Patient Empowerment by Interactive Cancer Pain Management

Bridging the gap between patient and caregiver

Nienke te Boveldt

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by Interactive Cancer Pain Management

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Prof. dr. M.J.F.J Vernooij-Dassen
Prof. dr. K.C.P. Vissers

Copromotor

Dr. Y. Engels

Manuscriptcommissie

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Prof. dr. H. van Goor
Prof. dr. L. Schoonhoven *(University of Southampton, UK)*

Paranimfen

Dhr. G.H.J. te Boveldt, MSc
Dhr. J.A.J. te Boveldt, MSc

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Prologue

In this thesis we explore cancer pain management. During my Master Nutrition and Health at the Wageningen University, I gained special interest in improving quality of life in patients with cancer. As pain is one of the most common and feared symptoms of cancer I was inspired by this study.

One of the important lessons I learned during my PhD was that performing a study in clinical practice is not just applying the research protocol into practice.

I hope this thesis will encourage active involvement of patients in their own pain management and can help to change thinking about cancer pain management.

"Mijn motivatie om dit proefschrift tot een goed einde te brengen is onder andere geweest de pijn die jij hebt moeten doorstaan tijdens de ziekte die je K noemde, omdat je het zo`n naar woord vond." Lieve oma, ik draag dit proefschrift aan jou op.

1

Introduction

Introduction

Mrs A is diagnosed with cancer and suffers from pain in her back associated with bone metastasis. She is not able to dress herself anymore because of her back pain. She visits the outpatient clinic. Mrs A hesitates to talk about her pain with her oncologist, because she fears addiction to pain medication and that talking about pain might distract her medical specialist form the life prolonging anti- cancer treatment. The oncologist asks Mrs A if she is doing well. She answers that she is doing quite well and the oncologist writes "is doing well" in her medical record and starts to talk about cancer treatment.

Suffering from cancer pain

In our aging society, cancer prevalence is steadily on the rise. In 2012, the 10-year prevalence of cancer in the Netherlands was 454,388, with 101,864 patients newly diagnosed; in 2013, the 10-year prevalence was 468,939, with 101,848 patients newly diagnosed[1]. Trends from 1989 to 2011 show an average annual increase in incidence of 3%[2]. In 2012, the total number of deaths was 141,000 in the Netherlands of which 43,000 (31%) died of cancer[3]. This illustrates the number of patients in an advanced stage of the disease, which is associated with increased pain. Pain is one of the most prevalent symptoms of patients with cancer[4], with a prevalence ranging from 27%[5] to 60%[6]. Pain can be caused by the tumour itself, can be related to cancer (e.g. muscle spasm, lymphoedema), or to the anticancer treatment[7].

Pain treatment is still inadequate in 31%[8] to 65%[5] of all patients with cancer, whereas adequate pain relief is considered feasible in 71%[9] to 86%[10] of patients if adequately treated. Pain management is essential in all stages of the oncological disease process.

Undertreatment of cancer pain is associated with anxiety, depression and sleep disturbances[11-13]; It hampers daily activities[14], and therefore affects quality of life in these patients.

Undertreatment is the result of different patient- and care provider related barriers. A key patient-related barrier in cancer pain management is the reluctance of many patients to discuss pain with their doctor or to ask for pain medication[15]. This hesitation has a variety of reasons, such as concerns about addiction and fear that reporting pain will distract the physician from treating the cancer[15]. Care providers also experience barriers in cancer pain diagnosis. These include ineffective pain communication with patients[16] and inadequate pain assessment[17].

Pain treatment is inadequate despite the availability of evidence-based clinical practice guidelines (CPGs). The Dutch CPG "Pain in patients with cancer", developed in 2008, is one of the most recent guidelines on this subject in Europe[18]. One of the key recommendations of this CPG is assessment and registration of pain using a validated pain assessment tool each time the patient visits the outpatient clinic[8,18].

However, publishing a guideline alone is insufficient[19]; an implementation strategy is also needed. This strategy should address patient and physician related barriers in cancer pain management.

What this thesis adds

Pain in patients with cancer has been well studied[4-6,8]. However, pain management is poorly understood in medical oncology outpatients. To get more insight in cancer pain management, in this thesis we explored pain prevalence, pain treatment adequacy, pain-related interference with daily activities, pain assessment and pain registration. Exploring the problem of cancer pain management is essential to increase awareness.

In addition, we monitored patients to assess the effect using the interactive distance alert system (MIDAS 4 Cancer Pain) on inadequate cancer pain treatment and discussed the active involvement of patients with cancer in their pain management to provide recommendations for clinical practice.

Concept of pain

The international Association for the Study of Pain (IASP) defined pain as: 'an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage'[20].

Pain can be distinguished into nociceptive and neuropathic pain. Nociceptive pain is defined as 'pain that arises from actual or threatened damage to non-neural tissue and is due to the activation of nociceptors' and neuropathic pain as 'pain caused by a lesion or disease of the somatosensory nervous system'[20]. Pain is multidimensional including physical, psychosocial and existential dimensions. For example psychological distress (depression, anxiety, anger) has been shown to be significantly associated with an increased perception of pain[21].

Cancer pain relief

The aim of adequate pain management is to reduce pain intensity towards an acceptable level with minimal side effects[22]. Often cancer-related pain management initially consists of a combination of anti-tumour treatment and pharmacotherapy[23]. In 1986, The World Health Organization (WHO) published the three step analgesic ladder[23]. This WHO ladder describes the following analgesic treatment steps:
step 1 acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDs); step 2 weak opioids as codeine and tramadol; step 3 strong opioids such as morphine, fentanyl and hydromorphone. For optimal pain relief the multidimensional aspects including physical, psychological and spiritual aspects of pain should be taken into account.

The role of clinical practice guidelines

CPGs can play an important role in improving the quality of care[24,25]. Developing and publishing a guideline is not a guarantee that the guideline will be used[26].

Factors associated with the guideline itself, the organization or setting, the professional and the patient all effect guideline adherence. A structured implementation strategy is necessary to improve cancer pain management[26]. This comprises many challenges at the organisation, patient and caregiver level. In this thesis, challenges at different levels will be studied and discussed: Adequacy of cancer pain treatment, cancer pain registration by medical oncologists, medical oncologists` adherence to the guideline, the effects of pain monitoring with telemedicine on inadequate cancer pain treatment and active involvement of the patient with cancer in their own pain management.

Pain registration

An overview of the pharmacological history, including a list of medication, the response to this medication and possible side effects is important to reflect on prescribed treatment and to adjust treatment when needed[27]. This might improve communication between the patient and the physician and facilitates monitoring of pain treatment.

To improve accuracy of a patient`s current level of pain, validated quantitative measures of pain should be used. Numeric rating scales (NRS) and visual analogue scales (VAS) are validated and most commonly used. An NRS asks patients to rate their pain from 0 for no pain to 10 for the worst pain imaginable.

Although Serlin and colleagues established pain intensity cut-off points already 18 years ago, there is still no consensus on how to categorize pain intensity[14]. Most often, pain is categorized as mild pain (NRS 1-4), moderate pain (NRS 5-6), and severe pain (NRS 7-10)[14]. Despite the availability of simple validated pain assessment tools, in 2001, a study showed that pain was not systematically assessed and registered in oncology practice.[28] The authors reported that none of the medical records of patients with pain included quantitative documentation.

Implementation of guidelines addressing pain assessment has been demonstrated to improve pain outcomes[29].

Pain Management Index (PMI)

The Pain Management Index (PMI) considers pain treatment to be adequate if there is congruence between the patient`s reported level of worst pain and the prescribed analgesics[30,15]. To determine adequacy of analgesic pain treatment, Cleeland`s[30] or Wards`s Pain Management Index (PMI)[15] can be used. Cleelands PMI compares the most potent analgesic prescribed with patient`s reported worst pain intensity[30]. The levels of analgesic treatment are scored as 0, no analgesic; 1 a non-opioid analgesic; 2 a weak opioid; and 3 a strong opioid. The levels of worst pain are scored as 0, absence of pain; 1, mild pain; 2, moderate pain; and 3, severe pain. The PMI score is determined by subtracting the pain level from the analgesic level and can range from -3 (a patient with severe pain receiving no analgesic) to +3(a patient with no pain receiving a strong opioid or equivalent). A PMI score between 0 and 3 indicate adequate pain treatment.

The PMI is based on the WHO ladder and is the most frequently used measure for adequate pain treatment and is useful for evaluating the quality of analgesic treatment.

Theoretical background: patient empowerment

In the past 40 years adequacy of pain treatment in patients with cancer has not improved[4]. Today, both healthcare professionals and administrators clearly recognize that patient centered care is important[31]. Patient centered care could be defined as healthcare providers share control of consultations, decisions about interventions or the management of health problems with patients[32]. Patient centered care can be the backbone of a strategy to improve cancer pain management.

To become real partners in their own care, patients need to be empowered. Since 1988, patient empowerment has gained more attention in healthcare[33].

The European Network on Patient Empowerment (ENOPE 2012) defined patient empowerment as 'a process to help people gain control, which includes people taking initiative, solving problems, and making decisions'[34]. It has been highlighted as central to success in pain management[35]. An empowered patient probably self-manages his/her cancer pain to a larger extent than a non-empowered patient.

Telemedicine can support caregivers and patients to achieve patient centered care, because it might encourage patients to become a partner in their own pain management.

Monitoring pain with telemedicine

E-health, such as telemedicine, describes a range of information and communication technologies that are used to provide healthcare[36].

Telemedicine is defined as 'a subset of telehealth, that uses communication networks for delivery of healthcare services and medical education from one geographical location to another, primarily to address challenges like uneven distribution and shortage of infra-structural and human resources'[36].

Weiner et al. estimated that if information technology and e-health would be fully implemented in 30% of community-based physician`s offices, the healthcare demand for US physicians would be reduced with 4-9%[37]. However, it is unknown whether and how this will change quality of care, and it is unknown whether this is also true for the Netherlands, with a different culture and health care system.

Rationale for use of IVR-SMS to monitor pain

Interactive Voice Response (IVR) with Short Message Service (SMS) alerts allows patients to communicate with their healthcare professionals outside the consultation room. We will monitor patients to assess the effect using the interactive distance alert system (MIDAS 4 Cancer Pain) on the reduction of inadequate cancer pain treatment using IVR and SMS-alerts.

Patients hear a recorded message on their phone and respond to queries using their keypad. SMS-alerts are text messages used to alert health professionals when symptom scores need follow-up. Patients will be asked to report pain on an NRS twice daily, once a week, for 12 weeks. As part of the MIDAS 4 Cancer Pain treatment, an automatic alert (by SMS and email) will be sent to the study nurse when a patient reports a pain score of 5 or higher. The study nurse then contacts the patient within two hours and advises the patient or adjusts pain medication. In addition, the study nurse activates IVR calls and SMS-alerts for the next two days to monitor the clinical impact of the advice or medication change.

IVR-SMS is an example of a telemedicine tool to create a communication network to monitor pain. IVR -SMS creates the possibility to monitor pain at home between consultations. Although a pain diary can also be used to monitor pain between consultations, with IVR-SMS it is possible to act directly, without time delay, on high pain scores and thus shorten the period that patients unnecessarily suffer from pain.

In previous studies SMS-alerts were used in management of asthma[38-40], irritable bowel syndrome[41], diabetes[42] and recurrent pain in children[43].

A pilot test using IVR-SMS alerts to collect prospective and follow-up data on pain intensity in patients with cancer was considered acceptable[44].

In addition, results from a prospective audit exploring the usefulness of a nurse-led telephone intervention for supporting patients with cancer treated with capecitabine, suggested that nurse-led telephone follow-up can potentially lead to reduced severity of symptoms compared to home care[45].

These results encouraged us to set up a study to assess the effect of using the interactive distance alert system (MIDAS 4 Cancer Pain) to monitor patients to reduce inadequate pain management.

However, in a recent multicentre RCT with 253 patients with advanced lung cancer using IVR and alerts to monitor symptoms with nurse feedback appeared to be no more effective in reducing symptom burden than monitoring alone[46].

In 2009 already nine out of ten Dutch inhabitants used a mobile phone[47]; mobile phones are now part of daily life. Therefore, using a mobile phone as a telemedicine tool in healthcare seems to be an opportunity[48,49]. The use of mobile phone SMS-alerts and IVR may encourage active involvement of oncology outpatients in their own pain management. However, the effect of this intervention on the percentage of patients with inadequate cancer pain treatment has never been evaluated.

Research questions and outline of the thesis

In this thesis we monitor patients to assess the effect using telemedicine on the reduction of inadequate cancer pain treatment, discuss active involvement of the patient with cancer in their own pain management and provide recommendations for current practice. The overall objective is to increase awareness and to provide recommendations for clinical practice to improve cancer pain management.

The scope of the problem

The following research questions are addressed:

1. **What is the prevalence of pain and its interference with daily activities in medical oncology outpatients? Is pain treatment adequate in the medical oncology outpatient clinic?** In chapter 2 we describe a cross-sectional study in seven medical oncology outpatient clinics in the south-eastern part of the Netherlands to assess pain prevalence, pain intensity, its interference with daily activities and the adequacy of analgesic pain treatment.

2. **How is pain in patients with cancer registered in medical records by oncologists?** In chapter 3 we report on a multicentre study in six Dutch hospitals with retrospective analysis of medical records of 380 outpatients with cancer to explore pain registration.

3. **Adhere oncologists to the recommendations of the Dutch clinical practice guideline pain in patients with cancer?** In chapter 4 we describe the results of a case-vignette study to assess medical oncologists` reported adherence to evidence-based guidelines in cancer pain management.

How to improve cancer pain management in the outpatient clinic

The following research questions are addressed:

4. **Is IVR-SMS suitable as tool for systematic pain monitoring in patients with cancer?** In chapter 5 we describe the rationale, design and implementation protocol of the Dutch clinical guideline pain in patients with cancer.

