal trends are likely to occur and be evident in a long study period [39]. In our case, implementation of the intervention in the comparison region started before the end of the follow-up period of our study [30].

Comparison with Previous Work and Possible Reasons Why the Intervention Failed

Implementing complex interventions with the intentions to alter HCPs' behavior is difficult [18, 39, 40]. A cluster-randomized trial in Mid-Norway evaluating a care pathway for home-dwelling elderly after hospital discharge was inconclusive due to incomplete use of the intervention [41]. The authors of that study suggested that intervention adherence should be ensured before study start. Another Norwegian cluster-randomized trial investigating the effect of PC on the use of anticancer treatment at the EOL found no differences between the groups [42]. As in our study, the intervention did not have the desired effect, probably due to the HCPs having a too low fidelity to the intervention to change clinical practice [42]. The reasons for insufficient implementation in our study are heterogeneous and may include factors such as differences in hospital and primary care cultures, lack of management anchoring, different information and

communications technology systems, and preconceptions about PC referrals [17, 18, 43, 44]. Implementation of the intervention stretched over a 5-year period, and change in key staff during this period may have contributed negatively to the follow-up of adherence to the SCP [17]. Data from the comparison region showed that 50% of patients with advanced cancer got an ACP in primary care between 2018 and 2020 [30]. The intervention in the Romsdal Region was simpler, had a stronger focus on EOL care, and involved HCPs who had devoted their time and focus on EOL care.

A study comparing hospital expenditures for dying patients with cancer demonstrated that Norway is at the top of the list in terms of per capita hospital days during the last 180 days of life [45]. Currently there is a national political effort to better facilitate EOL home care and home death [46]. In 2010, 44% of all cancer deaths in Norway occurred in hospitals; by 2019 this proportion had decreased to 33% [14]. During the same period, the proportion of cancer deaths at home was stable (11% vs. 12%) [14]. In our study, we found that more than half of the patients preferred home death, which is not in line with what happens in "real life."

Implications for Further Work

Our intervention was complex and insufficiently implemented [17]. In the comparison group (C), the ACP project in primary healthcare probably had a higher uptake than the more comprehensive SCP in I [30]. The ACP intervention was highly anchored and represented a 'simpler' intervention than the SCP, with the former more focused on the clinical endpoints chosen for this study. One may reflect whether an SCP containing fewer 'active PC components' would be less challenging to implement, and whether it represents possible strategy for the future efforts to study integration of PC into "main stream" oncology. Still, the dilemma remains: Which are the most important components of early integrated PC, and how do we develop interventions simple enough for practicality and complex enough for effect [47]?

In the current study, most of the patients in both groups were cared for close to their homes and died in their municipalities [15]. Care and death where preferred are regarded as important healthcare quality measures [46]. Most of the included patients preferred to be cared for and die at home. However, a substantial fraction preferred to be cared for and die in nursing homes or hospitals. Identifying these patients is important both from research and healthcare planning perspectives.

CONCLUSION

Patients in the intervention group (I) did not spend more of their final 90 days of life at home than patients in the comparison group (C). The situation in C differs from the general situation in Norway in general. The study intervention focused on the whole disease trajectory, while an alternative intervention in C was more directed towards EOL care. “Simpler” interventions may be relevant for future studies of integration of PC into oncology.

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Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole and have given their approval for this version to be published.

Author Contributions. Anne Kari Knudsen, Jo-Åsmund Lund, Morten Thronæs, and Stein Kaasa designed the study. Anne-Tove Brenne, Erik Torbjørn Løhre, Anne Kari Knudsen, and Bardo Driller recruited participants and collected data. Anne-Tove Brenne, Anne Kari Knudsen, and Cinzia Brunelli analyzed the data. Anne-Tove Brenne, Erik Torbjørn Løhre, and Stein Kaasa wrote the manuscript. Anne-Tove Brenne had the primary responsibility for the final content. All authors commented on previous versions of the manuscript, read, and approved the final version and consented to submission.

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Data Availability. The data analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of Interest. Anne-Tove Benne, Erik Torbjørn Løhre, Anne Kari Knudsen, Jo-Åsmund Lund, Morten Thronæs, Bardo Driller, and Cinzia Brunelli declare that they have no competing interests. Stein Kaasa led the committee constituted by the Government from May 2016 to December 2017 that published the Official Norwegian Report on palliative care [6]. Anne Kari Knudsen’s affiliation has changed since the time of the study, and is now affiliated with County Governor Oslo and Viken, Oslo, Norway.

Ethical Approval. This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Regional

Committee for Medical Research Ethics Central Norway, REK Central (2014/212). Written informed consent was obtained from all individual participants included in the study. In cases where the participant was competent to give oral informed consent but not able to write, an adult family member or HCP signed a proxy consent.

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