5. **Is patient monitoring using interactive distance alert system (MIDAS 4 Cancer Pain) more effective in reducing the percentage of patients with inadequate cancer pain treatment than usual care?** In chapter 6 we report on the results of a cluster randomised trial (RCT). We monitored patients to assess the effect using the interactive distance alert system (MIDAS 4 Cancer Pain) on the reduction of the percentage of patients with inadequate cancer pain treatment.

6. **How to promote active patient participation in cancer pain management?** In chapter 7 we describe an integrative literature review evaluating papers discussing empowerment or related concepts in relation to pain management in patients with cancer. We propose a conceptual model to empower patients in controlling cancer pain.

In chapter 8 the results were discussed.

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2

Pain and its interference with daily activities in medical oncology outpatients

Nienke te Boveldt
Myrra Vernooij-Dassen
Nathalie Burger
Michiel IJsseldijk
Kris Vissers
Yvonne Engels

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Abstract

Background. Pain prevalence at various stages of cancer ranged from 27% to 60% for outpatients. Yet, how pain is managed in this patient group is poorly understood. The primary objective was to assess pain prevalence, pain intensity and its interference with daily activities in medical oncology outpatients. The secondary objectives were the adequacy of analgesic pain treatment and to identify independent predictors for moderate to severe pain. **Methods.** Four hundred twenty-eight medical oncology outpatients were assigned to the study. Pain prevalence and interference of pain with daily activities were assessed using the Brief Pain Inventory. Adequacy of analgesic treatment was determined by calculating the Pain Management Index (PMI). Descriptive statistics, non-parametric tests and logistic regression analysis were conducted. **Results.** More than one third of all participants reported pain (39%). Eighty-three patients (20% of all) had moderate to severe pain (NRS 5 -10). Analgesic treatment was inadequate in more than half of the patients with pain (62%). Interference of pain with daily activities increased with increased intensity, yet even 10%-33% of patients suffering mild pain reported high interference with daily activities. High current pain intensity and high interference with general daily activities predicted moderate to severe pain. **Conclusion.** Pain remains a significant problem in medical oncology outpatients and pain is often insufficiently managed. Patients with a high pain intensity were more at risk to experience pain related interference with daily activities, but even quite some patients suffering mild pain experienced this. As adequate pain relief for up to 86% of the patients with cancer should be feasible, pain in medical oncology outpatients is still undertreated. Interference of pain with daily activities and predictors of pain should be taken into account to facilitate cancer pain management.

Background

Pain is one of the most prevalent symptoms in patients with cancer[1] and appeared to interfere with daily activities in patients with advanced cancer.[2] In patients with cancer visiting outpatient clinics, pain prevalence ranged from 27% [3] to 60%[4]. Additionally, 19% to 39% of patients with cancer suffered from neuropathic pain, caused by the tumour, the operation or the treatment[5]. Adequate pain relief in 71%[6] to 86%[7] of cancer pain is considered feasible. As inadequate pain treatment ranged from 31%[8] to 65%[3] in patients with cancer, pain is still undertreated.

Undertreatment is the result of different patient and care provider related barriers. A key patient related barrier in pain management is the reluctance of many patients to discuss pain with their doctor or to ask for pain medication[9]. This hesitation has a variety of reasons, such as concerns about addiction and fear that reporting pain will distract the physician from the treatment of their cancer[9]. Care providers also experience barriers in cancer pain diagnosis. These include ineffective pain communication with patients[10] and inadequate pain assessment.[11] This underassessment and undertreatment of cancer pain influences the quality of life of these patients.

Moreover, cancer pain is associated with anxiety, depression and sleep disturbances[12-14]. It hampers daily activities[15], which also affects the quality of life. Putting it in day-to-day terms: if you are unable to work because you experience severe pain when moving your arm, this obviously reduces the quality of your life.

Pain related interference with daily activities has been well studied[16-19]. However, pain management patterns are poorly understood in medical oncology outpatients.

To get more insight in these patterns, we explored pain prevalence and intensity, analgesic pain treatment, neuropathic pain characteristics, breakthrough pain, pain related interference with daily activities and predictors of pain in outpatients with cancer.

The primary objective was to assess pain prevalence, pain intensity and its interference with daily activities in medical oncology outpatients. The secondary objectives were the adequacy of analgesic pain treatment and to identify independent predictors for moderate to severe pain.

Methods

Patients and procedures

A cross-sectional survey study was performed. Patients with cancer, visiting the medical oncology outpatient clinic of one of seven Dutch regional hospitals, were invited to participate.

Patients were eligible to participate if they had been diagnosed with cancer and were 18 years or older. Exclusion criteria were severe cognitive dysfunction or inability to understand or read the Dutch language.

In each hospital, in two periods of five consecutive working days, one period in 2011 and one in 2012, all patients visiting the medical oncology outpatient clinic were asked to participate.

Data collection

Patients were asked to complete the questionnaire during their stay at the outpatient clinic. A medical student helped them to fill in the questionnaire. The questionnaire consisted of the Brief Pain Inventory (BPI), Douleur Neuropathic 4 (DN4) interview, a question about breakthrough pain, intake of medication in the last 24 hours, demographics and medical data.

Besides, of those patients that took part in 2012, additional information was extracted from their medical records after they had provided their informed consent.

Brief Pain Inventory (BPI)

The BPI was used to assess pain prevalence and interference with daily activities[21]. This BPI is linguistically validated in many languages, including Dutch[21]. The BPI consists of seven questions with 15 items and has 11-point Numeric Rating Scales (NRS) of 0 (no pain) to 10 (worst pain imaginable), in which patients are asked to rate their mean pain over the last 24 hours. Additionally, the BPI was used to ask for interference of pain with daily activities over the last 24 hours (mood, walking ability, normal work, relationships, sleep and enjoyment of life).

Pain management index (PMI)

To determine the adequacy of analgesic pain treatment, Cleeland's[22] and Ward's PMI[9] were used. Based on the WHO pain ladder[24]. the PMI is the most frequently used measure for adequate pain treatment and is useful for evaluating the quality of analgesic care in large sample cases[25]. Ward's PMI was calculated for participants when prescribed analgesics were not described in the medical record[9,23]. Pain treatment is considered adequate if there is a congruence between the patient`s reported level of worst pain and the prescribed analgesics[25]. Cleeland's PMI compares the most potent analgesic prescribed with the patient's reported worst pain on the BPI[22]. Ward's PMI compares the most potent analgesic drug therapy actually used by the patient with his worst pain[1,9].

In both variations of the PMI, the levels of analgesic drug therapy are scored as 0, no analgesic; 1, a non-opioid analgesic; 2, a weak opioid and 3, a strong opioid. Absence of pain is defined as 0, mild pain as 1, moderate pain as 2 and severe pain as 3[9,22]. The PMI can be determined by subtracting the pain level from the analgesic level. The outcome ranges from -3 (a patient with severe pain receiving no analgesic drug) to +3 (a patient with no pain receiving a strong opioid or equivalent). Negative scores indicate inadequate pain treatment, whereas scores of 0 or higher represent adequate pain treatment[9,22].

DN4

Neuropathic pain was, as accepted by the IASP, defined as "pain arising as a direct consequence of a lesion or disease affecting the somatosensory system" [26,27]. We assessed the presence of characteristics of neuropathic pain (NP) by using the seven-item DN4-interview[28]. The complete DN4 has been linguistically validated in Dutch[29]. The DN4-interview includes pain descriptors namely burning, painful cold, electric shocks and associated abnormal sensations, tingling, pins and needles, numbness and itching. Each positive answer is assigned a score of 1.

If at least three out of seven characteristics of neuropathic pain are answered with yes, pain includes neuropathic characteristics and this might be an indication that neuropathic pain is present.

Additional data from medical records

Of those patients participating in 2012, additional data were retrieved from their medical records, namely disease characteristics, prescribed analgesics and treatment intention.

Statistical analysis

Descriptive statistics were conducted with SPSS version 20. Outcome variables were pain prevalence, pain intensity and interference of pain with daily activities. Worst, least, average and current pain levels were obtained. A numeric rating scale (NRS) from 1-4 was categorized as mild, 5-6 as moderate and 7-10 as severe pain[30]. This categorization was used because the present study was based on the principles of the Dutch clinical practice guideline (CPG) on cancer pain, being one of the most recent and best CPGs in Europe[30,31]. Disease groups were categorized as 1a: patients treated with curative intention more than 6 months ago; 1b: patients treated with curative intention less than 6 months ago; 2: patients with palliative anti-cancer treatment; 3: patients for whom anti-cancer treatment was not or no longer feasible and patients with palliative treatment more than 6 months ago (1). Differences in proportions were tested with Chi-square test or Fisher's exact test. Reported p-values are two-tailed and considered significant at the $p < 0.05$ level. Kruskal-Wallis tests were conducted to compare median pain scores and median pain related interference with daily activities scores.

Additionally, multiple regression analyses were conducted to determine the extent to which pain intensity rating (least, worst, average and current) was related to interference of pain with daily activities once other ratings were controlled. Mean interference of the six daily activities was the dependent variable and each pain intensity rating (least, worst, average and current) was added as a predictor of interference in the second step of the regression analysis after the other three were entered in the first step (methodology adapted from Chi et al)[31].

Finally, univariable and multivariable logistic regression analysis were conducted with the presence of moderate to severe pain (yes/no) as dependent variable.

The following independent variables were examined: age, gender, education, cancer type and disease group, current pain, metastasis, more than 5 years after diagnosis (yes/no), and interference with daily activities. Criterion to add a variable into the multivariable logistic regression analysis was p<0·10. Moreover, sub-analysis was conducted for gender as gender might be a potential confounder for the effect of tumour type on the prevalence of moderate to severe pain. All values given are worst pain values, unless otherwise stated. Pain intensity values are given as median with the inter quartile range (IQR).

Results

Of 629 invited patients, 428 (68%) completed the questionnaire. Median age of the participants was 67 (58-74). For characteristics of patients see table 1. Nonparticipants were patients who had no time to participate because of another appointment, being too ill or too tired to participate or patients who said that this would be too confrontational.

Pain prevalence

One hundred and sixty-seven patients (39%) reported pain in the last 24 hours and 36 (8%) experienced breakthrough pain. Table 1 shows that pain prevalence appeared higher in patients with metastasis than in patients without (p=0.022). A subgroup of 231 patients completed the DN4-interview. Fifty-three of them (23%) answered yes for at least 3 out of seven characteristics of neuropathic pain.

Pain intensity

Pain intensity was obtained for worst, least, average and current pain. Forty-three patients out of 167 patients in pain (26%) rated their worst pain as moderate and 40 patients (24%) as severe. This means that 83 patients out of all 428 patients (20%) had moderate to severe pain.

Patients experienced a median worst pain of 4.0 (IQR 2.0-6.0), least pain of 2.0 (IQR 0.0-4.0), average pain of 4.0 (IQR 2.0-5.0) and current pain of 2.0 (IQR 1.0-5.0).

Table 2 shows median pain intensities in relation to demographics of patients with pain. Median pain intensity was higher in women than in men for worst, average and current pain (p=0.015; p=0.006; p=0.005). Additionally, table 2 shows that median worst pain intensity was higher in disease group 3 than in the other disease groups (p=0.003) (n=7).

Patients with metastasis had an increased risk of pain (P=0.025), but did not have an increased risk for higher pain intensity than patients without metastasis. Finally, there were no significant differences in mean scores per pain intensity category between different tumour types and presence of metastasis.

Table 1 Demographic characteristics of patients (N=428)

Characteristics	All (N=428)	With pain (N=167)		Without pain (N=261)	
	N	N	(%)	N	(%)
Gender					
Men	177	64	(36.2)	113	(63.8)
Women	251	103	(41.0)	148	(59.0)
Age groups in years					
< 45	21	9	(43.0)	12	(57.1)
45-60	97	45	(46.4)	52	(53.6)
60-75	216	81	(37.5)	135	(62.5)
≥ 75	93	31	(33.3)	62	(66.7)
Unknown	1	1	(100.0)	0	(0.0)
Education level					
Secondary school or less	117	41	(35.0)	76	(65.0)
Lower vocational education	97	37	(38.1)	60	(61.9)
Middle vocational education	128	52	(40.6)	76	(59.3)
Higher vocational education or higher	84	36	(43.0)	48	(57.1)
Unknown	2	1	(50.0)	1	(50.0)
Primary cancer type					
Gastrointestinal	123	47	(38.2)	76	(61.8)
Urogenital	59	25	(42.4)	34	(57.6)
Breast	153	68	(44.4)	85	(55.6)
Lymphatic-hematological	67	18	(26.9)	49	(73.1)
Other (lung, skin, glands, bone)	21	7	(33.3)	14	(66.7)
Unknown	5	2	(40.0)	3	(60.0)
Presence of metastases[a]					
Yes	222	98	(44.1)	124	(55.9)
No	203	67	(33.0)	136	(67.0)
Unknown	3	2	(66.7)	1	(33.3)
Period with cancer in years					
≤ 1	184	70	(38.0)	114	(62.0)
2 - 5	124	46	(37.1)	78	(62.9)
≥5	118	51	(43.2)	65	(55.1)
Unknown	2	0	(0.0)	2	(100.0)
Disease group[b]					
1a	11	2	(18.2)	9	(81.8)
1b	58	26	(44.8)	32	(55.2)
2	93	46	(49.5)	47	(50.1)
3	18	7	(39.0)	11	(61.1)
Unknown[c]	197	65	(38.9)	132	(50.6)

[a] chi-square or fishers exact test p<0.05 (2-sided); [b] 1a, patients who had been treated with curative intent, last treatment more than 6 months ago; 1b, patients receiving anti-cancer treatment with curative intention or last treatment less than 6 months ago; 2, patients who were receiving palliative anti-cancer treatment; 3, patients for whom anti-cancer treatment was not or no longer feasible and patients with palliative treatment more than 6 months ago.[1] [C] obtained from medical records, these data were only available for a subgroup of 231 participants.

Table 2 Median and IQR of pain intensity (NRS) in the last 24 hours for different demographic characteristics of patients with pain (N=167)

Characteristics	N	Worst pain in last 24 h			Least pain in last 24 h			Average pain in last 24 h			Current pain in last 24 h		
		Med	*(IQR)*	p-value	*Med*	*(IQR)*	p-value	*Med*	*(IQR)*	p-value	*Med*	*(IQR)*	p-value
Gender				**0.015**			0.119			**0.006**			**0.005**
Men	64	3.5	(2.0-6.0)		1.5	(0.0-3.0)		3.0	(2.0-4.8)		2.0	(1.0-3.0)	
Women	103	5.0	(3.0-7.0)		2.0	(0.0-5.0)		4.0	(2.8-6.0)		3.0	(1.0-6.0)	
Age groups (years)				0.324			0.988			0.876			0.776
< 45	9	3.0	(2.5-5.0)		2.0	(0.0-4.0)		4.0	(2.0-6.0)		2.0	(1.0-3.5)	
45-60	44	4.0	(3.0-6.0)		2.0	(1.0-3.0)		4.0	(2.0-5.0)		3.0	(1.0-5.0)	
60-75	81	4.0	(2.0-6.0)		2.0	(0.0-4.0)		3.0	(2.0-5.0)		2.0	(0.5-5.0)	
≥ 75	31	5.0	(3.0-7.0)		2.0	(0.0-4.0)		4.0	(2.0-5.0)		2.0	(1.0-6.0)	
Education level				0.341			0.259			0.511			0.553
Secondary school or less	41	5.0	(2.0-7.0)		2.0	(1.0-5.0)		4.0	(2.0-6.0)		5.0	(1.0-6.0)	
Lower vocational	37	4.0	(3.0-7.0)		2.0	(1.0-4.0)		3.0	(2.0-5.0)		3.0	(1.0-5.0)	
Middle vocational	51	4.0	(2.0-5.8)		1.5	(0.0-3.8)		3.0	(2.0-5.0)		2.0	(1.0-4.8)	
Higher vocational or higher	36	5.0	(3.0-6.0)		1.5	(0.0-3.0)		4.0	(2.0-5.8)		2.0	(1.0-6.0)	
Primary cancer type				0.835			0.333			0.654			0.711
Gastrointestinal	47	5.0	(2.0-7.0)		2.0	(0.0-4.0)		3.0	(2.0-5.0)		2.0	(1.0-5.0)	
Urogenital	24	4.0	(2.0-5.0)		1.0	(0.0-3.0)		3.5	(2.0-5.0)		2.0	(0.0-5.0)	
Breast	68	5.0	(3.0-6.8)		2.0	(0.0-5.0)		4.0	(2.0-6.0)		3.0	(1.0-6.0)	
Lymphatic-haematological	18	4.0	(2.8-6.0)		2.0	(0.8-4.0)		3.5	(2.0-6.0)		3.0	(1.0-6.0)	
Other (lung, skin, glands)	7	3.0	(3.0-6.0)		2.0	(1.0-3.0)		3.0	(3.0-4.0)		3.0	(1.0-3.0)	
Presence of metastases				0.491			0.824			0.552			0.781
Yes	98	5.0	(0.0-4.3)		2.0	(2.0-5.0)		4.0	(1.0-5.0)		2.0	(1.6-5.0)	
No	67	4.0	(3.0-6.0)		2.0	(0.0-3.0)		4.0	(2.0-5.0)		3.0	(1.0-5.0)	
Period with cancer (years)				0.419			0.976			0.468			0.805
≤ 1	70	4.0	(2.0-6.0)		2.0	(0.0-4.0)		3.0	(2.0-5.0)		2.0	(1.0-5.0)	
2 – 5	47	4.0	(3.0-6.0)		2.0	(0.0-3.0)		4.0	(3.0-5.0)		3.0	(1.0-5.0)	
≥5	49	5.0	(2.0-7.0)		2.0	(0.0-4.3)		4.0	(2.0-6.0)		2.5	(0.8-6.0)	
Disease group[a]				**0.022**			0.318			0.313			0.355
1a	2	5.0	(4.0-6.0)		1.0	(0.0-2.0)		4.5	(3.0-6.0)		3.0	(0.0-6.0)	
1b	26	3.0	(2.0-5.3)		1.5	(0.0-4.3)		3.0	(2.0-5.0)		1.5	(1.0-5.0)	
2	46	3.5	(2.0-5.0)		1.0	(0.0-2.3)		3.0	(2.0-5.0)		2.0	(0.0-3.3)	
3	7	7.0	(5.0-9.0)		3.0	(2.0-4.0)		4.0	(3.0-7.0)		3.0	(2.0-7.0)	

p= p-value, IQR= Inter Quartile Range, NRS= Numeric rating Scale. Note: the bold values are reaching significance with Kruskal- Wallis tests at p<0.05 (2-sided); [a] Adapted from van den Beuken et. al. 2007[1] : see method section statistical analysis.

Pain related interference with daily activities

Figure 1 shows interference with daily activities per pain intensity category. One patient did not respond to the questions on interference with daily activities and was therefore excluded from this part of the analysis (n=166). One hundred and forty-eight out of 166 patients with pain (89%) experienced interference of pain with one or more daily activities. The overall median interference of pain with daily activities of patients with pain was 2.6 (IQR 0.8-5.0). Five percent of patients without pain reported interference with daily activities (see figure 1a).

Patients who rated their worst pain in the last 24 hours as mild (n=84) had an overall median interference of pain with daily activities of 1.1 (IQR 0.2-3.3). This figure is 3.1 (IQR 2.0-4.9) for patients with moderate pain (n=42) and 4.9 (IQR 2.7-5.8) for patients with severe pain (n=40) ($p<0.0001$).

However, prevalence of interference with daily activities ≥ 5 in patients with mild pain ranged from eight out of 84 (10%) to 27 out of 84 (33%) over the various activities. Even up to eight out of 42 patients (19%) with a pain intensity of NRS 1-2 reported interference with daily activities ≥ 5 for work (including household). Most often pain negatively interfered with work/household and general activity.

Figure 1 also shows that median interference with daily activities was higher in patients with moderate pain than in those with mild pain for all activities ($p<0.05$) except for sleep ($p=0.125$).

Severe pain interfered significantly more than moderate pain with sleep and general activity. Severe pain interfered significantly more with each daily activity than mild pain ($P<0.05$). Additionally, figure 1 shows higher interference with daily activities in patients with high pain intensity. Negative interference with enjoyment, work, mood, sleep, and general activities with an NRS score of 7-10 was more common regarding severe pain than regarding mild and moderate pain.

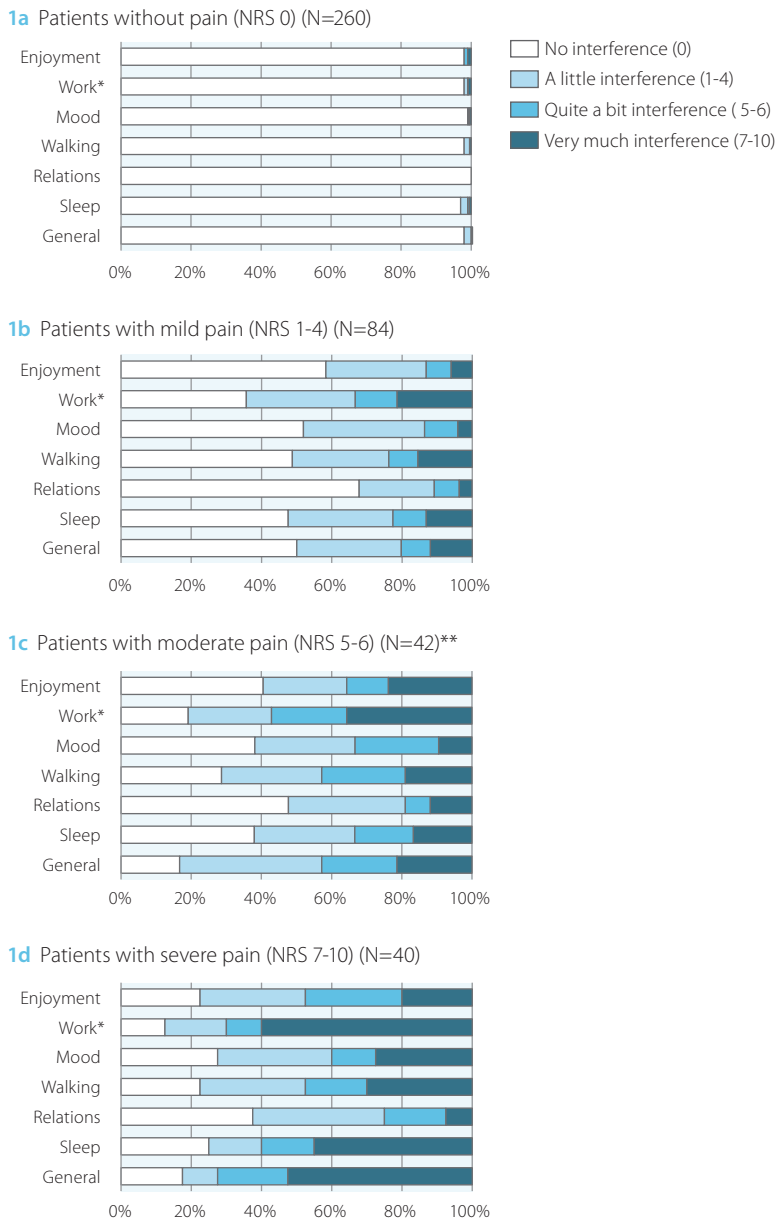
Worst pain contributed most to interference with daily activities ($R^2=0.014$; F 16.15; $p=0.00$). Worst pain contributed more to interference with daily activities than current pain ($R^2=0.008$; F 9.37; $p=0.002$).

Evaluation of analgesic pain treatment

Analgesic pain treatment in relation to pain severity is summarized in figure 2. Strong opioids were used by one out of eight patients with mild pain and moderate pain, whereas in patients with severe pain one out of three strong opioids were used. Of patients with moderate to severe pain 28.6% were not treated with analgesics and 42.9% with a non-opioid drug.

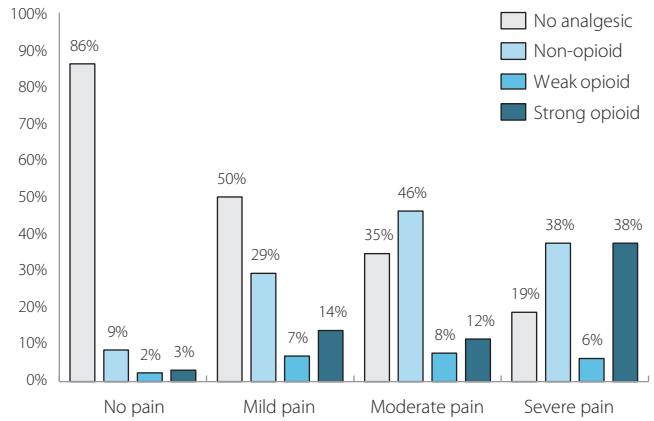
Due to unclear recording of prescribed analgesics, data of 22 patients could not be included in calculating Cleeland's PMI. For these patients Ward's PMI was calculated. One hundred and three out of 167 patients in pain (62%) were inadequately treated according to the PMI. Patient characteristics did not influence adequacy of analgesic treatment.

Figure 1 Pain related interference with daily activities of patients with cancer by pain intensity category (%)



Note: Pain intensity categories used were adapted from the Dutch guideline: pain in patients with cancer (28). *includes household; ** Data was missing of one pateint (patient was excluded from figures); NRS= Numeric Rating Scale.

Figure 2 Analgesic pain treatment in relation to pain severity*



However, patients with breast cancer and pain were more often inadequately treated than patients with other tumour types (p=0.001). Forty-seven percent of patients who answered yes for at least 3 neuropathic pain characteristics out of seven were inadequately treated for their pain compared to 20% of patients who answered yes for less than 3 out of seven neuropathic pain characteristics (p=0.00).

Logistic regression

Gender, having a lymphatic-haematological tumour, presence of metastasis, current pain and interference with daily activities were related to moderate to severe pain, whereas education level, tumour type, more than five years since diagnosed with cancer and disease group were not (see table 3). Multiple regression analysis revealed that current pain (OR 2.96, CI 2.28-3.85), interference with daily activities for general activity (OR 1.14, CI 1.14-1.52), and having a lymphatic-haematological tumour (OR 0.11, CI 0.02-0.54) were independently related to moderate to severe pain.

Multiple regression analysis for men revealed that current pain (OR 3.3, CI 2.19-4.96) and interference with sleep (OR 1.43, CI 1.14-1.80) were related to moderate to severe pain. Multiple regression analysis for women revealed that current pain (OR 3.2, CI 2.40-4.34) and interference with general daily activities (OR 1.43, CI 1.14-1.80) were related to moderate to severe pain.

Table 3 Odds ratios and 95% CI of the probability of moderate to severe pain (NRS 5-10) in patients with cancer

Characteristics	N	Univariable regression		Adjusted	
		OR	*(95% CI)*	*OR*	*(95% CI)*[b]
Gender					
Men	177	1.00	(reference)	-	
Women	251	1.79	(1.07-2.99) [a]	Not in model	
Age (years)	427	1.00	(0.98-1.03)	-	
Education level					
Secondary school or less	177	1.00	(reference)	-	
Lower vocational education	97	0.87	(0.48-1.57)	-	
Middle vocational education	128	0.60	(0.34-1.07)	-	
Higher vocational education or higher	84	1.42	(0.80-2.52)	-	
Primary cancer type					
Gastrointestinal	123	0.84	(0.48-1.47)	-	
Urogenital	59	0.91	(0.44-1.90)	-	
Breast	153	1.00	(reference)	-	
Lymphatic-haematological	67	0.37	(0.15-0.89)[a]	0.11	(0.02-0.54)[a]
Other (lung, skin, glands, bone)	21	0.43	(0.10-1.89)	-	
Presence of metastases	425	1.76	(1.07-2.90)[a]	Not in model	
More than 5 years diagnosed	426	1.39	(0.82-2.33)	-	
Disease group[c]					
1a	11	0.41	(0.05-3.33)	-	
1b	58	0.71	(0.31-1.64)	-	
2	93	1.00	(reference)	-	
3	18	2.39	(0.83-6.92)	-	
Current pain	428	3.26	(2.57-4.13)[a]	2.96	(2.28-3.85)[a]
Daily activity interference[d]					
Enjoyment	427	1.64	(1.47-1.83)[a]	Not in model	
Work (includes household)	427	1.53	(1.41-1.67)[a]	Not in model	
Mood	427	1.70	(1.50-1.90)[a]	Not in model	
Walking	427	1.58	(1.43-1.74)[a]	Not in model	
Relations	427	1.79	(1.54-2.10)[a]	Not in model	
Sleep	427	1.53	(1.39-1.70)[a]	Not in model	
General	427	1.70	(1.53-1.90)[a]	1.14	(1.14-1.52)[a]

NRS= Numeric Rating Scale; 95% CI= 95% confidence interval; OR= odds ratio. [a] p≤0.10. [b] Stepwise univariable regression analysis. Criterion to add a variable was p≤0.10. [c]Adapted from van den Beuken et. al. 2007[1]: disease group 1a, patients who had been treated with curative intent, last treatment more than 6 months ago; 1b patients receiving anti-cancer treatment with curative intention or last treatment less than 6 months ago; 2, patients who were receiving palliative anti-cancer treatment; 3, patients for whom anti-cancer treatment was not or no longer feasible and patients with palliative treatment more than 6 months ago: Obtained from medical records, these data were only available for a subgroup of 231 participants. [d] Data of one patients was missing.

Discussion

The present study shows that more than one third of all participants, i.e. patients with cancer visiting a medical oncology outpatient clinic, reported pain. Half of those in pain had inadequate analgesics treatment. Additionally, high pain intensity strongly interfered with daily activities and even 10%-33% of patients with mild pain, which pain level is not usually treated with opioids, experienced moderate to severe interference with daily activities. High current pain intensity and high interference with general daily activities were related to moderate to severe pain.

Subsequently, pain prevalence appeared higher in patients with metastasis than without and patients with breast cancer and pain were more often inadequately treated than patients with other tumour types. Positive predictors for moderate to severe worst pain in the last 24 hours were current pain and interference with general daily activity while having a lymphatic-haematological tumour was a negative predictor.

Earlier studies in Europe found pain prevalence at various stages of cancer from 27%[3] to 60%[4] for patients visiting outpatient clinics with cancer. Inadequate pain treatment ranged from 31%[8] to 65%[3] in patients with cancer. The prevalence rates in the present study fall within the range found in previous studies. As adequate pain relief for up to 86% of patients with cancer is considered feasible, pain in patients with cancer is still undertreated[7].

In previous studies, prevalence rates of neuropathic pain in patients with severe cancer pain ranged from 34%-40%[5]. In our study, in which also patients without pain participated, neuropathic pain prevalence rate was less. Additionally, our study shows that patients who answered yes for at least 3 NP characteristics were more often inadequately treated for their pain than patients without or with less NP characteristics (p=0.00).

As neuropathic pain is generally treated with opioids and adjuvants and is relatively opioid resistant, this might have an impact on the PMI.

However, pain prevalence and pain intensity alone are not enough to illustrate the problem of cancer pain. Interference of pain with daily activities should also be taken into account. Although pain related interference with daily activities has been well studied[16-19], pain management patterns are poorly understood in medical oncology outpatients.

A recent study by Fisch and authors reported pain prevalence, pain management adequacy and pain related interference with daily activities[32]. They found the same prevalence of moderate to severe pain as in the present study. However, they did not report on interference with daily activities of mild pain, neuropathic pain characteristics and breakthrough pain[32]. To get more insight in pain management patterns, our study explored the combination. Our findings are in line with those of Vallerand et al. They studied 304 oncology outpatients who experienced cancer-related pain within the past two weeks[33].

Shi et al have previously reported that recall of worst pain in the last week contributes the most to patient reports of pain interference with daily activities[34].

Our data confirms these findings. This indicates that ratings of worst pain in the last 24 hours, rather than current pain, might improve insight in overall experience of pain and its impact on interference with daily activities in medical oncology outpatients[34]. This might guide the choice of recall period for outpatients with cancer for future studies.

Previous literature stated that patients with a pain intensity <5 are adequately treated and that mild pain intensity hardly interferes with daily activities[15,30].

However, the present study shows that some patients with mild pain (NRS 1-4) and even some patients with an NRS of 1-2 do experience moderate to high interference with daily activities, as also described by Wu et al[35].

Although Serlin and colleagues established cut-off points for pain intensity based on its interference with daily activities 18 years ago[15], there is still no consensus on how to categorize pain intensity. Often pain is categorized as mild pain (NRS 1-4), moderate pain (5-6) and severe pain (7-10)[15,30].

As a complicating but important factor in this discussion on cut-off points, we suggest including interference with daily activities as an additional factor to determine, in combination with pain intensity, whether a patient with cancer and pain needs treatment. Little is published on predictors of the prevalence of moderate to severe pain. In our study, women were more at risk for moderate to severe pain than men. Some studies confirm this finding[36], others do not[1]. Additionally, in our study patients with metastasis were more at risk for moderate to severe pain, which confirms a previous finding that patients with more advanced disease had higher pain intensities[20]. None of the previous studies explored interference with daily activities and current pain as possible related variables for moderate to severe worst pain in the last 24 hours.

Unfortunately, we were not able to obtain characteristics from the 32% non-participants, as informed consent would have been needed to obtain information from medical records.

The present study was based on the recommendations in the Dutch CPG "Pain in patients with cancer"[30] which is one of the most recent cancer pain guidelines in Europe. In a comparative study of European CPGs on pain management in patients with cancer this Dutch CPG appeared to have followed a good development process[31].

So far, it is not known whether this CPG has already improved adequate pain treatment in the Netherlands[37]. The present study contributes to awareness on pain prevalence, pain treatment adequacy and interference of pain with daily activities. It is an essential step in improving cancer pain management.

Conclusions

In conclusion, pain remains a significant problem in medical oncology outpatients. As adequate pain relief for up to 86% of patients with cancer should be feasible, pain in medical oncology outpatients is still undertreated.

To avoid an on-going discussion on cut-off points, it would be interesting to focus in future research on the possibilities of using interference of pain with daily activities as an additional factor and not only as a determining factor for pain intensity categories. As patients often are reluctant to talk about their pain, it might be interesting to ask patients additionally about interference with daily activities related to their pain intensity. Pain might become more related to daily life and less to disease and medicine. Thus multi-dimensional tools to assess cancer pain, taking into account interference with daily activities and predictors of pain, will facilitate improvements in cancer pain management.

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3

Pain is not systematically registered in Dutch medical oncology outpatients

Nienke te Boveldt
Myrra Vernooij-Dassen
Nathalie Burger
Michiel IJsseldijk
Kris Vissers
Yvonne Engels

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Abstract

Background. Systematic pain registration and assessment with a visual analogue scale (VAS) or numeric rating scale (NRS) at each visit are key recommendations in one of the most recent guidelines on cancer pain management. It is unclear whether this recommendation is applied. The aim was to explore registration of pain in medical records of patients visiting the medical oncology outpatient clinic. **Methods.** In a multi-centre study in six Dutch hospitals, data were extracted from medical records of 380 outpatients with cancer. Data of the first three visits at the outpatient clinic were studied. Descriptive statistics were conducted. **Results.** In 23% of all 987 visits at the outpatient clinic, pain or absence of pain was registered, and in an additional 15% a nonspecific symptom description was given. Regarding all other visits, (62%) pain or absence of pain was not documented at all. Pain measurement using a VAS or NRS was documented in only one visit. Pain was more often registered in medical records of patients with metastasis, as well as in those of patients with urogenital tumours. **Conclusion.** Pain in medical oncology outpatients is not systematically registered in their medical records. With one exception, pain was not registered with a VAS or NRS. Yet, registration and assessment of pain in order to monitor pain are essential to evaluate and adapt pain treatment over time. Pain registration has not improved since 2001 and therefore, implementing the recommendations regarding systematic monitoring of pain is needed.

Introduction

Pain is one of the most prevalent symptoms of patients with cancer[1], which hampers daily activities[2] and quality of life[3–5]. Cancer pain is also associated with anxiety, depression, and sleep disturbances[3–5]. Prevalence of pain ranged from 27%[6] to 60%[7] in patients with cancer visiting outpatient clinics. Inadequate pain treatment ranged from 31%[8] to 65%[6] in patients with cancer. Although adequate pain relief in 71%[9] to 86%[10] of cancer pain is considered feasible, pain is still undertreated. Despite the availability of many evidence-based therapies for cancer pain and clinical practice guidelines (CPGs)[11–13], pain in patients with cancer is still a major problem.

Systematic pain assessment and documentation using a validated pain assessment tool, such as a visual analogue scale (VAS) or numeric rating scale (NRS), at each visit of the most recent CPGs on cancer pain management[11,14]. However, pain was not systematically assessed and documented[15,16]. Infrequently pain documentation leads to inadequate pain management. Systematic screening and documentation of pain are essential for quality improvement of cancer pain treatment, because a key patient-related barrier is that patients are reluctant to discuss pain with the doctor or to ask for pain medication[17,18]. This hesitation has a variety of reasons, including concerns about addiction and fear that reporting pain will distract the physician from the treatment of their cancer[17]. Additionally, care providers tend to show lack of attention to and knowledge about pain management[18].

Ineffective pain communication between physicians and patients[19] and inadequate pain assessment contribute to inadequate pain management[20,21]. Thus, healthcare professionals should systematically ask for pain and document it[22,23].

The patient's medical record should be the primary source of information about pain or its absence, as it gives the opportunity to monitor pain, treatment, and side effects over time[24–26].

Accurate and consistent cancer pain registration improves the perception of physicians concerning cancer pain and enhances pain management[18,24]. No recent data on cancer pain registration have been published. Earlier studies do not report on pain registration by oncologists or in a small sample of oncologists from a single outpatient practice[15,16]. Little is known about the frequency and how pain is registered in medical records of medical oncology outpatients. This study on the documentation of pain in Dutch outpatient oncology clinics explored an important area for quality improvement in cancer pain management, whereas systematic pain assessment and documentation are essential in cancer pain treatment. Therefore, we explored registration of pain by the medical oncologist in medical records of outpatients with cancer.

Methods

Study design and ethical consideration

In a multicentre study in six Dutch hospitals, retrospective data were extracted from medical records of outpatients with cancer. This study was conducted as part of a study that was granted by the Dutch Cancer Society (KWF)[27] and has been approved by the Medical Ethics Committee (CMO) of the Radboud university medical center (METC protocol number 2011/020). The local ethical committees of each participating hospital have also approved this study. The ethical committees agreed that it was not advisable to ask patients to sign informed consent, because part of the population died and it might be too confrontational for others.

Study setting

Hospitals that were studied have both electronic and paper medical records, as they converted to electronic medical records in 2010 and 2011. These hospitals have protocols for nurses to record pain scores; however, nurses do report these scores in different medical records than oncologists. The hospitals are similar sized and have similar expertise as other Dutch medical centres.

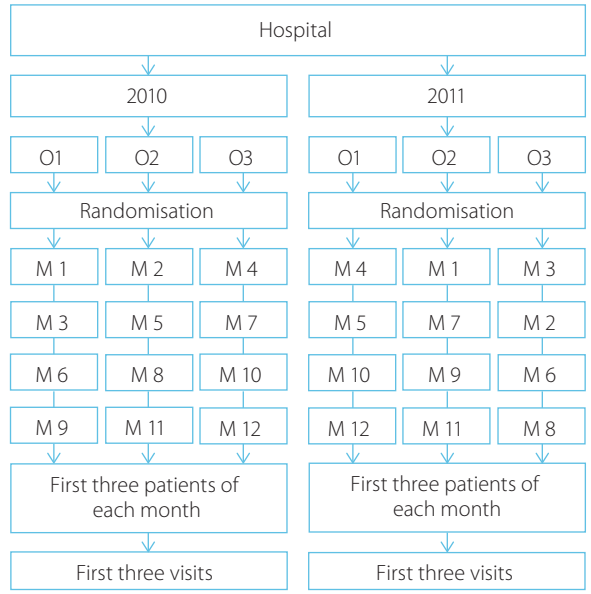
Patients and data collection

In 2010 and 2011, data were extracted from paper and/or digital medical records of patients with cancer visiting an outpatient clinic of one of five general hospitals and one academic medical centre in the Netherlands. Available data were extracted both manually and electronically. Data were extracted by a medical student with practice experience. Medical records of patients were included, when patients were diagnosed with cancer and were 18 years or older. Medical records of patients were excluded if patients were not visiting the clinic for the first time (previously seen). For each excluded medical record, the medical record of the patient next in line of that month was analysed. Medical records of all medical oncologists (N = 28) of all participating hospitals were included in the study. Sampling methodology was used. First, to obtain an equal (and feasible) number of medical records per oncologist per setting, months were randomly assigned to medical oncologists (Figure 1). Second, a predetermined sample of patients was selected: the first three patients of each month visiting the outpatient clinic for the first time. Finally, a predetermined sample of visits was selected: the first three visits of the selected patients.

For example, medical records of the first three patients each month visiting the outpatient clinic were obtained for months 1, 3, 6, and 9 of oncologist 1, months 2, 5, 8, and 11 medical records of oncologist 2, and months 4, 7, 10, and 12 of oncologist 3 (see Figure 1). The first three visits of these patients were analysed. When only one or two patients visited the outpatient clinic for the first time in a certain month, no additional medical records were extracted.

The following data were obtained from each medical record: patient characteristics (gender and age); disease characteristics (tumour type, intention of treatment (palliative/curative); TNM stage (presence of metastasis and treatment); pain registration (all data on pain registration categorized as quantitative, qualitative, and nonspecific symptom description); and additional data (dates of the first three consultations and primary treating oncologist).

Figure 1 Flow diagram data-collection



O= Oncologist; M= Month

Categorized pain registration

Pain registration was categorized as quantitative, qualitative, or a nonspecific symptom description (adapted from Rhodes et al.)[16]. (1) Only documentation of a pain score was considered as quantitative pain registration; (2) Qualitative pain registration was defined as any other type of documentation of pain or absence of pain. It was categorized as: (A) Only documentation of pain or its absence, (B) A in combination with pain location, (C) A in combination with pain intensity or pain intensity change in words (e.g. pain is reduced), (D) As well A, B, and C; (3) Nonspecific symptom description was defined as any documentation of symptoms or their absence without specifically mentioning pain (e.g. no complaints, is doing well).

Statistics

Descriptive statistics were conducted with SPSS version 20 (IBM SPSS Statistics, Armonk, NY, U.S.A). Outcome variables were frequency of pain documentation (yes/no) and how pain was documented at first, second, and third consultation (quantitative pain registration, qualitative pain registration, and nonspecific symptom description). Additionally, patients' characteristics were identified for patients with and without pain documentation. Differences in proportions were tested with chi-squared test or Fisher's exact test. Reported P-values are two-tailed and considered significant at the P≤ 0.05 level.

Results

A total of 395 medical records were selected for review. Although all of them were labelled as new patients with cancer in a digital overview database of medical records, 15 of them did not meet the inclusion criteria. Two medical records were of patients not diagnosed with cancer, 10 had visited the outpatient clinic before, and three medical records were not available. In total, documentation of 996 visits of 380 patients was obtained (Table 1). In nine visits of three patients, nothing was registered. These visits were reported as missing and were excluded from analysis. In total, 987 visits of 377 patients were analysed. Mean age of the patients was 61.3 ±13.9 (21 to 90). For patient characteristics, see table 2.

Table 1 Data-collection characteristics

Hospital	No. of patients		No. of physicians		No. of visits		*Missing	
	N	*(%)*	*N*	*(%)*	*N*	*(%)*	*N*	*(%)*
A	63	(16.5)	5	(17.9)	168	(16.9)	1	(11.1)
B	44	(11.5)	5	(17.9)	121	(12.1)	6	(66.7)
C	63	(16.5)	3	(10.7)	149	(15.0)	0	(0.0)
D	72	(18.9)	2	(7.1)	193	(19.4)	0	(0.0)
E	72	(18.9)	2	(7.1)	202	(20.3)	0	(0.0)
F	66	(17.3)	11	(39.3)	163	(16.4)	2	(22.2)
Total	380		28		996		9	

*Missing documentation of 3 patients = 9 visits; A-E = non-academic medical centre, F= academic medical centre

Table 2 Demographic characteristics of patients with and without pain registration*

Characteristics	Overall (N=377)*	Pain registration (N=163)		No pain registration (N=214)	
	N	*N*	*(%)*	*N*	*(%)*
Gender					
Men	181	79	(43.6)	102	(56.4)
Women	196	84	(42.9)	112	(57.1)
Age groups in years					
< 45	40	18	(45.0)	22	(55.0)
45-60	119	54	(45.4)	65	(54.6)
60-75	160	69	(43.1)	91	(56.9)
≥ 75	58	22	(37.9)	36	(62.1)
Primary cancer type[a]					
Gastrointestinal	136	59	(42.8)	77	(56.6)
Urogenital	38	20	(52.6)	18	(47.4)
Breast	106	39	(36.8)	67	(63.2)
Lymphatic-haematological	28	8	(28.6)	20	(71.4)
Other (e.g. lung, skin, glands, bone)	67	37	(55.2)	30	(44.8)
Unknown	2	0	(0.0)	2	(100.0)
Metastasis[a]					
No	129	50	(38.8)	79	(61.2)
Yes	107	60	(56.1)	47	(43.9)
Unknown	141	53	(37.6)	88	(62.4)
Years between diagnosis and first consult					
<1	286	122	(42.7)	164	(57.3)
1 - 2	23	11	(47.8)	12	(52.2)
2-5	27	14	(51.9)	13	(48.1)
>5	28	13	(46.4)	15	(53.6)
Unknown	13	3	(23.1)	10	(76.9)
Year of first consult					
2010	200	96	(48.0)	104	(52.0)
2011	177	67	(37.9)	110	(62.1)

[a] Chi-square test or Fishers exact test p≤0.05 (2-sided); *Pain registration in one or more out of three first consultations. Data on pain registration of three patients of 380 were missing.

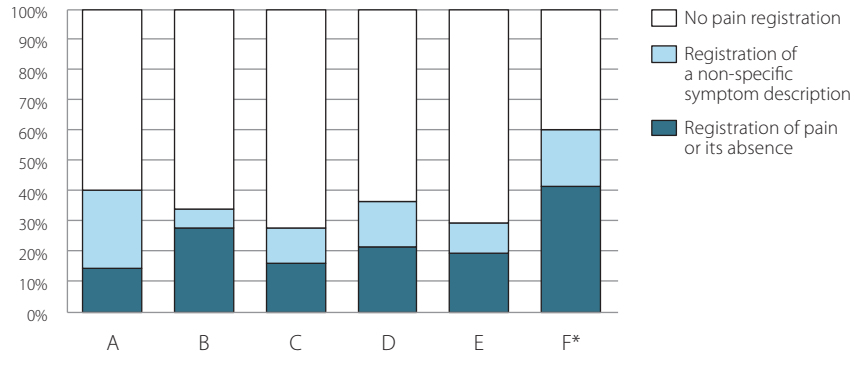
Pain registration

In 229 of 987 visits (23.2%), pain or its absence was registered. Quantitative pain registration, with a VAS, was only recorded in one of 987 visits. In 228 of 987 visits (23.1%), qualitative pain registration was used. Of these, 39 (17.1%) were illegible, in 140 (61.4%) visits pain was reported, and in 49 (21.5%) visits the absence of pain was reported. In 17 (12.1%) of 140 visits reporting pain, only pain or its absence was registered; in 78 visits (55.7%), pain, as well as pain location, was registered; in 13 visits (9.3%), pain and intensity, or pain intensity change was registered in words (e.g. less pain, pain is worse, decreased pain, moderate pain). Moreover, in 28 visits (20.0%) as well pain, pain intensity or intensity change in words and location of the pain were documented. Finally, data were illegible in four visits. In 14.8% of all 987 visits, pain description was nonspecific. The majority of nonspecific symptom descriptions referred to absence or reduction of symptoms (e.g. is doing well, no complaints, is feeling well, is doing better).

Variation between hospitals

Figure 2 and table 3 show frequencies of pain registration per hospital. It shows that the academic medical centre most frequently registered pain (41.6%) and in another 19.3%, a nonspecific symptom description was given (academic vs. non-academic P = 0.000). As overall mean of all hospitals in 23.6% of the visits, pain or its absence was documented and additionally, a nonspecific symptom description was recorded in 14.8% of visits.

Figure 2 Analgesic pain treatment in relation to pain severity*



*chi-square test significant at p≤0.05 (2-sided); F=academic medical centre vs. A-E= non-academic medical centre (p=0.00)

Table 3 Pain registration N(%)

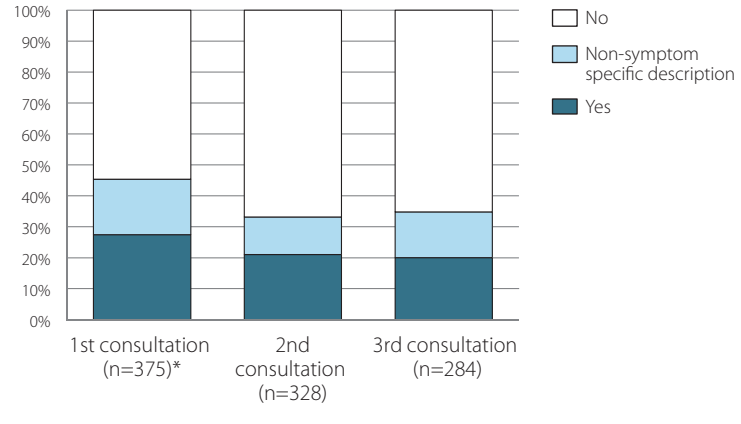
Hospital	Total visits*	Registration of pain or its absence		Registration of a non-specific symptom description		No pain registration	
	N	N	(%)	N	(%)	N	(%)
A	167	24	(14.4)	43	(25.7)	100	(59.9)
B	115	32	(27.8)	7	(6.1)	76	(66.1)
C	149	26	(17.4)	19	(12.8)	104	(69.8)
D	193	41	(21.2)	29	(15.0)	123	(63.7)
E	202	39	(19.3)	20	(9.9)	143	(70.8)
F**	161	67	(41.6)	31	(19.3)	63	(39.1)
Total	987*	229	(23.2)	149	(15.1)	609	(61.7)

* Number of visits without visits (n=9) of which documentation is missing; ** Chi-square test was significant at p<0.05 (2-sided); F= academic medical centre vs. A-E= non-academic medical centre (p=0.00)

Variation between consultations

Figure 3 shows frequencies of pain registration in sequential visits. Of all 380 patients, 329 also had a second visit and 287 a third visit by the same oncologist. In 27.1% of all first consultations, the existence or absence of pain was registered. In 17.6%, a nonspecific symptom description was given, whereas during second (respectively, 21.0% and 12.2%) and third visits (respectively, 19.9% and 14.6%), this frequency decreased (P = 0.009).

Figure 3 Pain registration by consultation



*chi-square test significant at p>0.05 (2-sided); Difference between consultations p=0.01

Pain registration by patient characteristics

Gender, age, years between diagnosis and first consultation, and year of first visits were not related to pain registration (Table 2). Pain registration (in one or more of the three visits) was more common in patients with urogenital tumours (52.6%) and less common in patients with breast cancer (36.4%) (overall P = 0.027). Additionally, pain registration was more common in patients with metastasis (55.6%) than in those without metastasis (38.5%) (P = 0.003).

Discussion

This study reveals that in the majority of medical records of oncology outpatients, pain was not systematically registered. We found that in only one of four visits, pain or its absence was registered. Pain scores with a validated scale were absent, with an exception. Since 2001, pain registration has not improved despite that systematic pain documentation has shown to be feasible in a busy outpatient oncology practice and is sustainable over time[16]. Previous studies have either not reported on pain registration by medical oncologists or reported only small samples from single outpatient clinics[15,16].

In 1999, Weber et al. also analysed medical records of outpatients with cancer and severe pain and found that only three of 12 physicians registered pain severity in more than 15% of their consultations[15]. We not only analysed medical records of patients known with pain, but of all outpatients with cancer. Their results are shown as number of physicians reporting pain severity, whereas we reported the percentage of visits in which pain was reported, which makes comparison with our results difficult.

Another study by Rhodes et al. found that health providers and health assistants at the radiation and medical oncology outpatient clinic did not routinely assess pain[16]. Additionally, Rhodes et al. showed that, before training, physicians never documented quantitative pain assessment in their medical records. In their study, qualitative pain registration by physicians was higher in medical (53.8%) and radiation oncology (72.7%) than in ours (23.2%)[16]. Unlike Rhodes et al., we made a distinction between quantitative, qualitative, and nonspecific symptom registration in oncology outpatient clinics[16]. As well as the study of Weber as that of Rhodes shows that in the majority of medical records, pain was not systematically registered 12 years ago[15,16]. In our study, we found that pain was more often registered in first visits than in second and third visits.

Often, during second and third visits, anticancer treatment has already started, which often causes pain. Therefore, in second and third visits, systematic screening for pain is even more important than in the first visit.

Additionally, pain was more often registered in patients with urogenital tumours and in patients with metastasis. This is important because pain management in specific patient groups needs more attention[28].

Van den Beuken et al. found that patients with more advanced stages of cancer were more at risk for pain[28]. Although systematic pain assessment and pain registration during each outpatient visit are recommended in the Dutch CPG on pain in patients with cancer[24], our figures show a lack of implementation of this recommendation. Therefore, an RCT to evaluate an implementation strategy with training for medical staff and short message service (SMS), interactive voice response (IVR) for patients is running in six Dutch hospitals[27]. Our study has several strengths. First, we conducted a large, multicentre study. Second, we included medical records of all medical oncologists of all participating hospitals of a period of 2 years.

Medical records (paper or electronic version) of both patients with and without pain were studied, and finally, this is the first study that also included nonspecific pain descriptions as a separate category.

Our study assessed pain registration for both patients with and without pain. We documented the absence of pain to avoid nonspecific symptom descriptions and monitor pain over time. Additionally, our study included nonspecific pain descriptions as separate category. Nonspecific symptom questions do not specify whether a patient has pain, the intensity of pain, and whether it changes over time. Nonspecific symptom questions might not help patients to initiate talking about their pain with their physician.

Our study also has some limitations. First, our data might not be representative for other European countries. Gynaecological-related cancers were hardly included in this study because these patients are not primarily treated by a medical oncologist in the Netherlands. Additionally, we were not able to distinguish between cancer-related pain and non-cancer related pain, as this information was not available in the medical records.

Third, a sampling methodology was used; therefore, this study does not cover all pain documentation. However, we are convinced that data are representative for documentation of oncologists in these Dutch hospitals because all oncologists participated and months were randomized. The data are representative of the multi-institutional, but do not cover all documentation. Finally, oncologists might screen for pain but do not document it, and we do not know whether the general hospitals are representative for other hospitals. Our study shows several issues for further research. Implementation strategies for guidelines to improve systematic pain screening and registration and implementing the recommendations regarding systematic monitoring of pain is needed.

Despite the fact that pain prevalence is high in patients with cancer, its treatment is inadequate, it severely impacts quality of life[7], and patients are reluctant to talk about pain[17,18], we found that screening for pain with a VAS or NRS appeared practically absent. Previous studies have shown that accurate and consistent cancer pain registration improves the perception of physicians concerning cancer pain and enhances pain management[17,23,18,24]. Implementing the recommendations regarding systematic monitoring of pain is needed: (1) Pain should be systematically screened and registered in oncology outpatients at each visit; (2) Use pain-specific questions, because patients are reluctant to report pain; (3) Document absence of pain.

Conclusion

Pain in medical oncology outpatients is not systematically registered in their medical records. With one exception, pain was not registered with a VAS or NRS. Yet, registration and assessment of pain in order to monitor pain are essential to evaluate and adapt pain treatment over time. Pain registration has not improved since 2001 and therefore, implementing the recommendations regarding systematic monitoring of pain is needed.

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4

Adoptation of an evidence-based clinical practice guideline in cancer pain management by medical oncologists: A case vignette study

Nienke te Boveldt
Myrra Vernooij-Dassen
Kees Besse
Kris Vissers
Yvonne Engels

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Abstract

Background. Pain is a major problem in all cancer stages. Cancer pain guidelines are developed to improve management of pain. It is unclear whether these recommendations are applied in daily practice. Therefore, the objective of this study was to assess medical oncologists' adherence to an evidence-based clinical practice guideline in cancer pain management and their confidence in treatment choices. **Methods**. A cross-sectional case vignette survey describing a patient with intractable pancreatic cancer and pain was sent to all 268 medical oncologists registered at the Netherlands Association of Internal Medicine. Descriptive statistics were conducted. **Results.** Sixty-three of 268 medical oncologists (24%) completed the survey. Adherence to the different recommendations of the guideline ranged from 18 to 100%. Confidence for treatment choice ranged from 5.6 to 9.5 on a Numeric Rating Scale (0–10). Most of the responding oncologists (94%) adhered to prescribing paracetamol as first-line pain treatment, and all prescribed a laxative in combination with opioids to prevent constipation. However, only 24% of the respondents adhered to the guideline when first-line treatment had insufficient effect. Additionally, only 35% adhered to the recommendation for insomnia treatment providing psychosocial support or using a multidimensional pain questionnaire besides pharmacological treatment. Finally, only 18% adhered to the recommendation to perform a multidimensional pain assessment when disease worsens and pain increases. **Conclusions.** The recommendations of the guideline have been partly adopted in cancer pain practice by medical oncologists. Particularly, pain assessment is not applied in the recommended manner. Therefore, implementation strategies should focus on adequate pain assessment in patients with cancer.

Introduction

Pain prevalence in patients after curative treatment is 33%, 59% during curative treatment, and 64% in patients with metastases or an advanced disease stage[1]. Pain is undertreated in 31%[2] to 65%[3] of these patients, although adequate pain relief is considered feasible in 86% of patients with cancer[4]. These figures show that pain is a major problem in all cancer stages. Pain is one of the most frequently feared symptoms for patients[5,6] and is associated with anxiety, depressed mood, and sleep disturbances[6-9]. For those reasons, pain in patients with cancer strongly hampers patients' daily activities[10] and decreases their quality of life[7-9].

It has been shown that treatment of pain in combination with treatment of anxiety, depression, and sleep disturbances related to pain was more effective than pain medication alone[11]. However, physicians tend to show lack of attention for and knowledge about pain management[12], do not systematically assess pain[13,14], and inadequately communicate with patients about their pain[15]. Besides, for a variety of reasons, patients are reluctant to discuss pain with their doctor[12,14,16]. Some patients, for example, have concerns about addiction to pain medication, and others fear that reporting pain will distract the physician from cancer treatment[16].

Therefore, systematic screening and documentation of pain are essential. Clinical Practice Guidelines (CPGs) can be helpful to improve cancer pain management[11,17,18]. Systematic screening and documentation of pain are recommendations in the Dutch multidisciplinary evidence-based CPG "pain in patients with cancer," one of the most recent CPGs on this subject in Europe and developed in 2008[11]. This Dutch CPG has high quality regarding the process of development and the way of reporting[19]. It has been developed for all professional caregivers involved in cancer pain treatment, including medical oncologists.

As medical oncologists play a key role in planning, delivering, and coordinating cancer care and pain management in these patients, it is important to assess whether they are familiar with this CPG and adhere to its recommendations.

For this reason, a case vignette including most important recommendations of the CPG has been developed. A case vignette is an accurate tool for measuring care practices[20]. The objective of the case vignette study was to assess whether medical oncologists in the Netherlands adhere to the evidence-based recommendations in the Dutch cancer pain CPG as well as their confidence with treatment choices.

Methods

A national cross-sectional case vignette survey describes a patient with intractable pancreatic cancer and pain (see appendix I).

Study procedure

Of all 304 medical oncologists registered at the Netherlands Association of Internal Medicine (NIV), 36 were excluded because they were retired (n=7), were working in a foreign practice (n=11), were not a medical oncologist (n=4), were not clinically active (n=4), or could not be linked to a hospital or practice (n=10) (Fig. 1). This information was obtained from hospital Web sites, secretaries, or from the oncologists themselves after having sent the vignette for the first time.

The remaining 268 medical oncologists were invited to participate in this study in October 2013. Nonrespondents received a reminder 3 weeks later and a second e-mail remainder 3 weeks after the first reminder. All questionnaires received before 1 February 2014 were included in the analysis.

Case vignette

According to Hughes and Huby "vignettes consist of text, images or other forms of stimuli to which research participants are asked to respond"[21]. The case vignette used, concerned a woman with pancreatic cancer and was developed by two anesthesiologists who, respectively, participated in and chaired the Dutch cancer pain CPG development group in 2008 (KB, KV). It was pilot tested in four physicians.

The case vignette was divided in four consecutive parts, in which the disease stage worsens and the pain increases. Part I concerns questions on first-line pain management; part II describes an adaptation of pain treatment; part III concerns how oncologists manage pain-related impairment; and Part IV relates to end-of-life pain management. The case vignette consisted of 14 questions reflecting the most important recommendations of the CPG. Additionally, demographic characteristics of the respondents were assessed (gender, date of birth, number of years of experience in clinical practice, working in an academic/ non-academic hospital), the number of patients with cancer on their yearly patient list, an estimation of the percentage of these patients in pain, and whether the respondents were familiar with the Dutch CPG pain in patients with cancer. Finally, we asked them to report per question how confident they were with their treatment choice. Confidence in treatment choice was assessed on a Numeric Rating Scale (NRS) with 0 being "not confident at all" and 10 being "completely confident." Additionally, most common answers or combination of answers were shown.

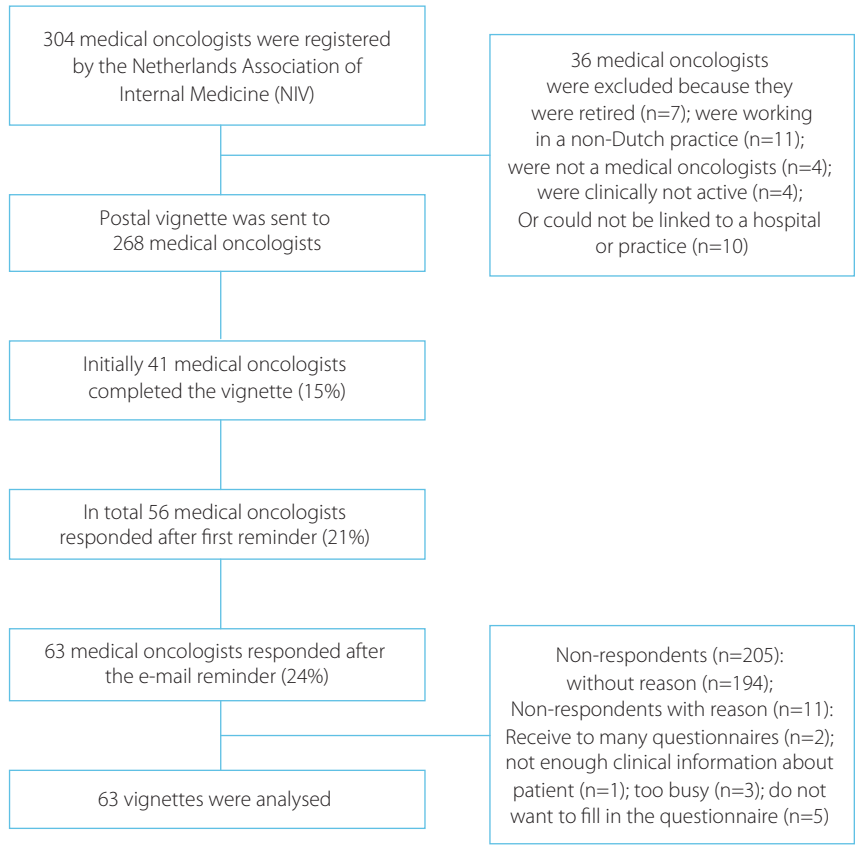
Statistical analysis

Descriptive statistics were conducted. Percentages of medical oncologists adhering to the recommendations of the CPG were assessed. Statistical analyses were performed with SPSS 20.0 (IBM SPSS Statistics, Armonk, NY, USA).

Results

Initially, the response rate was 15%. After the first reminder, it increased to 21% and after the second reminder to 24% (63 medical oncologists) (Figure 1). Mean age of the medical oncologists was 45 ± 8.9 years (32–65 years). Oncologists estimated that 41± 21% (5–90%) of their patients with cancer have pain. Almost all respondents (94%) reported to be familiar with the CPG (Table 1). Eleven of 205 nonrespondents reported a reason for not responding; five medical oncologists did not want to participate, two reported that they receive too many questionnaires and were not able to answer all, one reported that there was not enough clinical information given to answer the questions and finally, three reported that they were too busy.

Figure 1 Study flow diagram



Part I first-line pain management

Table 2 shows oncologists' adherence to the recommendations of the CPG. Sixty-five percent of the respondents adhered to the recommended first-line pain management strategy. This includes at least pharmacological treatment and assessment of pain with a one-dimensional or a multidimensional pain questionnaire. Ninety-four percent of the respondents reported to prescribe paracetamol (and an NSAID) and not codeine as first-line pharmacological treatment. Figure 2 shows the most frequently reported answers or combination of answers. Most often, respondents (32%) reported as first-line pain management strategy pharmacological treatment, pain assessment with a one-dimensional pain scale, and further diagnostics (Fig. 2a, Q1). Thirty-eight percent of the respondents reported to prescribe paracetamol as single first-line pharmacological treatment. In addition, 27% of the respondents reported to prescribe paracetamol in combination with a strong opioid, which is recommended in the CPG as second step in pain management and not as first step. Finally,10% of respondents reported to prescribe paracetamol and NSAIDs (Fig. 2a, Q2).

Part II adaptation of pain treatment

In part II of the case vignette, patient's pain increases, and first-line pain treatment has insufficient effect. Adaptation of pain treatment is needed. Twenty-four percent of the respondents adhered to the recommendations of the CPG by at least adapting pharmacological treatment, conducting pain assessment with a one dimensional pain scale, and discussing possibilities for invasive treatment with an anesthesiologist (Table 2, Q3). Besides, much variation in answer or combination of answers existed for question 3 (choosing a strategy for adaptation of pain treatment)(Fig. 2B).

Eighty-nine percent of the respondents, as recommended, would add a strong opioid to paracetamol (and NSAIDs), which was already prescribed in the previous treatment phase (Table 2, Q4), and all respondents prescribed a laxative to prevent constipation caused by opioids (Table 2, Q5). The invasive treatment as part of the adapted pain management strategy should be a celiac plexus block and/or a splanchnic nerve block for patients with pain located in the upper abdomen, caused by primary tumour or metastases, which was chosen by 78 % of the respondents (Table 2, Q6).

Part III impairment of pain

In part III of the vignette, the patient has concerns about her children: How will they cope with the fact that she will die. The CPG recommends to consider psychosocial support, as this can also improve pain control. However, to whom the patient should be referred to for help is not specified in the CPG (Table 2, Q7). The patient's pain intensity is decreased, but insomnia is still a problem. Thirty-five percent of the respondents adhered to the recommendations for insomnia treatment by adaptation of pharmacological treatment,

Table 1 Participants and practice characteristics of survey respondents (N=63)

	N	(%)
Gender		
Man	26	(41.3)
Women	37	(58.7)
Age (years)		
30-45	33	(52.4)
45-60	23	(36.5)
≥60	7	(11.1)
Years' experience in practice		
<1	3	(4.8)
1-5	22	(34.9)
5-10	12	(19.0)
>10	26	(41.3)
Practice type		
Academic	19	(30.2)
Non-academic	43	(68.3)
Other	1	(1.6)
Estimated number of patients per year consulted		
50-100	4	(6.3)
100-500	32	(50.8)
=>500	21	(33.3)
missing	6	(9.5)
Percentage of patients with cancer and pain		
<10%	2	(3.2)
10-25%	15	(23.8)
25-40%	12	(19.0)
40-55%	17	(27.0)
55-70%	7	(11.1)
>70%	8	(12.7)
Missing	2	(3.2)
Are you familiar with the CPG?		
Yes	59	(93.7)

pain assessment with a multidimensional pain questionnaire, and/or referral to a psychologist (Table 2, Q8). The recommendation to prescribe a benzodiazepine was followed by 73% of the respondents (Table 2, Q9). Despite this treatment, the patient still has sleeping problems and experiences severe anxiety for future suffering. Seventy-five percent of the respondents would discuss patient's problems in a multidisciplinary team meeting and/or refer the patient to a psychologist, as recommended by the CPG (Table 2, Q10).

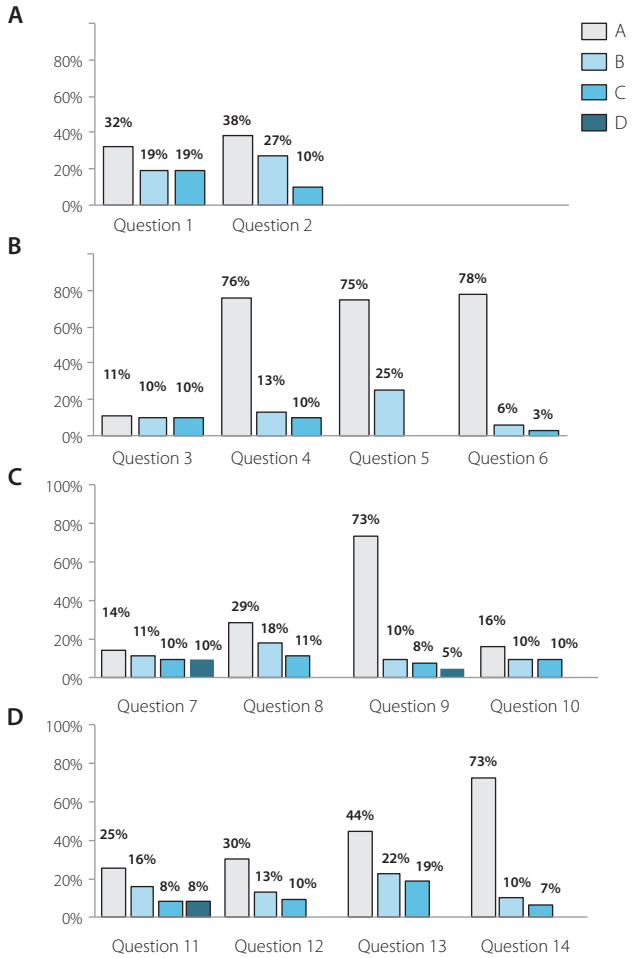
Table 2 Adherence to CPG and summaries of CPG recommendations

Questions	Recommendation	Answer	% adh.*
Part I first line pain management			
Q1 Strategy of pain management	Use a one-dimensional scale or multi-dimensional pain questionnaire for pain assessment[1-4]. (p 26-27)	- Pharmacological treatment and pain assessment with a one-dimensional scale OR - Pharmacological treatment and multi-dimensional questionnaire.	65%
Q2 Treatment of pain	Prescription of paracetamol as first step in pain treatment[5, 6]. (p 69)	- Paracetamol OR - Paracetamol and NSAID	94%
Part II adaptation of pain treatment			
Q3 Strategy of pain management	Use a one-dimensional pain scale or multi-dimensional pain questionnaire for pain assessment[1-4]. (p 26-27)	- Adaptation of pharmacological treatment and assessment of pain with a one-dimensional pain scale and discuss possible invasive treatment with anaesthesiologist.	24%
Q4 Treatment of pain	Use NSAIDS in combination with paracetamol or opioids if these have insufficient effect.(p 73)	- Depends on answer Q2. Paracetamol (and NSAID) are given as first-line treatment, here a strong opioid should be added.	89%
Q5 Prevention of side effect	Prescription of a laxative to prevent constipation and an anti-emetic drug if persistent nausea is present[7-9]. (p 104-105)	- At least prescribe a laxative.	100%
Q6 Choice of invasive treatment	Celiac plexus block is recommended for patients with pain localized in upper abdomen as a result of metastasis.[10] (p 147)	- Celiac plexus block OR - Splanchnic nerve block** OR - Celiac plexus block and Splanchnic nerve block**	78%
Part III Impairment of pain			
Q7 Mourning management	Psychosocial support can improve pain treatment and should be considered (p 139-140). Pain treatment needs to be multi-dimensional. (p 125)	- Not specified in CPG.	n/a
Q8 Strategy of insomnia treatment	Use a multi-dimensional pain questionnaire for pain assessment [1-4]. (p 26-27) Psychosocial support can improve pain treatment and should be considered. (p139-140)	- Adaptation of pharmacological treatment and pain assessment with a multi-dimensional pain questionnaire OR - Adaptation of pharmacological treatment and refer to psychologist OR - Adaptation of pharmacological treatment and pain assessment with a multi-dimensional pain questionnaire and refer to psychologist	35%
Q9 Treatment of insomnia	Prescribe a drug against insomnia: benzodiazepine or tricycle antidepressant. (p125) Pain treatment needs to be multi-dimensional. (p 125) Treating insomnia can also reduce pain or pain experience. (p 124)	- Benzodiazepine	73%
Q10 Strategy of depression management	Psychosocial support can improve pain treatment and should be considered. (p 139-140) Pain treatment needs to be multi-dimensional. (p 125)	- Discussing patient in multidisciplinary team meeting - Refer to psychologist - Discussing patient in multidisciplinary team meeting and refer to psychologist	75%
Part IV pain management in end of life			
Q11 Strategy of pain management	Thorough history and physical examination; further investigation on indication. (p 27) Use a one-dimensional pain scale or multi-dimensional pain questionnaire for pain assessment[1-4]. (p 26-27) Consider invasive treatment if adaptation of pharmacological treatment will not be effective to further reduce pain. (p 145-147)	- Adaptation of pharmacological treatment and multi-dimensional pain questionnaire OR - Adaptation of pharmacological treatment and multi-dimensional pain questionnaire and discuss possible invasive treatment with anesthesiologist	18%
Q12 Treatment of pain management	If pain reduction is not sufficient by using opioids, opioid-rotation is recommended, titration is necessary[11-15]. (p 90)	- Opioid-rotation	65%
Q13 Choice of invasive treatment	If oral and transdermal opioids have insufficient effect or to reduce their side effects, spinal opioid administration should be considered. (p 144)	- Spinal opioid administration	43%
Q14 Choice of administration route	Change opioid administration route (oral, transdermal, subcutaneous or intravenous). (p 95-96)	- Subcutaneous	71%

*adherence to CPG = percentage of respondents who treated the patient in adherence with the recommendations of the CPG, including respondents who also included other answer categories in their answer besides what has been recommended. **shows much similarity with the celiac plexus block. 1-15 See appendix II additional references table 2

Figure 2C Q7 shows that most frequently, the respondents would refer the patient to a psychologist, social worker, or pastoral worker (14%). Figure 2C Q8 shows that the most commonly chosen strategy for insomnia treatment (29%) was to adapt the pharmacological treatment without conducting pain assessment or referring the patient to a psychologist. Additionally, Fig 2C Q10 shows that most respondents would treat this patient for anxiety/ depression with treatments categorized as "other" (16%). For example, the respondents described strategies as talking with the patient about his/her concerns or discussing the medical status of the patient with the general practitioner or with the palliative care team.

Figure 2 Most common answers or combinations of answers *(see notes figure 2 next page)*



Notes figure 2:

First-line pain treatment: Q1 Strategy of first-line pain management: A= pharmacological treatment, one-dimensional pain measurement and further diagnostics; B= pharmacological treatment & one-dimensional pain measurement; C= pharmacological treatment. Q2 Treatment of pain: A = paracetamol; B= paracetamol & strong opioid; C= paracetamol & NSAIDS. **Adaptation of pain treatment:** Q3 Diagnose/characteristics of pain: A= pharmacological treatment & asking about constipation & one-dimensional pain measurement; B= pharmacological treatment & asking about constipation & further diagnostics & one-dimensional pain measurement & contact anesthesiologist for invasive treatment; C= pharmacological treatment & asking about constipation.. Q4 Treatment of pain: A= strong opioid B= NSAID & strong opioid; C= NSAID. Q5 Prevention of side effects: A= a laxative; B= a laxative and anti-emetic. Q6 Choice of invasive treatment: A= celiac plexus block; B= celiac plexus block & spinal administration of opioid; C= celiac plexus block & splanchnic nerve block. **Impairment of pain :** Q7 Mourning management: A= psychologist & social worker & pastoral worker; B= psychologist; C= psychologist & pastoral worker; D= other. Q8 Strategy of insomnia treatment: A= adaptation pharmacological treatment; B= adaptation pharmacological treatment & consultation psychologist; C= other. Q9 Treatment of insomnia: A=benzodiazepine; B= benzodiazepine & other; C= other; D=benzodiazepine & anti-depressant. Q10 Strategy of depression management: A= Other; B= referral to clinical psychologist; C= multidisciplinary team meeting. **Pain management in end of life:** Q11 Strategy of pain management: A= adaption of the pharmacological treatment & discuss with anesthesiologist for invasive pain treatment; B= discuss with anesthesiologist for invasive pain treatment; C= adaption of the pharmacological treatment & one-dimensional pain measurement & discuss with anesthesiologist for invasive pain treatment; D= Adaption of the pharmacological treatment & one-dimensional pain measurement. Q12 Treatment of pain management: A=opioid rotation; B=further increase of opioid dose; C=parenteral administration of opioids. Q13 Choice of invasive treatment: A= celiac plexus block; B= spinal opioid administration; C= celiac plexus block & spinal opioid administration. Q14 Choice of administration route: A= subcutaneous; B= transdermal; C= subcutaneous & transdermal.

Part IV impairment of pain

The patient's pain intensity increases and the disease progresses. Eighteen percent of the respondents adhered to the recommendation of the CPG to adapt pharmacological treatment and to conduct pain assessment with a multidimensional pain questionnaire (Table 2, Q11). Sixty-five percent of the respondents suggest opioid rotation if pain reduction is not sufficient (Table 2, Q12). Besides, 43% of the respondents chose for spinal opioid administration as invasive pain treatment. If oral and transdermal opioids have insufficient effect or too many side effects, spinal opioid administration should be considered (Table 2, Q13). At home, the subcutaneous route of an opioid is recommended, to which 71% of the respondents adhered (Table 2, Q14).

Figure 2D Q11 shows that most respondents (25%) would treat the pain with adaptation of pharmacological treatment and discuss possible invasive treatment with an anesthesiologist (Fig. 2D, Q11).

Confidence in treatment choices

Respondents were asked to report per question how confident they were with their answer, which ranged from 5.6 to 9.5 on an NRS. The confidence figures did not differ between respondents who adhered to the CPG and those who did not, except for confidence with the strategy for depression treatment (question 10). Regarding this question, respondents who did not adhere to the recommendation of the CPG appeared more confident with the treatment choice than respondents who did not (p=0.043, two-tailed).

Discussion

The results of this national case vignette survey to assess medical oncologists' adherence to evidence-based CPGs show that adherence to the recommendations of the CPG ranged from 18 to100%. Feeling confident with the chosen treatment ranged from 5.6 to 9.5 on an NRS. Particularly, pain assessment was not applied in the recommended manner. As medical oncologists play a key role in planning, delivering, and coordinating cancer care and pain management, it is important that they systematically assess pain. Therefore, we recommend to implement a quality indicator for assessing cancer pain, in order to facilitate diagnosis, evaluation, and documentation of cancer pain[22].

A quality indicator for standardized postoperative pain assessment is already implemented in Dutch practice[23]. In our study, adherence to the recommendations appeared somewhat higher than that in an equal case vignette study with pain specialists in France[24]. This study by Piano et al. showed that half of the respondents adhered to the recommendations of a French CPG for neuropathic pain in patients with cancer[24]. Although overall adherence in our study was higher than in the French study, adherence to 4 out of 13 recommendations was very low. Besides, much variation in answer or combination of answers existed in question 3 (choosing a strategy for adaptation of pain treatment).

Probably, this question was not well formulated which might have influenced adherence. Especially, adherence to pain assessment appeared to be low. An Australian survey among oncologists to identify barriers and facilitators to cancer pain assessment and management showed that only 22% of the respondents reported to use pain CPGs[25]. In agreement with our findings, they addressed that particular attention should be paid to promoting the use of validated pain assessment scales[25].

Additionally, another survey on attitudes of oncologists regarding cancer pain management showed that poor assessment is a key barrier in cancer pain management.

Besides, they also addressed the reluctance of patients to talk about opioids or to report pain as another key barrier in cancer pain management[14].

Adherence to the recommendations regarding pain assessment appeared low as compared to the recommendations on pain treatment. A possible explanation might be that in the Dutch CPG, the recommendations for pain assessment are not specified: when, why, and how pain should be assessed. A substantial part of the recommendations of evidence-based CPGs is based on consensus opinion. If systematic reviews or large prospective studies are not available, evidence-based guidelines use expert opinion. In the Dutch CPG, the recommendation whether or not paracetamol should be continued when an opioid is prescribed is one of these recommendations (see Table 2, Appendix 2). That might explain why opioids were prescribed early on for this scenario by 27% of the respondents. This recommendation on pain assessment should contain information on how and how often pain needs to be assessed. It should also mention when to make use of a one-dimensional pain scale and when to add a multidimensional pain questionnaire. Besides, structured registration of the results of the pain assessment in the medical record needs to be mentioned in CPGs as an essential part of the recommendation[26]. Second, publishing a CPG is not enough[27]. Implementation efforts are needed to improve cancer pain management, and examples should be given. Moreover, the CPG revision should focus on cancer pain management barriers, especially on ineffective patient -specialist communication. Additionally, the CPG recommends that psychosocial support should be considered as an essential part of the pain management strategy, because it can improve pain control.

However, to whom the patient should be referred to for this support is not specified in the CPG. Finally, a previously conducted study to assess how pain has been registered in medical records of patients with cancer by medical oncologists shows that pain was not systematically registered in their medical records and only in one out of 987 visits at the outpatient clinic pain was registered with an NRS or Visual Analogue Scale (VAS)[26]. Therefore, recommendations for pain registration in medical records should be included and specified in the CPG: how pain should be registered and who is responsible for registration.

The present study has several strengths. This is the first study to assess medical oncologists' adherence to evidence-based cancer pain CPGs. Additionally, we asked all medical oncologists registered at the Netherlands Association of Internal Medicine (NIV) to participate. Another strength of this study is that the use of a case vignette is an accurate tool for measuring care practices and it gives more information than retrospective analysis of medical records to assess adherence to CPGs[20].

Several limitations of this study should also be considered in the interpretation of the findings. The overall response rate of 24% is low. However, other recently conducted surveys on cancer pain in medical oncologists also showed low response rates between 15 and 33%[14,24,25,28].

This relatively low response rate raises concerns whether the results can be generalized to the Dutch medical oncologists' population. The responding medical oncologists probably were more interested in cancer pain management than nonrespondents, which might have caused higher adherence rates.

For this reason, the low response rate will not have influenced our conclusion that pain assessment needs further implementation.

This national case vignette survey to assess whether medical oncologists adhere to an evidence-based CPG shows that the recommendations of the CPG have not been well adopted, especially the recommendation for conducting pain assessment. Additionally, the CPG should advice whether an anesthesiologist is needed in a more advanced stage of the disease. We would encourage other case vignette studies to report most common answers, besides adherence, to be able to discuss the quality of the questions included.

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Appendix I: Case Vignette

Ms. A is 45-years old. She is married and has two children (12 and 15 years old). After she developed a silent icterus, an intractable pancreatic cancer was diagnosed. The family has been informed about her poor prognosis. The bile flow was restored using a stent. The patient is in good condition and has a good appetite. Ms. A is treated with chemotherapy. A few weeks after hospital discharge, Ms. A visits the outpatient clinic because she has pain in her upper abdomen with varying intensity.

1. You decide to treat the patient with the following strategy *(more than one answer is possible):*
☐ Pharmacological treatment
☐ Pain assessment with an one-dimensional pain scale (pain intensity)
☐ Pain assessment with a multidimensional pain questionnaire
☐ Further diagnostics, namely…
Please report how confident you are that this strategy is correct (please circle what applies)
Being not confident at all 0 1 2 3 4 5 6 7 8 9 10 Being completely confident

2. The pharmacological treatment includes *(more than one answer is possible):*
☐ Paracetamol
☐ Codeine
☐ NSAID
☐ Strong opioid
☐ Other, namely….
☐ N/A
Please report how confident you are that this treatment is correct (please circle what applies)
Being not confident at all 0 1 2 3 4 5 6 7 8 9 10 Being completely confident

The pain is acceptable for a couple of weeks. Then the pain increases. Ms. A experiences pain in her upper abdomen, especially during the night and she wakes up early in the morning because of her pain.

3. You decide to treat the patient with the following strategy *(more than one answer is possible):*
☐ Adaptation of the pharmacological treatment
☐ Ask about possible constipation problems
☐ Pain assessment with an one-dimensional pain scale (pain intensity)
☐ Pain assessment with a multidimensional pain questionnaire
☐ Contact an anesthesiologist for possible invasive treatment
☐ Further diagnostics, namely….
Please report how confident you are that this strategy is correct (please circle what applies)
Being not confident at all 0 1 2 3 4 5 6 7 8 9 10 Being completely confident

The adaptation of the pharmacological treatment includes:
- ☐ Add paracetamol
- ☐ Add NSAID
- ☐ Add or increase codeine
- ☐ Add or increase a strong opioid
- ☐ N/A

Please report how confident you are that this treatment is correct (please circle what applies)
Being not confident at all 0 1 2 3 4 5 6 7 8 9 10 Being completely confident

4. To treat or avoid possible side effects of strong opioids you prescribe the following medication:
- ☐ A laxative
- ☐ An anti-emetic
- ☐ Medication or treatment to treat drowsiness

Please report how confident you are that this strategy is correct (please circle what applies)
Being not confident at all 0 1 2 3 4 5 6 7 8 9 10 Being completely confident

5. A possible invasive pain treatment:
- ☐ Cordotomy
- ☐ Celiac plexus block
- ☐ Splanchnic nerve block
- ☐ Hypogastric nerve block
- ☐ Lower end block
- ☐ Spinal administration of an opioid
- ☐ Other, namely
- ☐ N/A

Please report how confident you are that this treatment is correct (please circle what applies)
Being not confident at all 0 1 2 3 4 5 6 7 8 9 10 Being completely confident

Ms. A worries about her children's reaction concerning her future death.

6. You suggest to contact additional help can be provided by:
- ☐ Foundation "de Einder"
- ☐ Foundation "Achter de Regenboog"
- ☐ A psychologist
- ☐ A social worker
- ☐ A pastoral worker
- ☐ Other, namely……

7. The pain decreases because of treatment, however insomnia remains a problem. You decide to treat the patient with the following strategy *(more than one answer is possible):*
- ☐ Adaptation of pharmacological treatment
- ☐ Pain assessment with an one-dimensional pain scale (pain intensity)
- ☐ Pain assessment with a multidimensional pain questionnaire
- ☐ Psychological consultation
- ☐ Other, namely……

Please report how confident you are that this strategy is correct (please circle what applies)
Being not confident at all 0 1 2 3 4 5 6 7 8 9 10 Being completely confident

8. The adaptation of pharmacological treatment includes:
- ☐ Add a benzodiazepine
- ☐ Add an antidepressant drug
- ☐ Add methylphenidate
- ☐ Other, namely……

Please report how confident you are that this treatment is correct (please circle what applies)
Being not confident at all 0 1 2 3 4 5 6 7 8 9 10 Being completely confident

Ms. A still suffers from insomnia after your treatment and tells you about her concerns for future suffering.

9. You decide to treat the patient with the following strategy *(more than one answer is possible):*
- ☐ Discuss this patient in a multidisciplinary team meeting
- ☐ Refer the patient to a clinical psychologist
- ☐ Advice to contact a pastoral worker
- ☐ Refer the patient to a nurse specialized in oncology
- ☐ Prescribe an antidepressant drug
- ☐ Other, namely……

Please report how confident you are that this strategy is correct (please circle what applies)
Being not confident at all 0 1 2 3 4 5 6 7 8 9 10 Being completely confident

After a short period of time the pain worsens and is localized in the whole abdomen. Illness progresses and the chemotherapy should be cancelled.

10. You decide to treat the patient with the following strategy *(more than one answer is possible):*
- ☐ Adaptation of the pharmacological treatment
- ☐ Pain assessment with an one-dimensional pain scale (pain intensity)
- ☐ Pain assessment with a multidimensional pain questionnaire
- ☐ Contact anesthesiologist for possible invasive treatment
- ☐ Other, namely…

Please report how confident you are that this strategy is correct (please circle what applies)
Being not confident at all 0 1 2 3 4 5 6 7 8 9 10 Being completely confident

11. Despite optimal titration of the strong opioid the pain increases; which adaptation of the pharmacological treatment can be proposed?

☐ Further increase of the opioid dose
☐ Opioid rotation
☐ Parenteral administration of opioids
☐ Adjuvant treatment, namely…
☐ N/A

Please report how confident you are that this treatment is correct (please circle what applies)
Being not confident at all 0 1 2 3 4 5 6 7 8 9 10 Being completely confident

12. The possible invasive treatment is?

☐ Cordotomy
☐ Celiac plexus block
☐ Splanchnic nerve block
☐ Hypogastric nerve block
☐ Lower end block
☐ Spinal administration of an opioid

Please report how confident you are that this treatment is correct (please circle what applies)
Being not confident at all 0 1 2 3 4 5 6 7 8 9 10 Being completely confident

The patients wants no invasive pain treatment anymore. The disease is complicated by a pelvic venous thrombosis, which is treated with acenocoumarol. After a few weeks her situation further deteriorates. She is very tired and unable to eat and drink The patient can't swallow the opioids. Her life expectancy is estimated one to two weeks.

13. What is the most suitable way of giving strong opioids at home?

☐ Intraspinal
☐ Subcutaneous
☐ Transdermal
☐ Intravenous

Please report how confident you are that this treatment is correct (please circle what applies)
Being not confident at all 0 1 2 3 4 5 6 7 8 9 10 Being completely confident

Appendix II: additional references table 2

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5

Implementation protocol of the Dutch clinical guideline pain in patients with cancer: a cluster randomised controlled trial with Short Message Service (SMS) and Interactive Voice Response (IVR)

Nienke te Boveldt
Myrra Vernooij-Dassen
Kees Besse
Kris Vissers
Yvonne Engels

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Abstract

Background. One-half of patients with cancer have pain. In nearly one out of two patients with cancer and pain, pain was undertreated. Inadequate pain control still remains an important problem in this group of patients. Therefore, in 2008 a national, evidence-based multidisciplinary clinical practice guideline 'pain in patients with cancer' has been developed. Yet, publishing a guideline is not sufficient. Implementation is needed to improve pain management. An innovative implementation strategy, Short Message Service with Interactive Voice Response (SMS-IVR), has been developed and pilot tested. To evaluate on effectiveness of this strategy to improve pain reporting, pain measurement and adequate pain therapy. In addition, whether the active role of the patient and involvement of caregivers in pain management may change. **Method.** A cluster randomised controlled trial with two arms will be performed in six oncology outpatient clinics of hospitals in the south-eastern region of the Netherlands, with three hospitals in the intervention and three in the control condition. Follow-up measurements will be conducted in all hospitals to study the long-term effect of the intervention. The intervention includes training of professionals (medical oncologists, nurses, and general practitioners) and SMS-IVR to report pain in patients with cancer to improve pain reporting by patients, pain management by medical oncologists, nurses, and general practitioners, and decrease pain intensity. **Discussion.** This innovative implementation strategy with technical tools and the involvement of patients, may enhance the use of the guideline 'pain in patients with cancer' for pain management. Short Message Service alerts may serve as a tool to support self-management of patients. Therefore, the SMS-IVR intervention may increase the feeling of having control.

Background

Pain is a major healthcare problem for patients with cancer[1] and is one of the most frequently feared symptoms[2,3]. In 2007, in a Dutch study 64% of patients with metastatic, advanced, or terminal disease[4], 59% of those on anti-cancer treatment and 33% of patients after curative treatment experienced pain[4]. Often, pain control is inadequate[2-9]. In 2007, Deandrea et al. demonstrated that pain is undertreated in 50% of patients with cancer[10]. For most patients acceptable pain reduction has not yet been reached. Up to now, no hospital-wide intervention has yet improved the treatment of pain[11].

A key barrier in cancer pain management is ineffective communication between patients and healthcare providers about their pain[12,13]. Patients often consider information they receive from providers to be unclear[14,15]. Generally, patients lack knowledge about pain and pain management[16,17]. Several studies show that informing and educating the patient about treatment of cancer pain reduces pain intensity[18-21].

Professionals do not ask their patients systematically about their pain[22,23]. Moreover, patients seem to be reluctant to talk about their pain or to ask for pain medication[24-26] for a variety of reasons, such as concerns about addiction, tolerance, desire to please providers, and fear that reporting pain will take the physician's time away from the treatment of their cancer[27,28].

One further aspect of underreporting pain concerns assessment and documentation. There is evidence that careful and regular, systematic assessment of pain improves the perception of physicians and nurses concerning cancer pain and enhances the quality of pain management[29,30].

Healthcare providers lack attention to and knowledge about pain management[29,31-33] and consequently do not always treat pain according to specific guidelines[31,32]. This has been regarded as one of the main factors causing inadequate pain relief in patients with cancer[29,34,35].

For these patient- and professional-related reasons, inadequate treatment of cancer pain persists, despite decades of efforts to provide clinicians with information on analgesics and pain-relieving techniques[36-42], and despite the availability of evidence-based guidelines on cancer pain[43].

The prevailing principle for treatment of cancer pain is the World Health Organization (WHO) three-step pain ladder, published in 1986[42]. If this guideline is well applied, it is possible to achieve adequate pain relief in 70 to 90% of patients with cancer[44-47].

Based on this pain ladder, a more detailed European recommendation for the use of morphine and alternative opioids has been published by the European Association for Palliative Care (EAPC)[48]. The final version of the 'Evidence-based guidelines for the use of opioids analgesics in the treatment of cancer pain: The EAPC recommendations' is in development[49].

The Dutch guideline 'Pain in patients with cancer'[50] is one of the most recent guidelines on this topic in Europe. It combines new insights and existing knowledge derived from evidence-based medicine. All relevant professional organizations of the Netherlands as well as the patient association have been involved in the development process. In a comparative study of European guidelines on this topic with the AGREE II instrument, this Dutch guideline appeared to have followed a good development process[51]. Yet, under-treatment of cancer pain may be partly caused by a lack of implementation of these clinical practice guidelines (CPGs)[10,52-54].

The present study aims to evaluate the implementation of the Dutch guideline 'Pain in patients with cancer'[50] to improve pain reporting, pain measurement, and hence pain control in patients with cancer and pain. A randomised controlled trial (RCT) with two arms will be performed in which professionals will be trained and Short Message Service with Interactive Voice Response (SMS-IVR) will be used to monitor and report pain.

Using Short Message Service (SMS) as a reminder and as tool to collect data on pain scores is innovative and promising[55]. Mobile phones are part of daily life; in 2009, nine out of ten Dutch inhabitants used a mobile phone[56].

SMS alerts have been used for asthma management[57-59], management of irritable bowel syndrome[60,61]management of diabetic patients[61] and recurrent pain in children aged 9 to 15[62]. These studies concluded that SMS can serve as a tool to support self-management of patients. The use of mobile phone SMS alerts in the present study may be a way to encourage patient empowerment, because the patients' role in their pain management becomes more active. Empowerment has been defined by its absence of helplessness, or the feeling of having greater control over one`s life[63].

We expect that SMS-IVR will increase the percentage of patients with cancer who receive adequate pain treatment and reduce pain intensity in patients with cancer, because pain will be measured systematically. In addition, patients are expected to become less reluctant to report pain and physicians will ask patient more frequently about pain.

The primary research question of the present study is: Will implementation of the Dutch guideline improve pain reporting, pain measurement, and adequate pain therapy?

A RCT will be implemented, with clustering based on number of beds and number of medical oncologists to increase comparability of hospitals and to reduce contamination[64]. Differences of the effectiveness of the intervention between subgroups are expected. Factors that may predict inadequate cancer pain treatment include gender, race, low education, a better physical condition without metastatic disease, and age[65]. This paper describes the aims and methods of an RCT to evaluate on effectiveness of implementation of the Dutch guideline to improve pain reporting, pain measurement, and adequate pain therapy. The results of this study will be published in several scientific papers.

Methods

Objectives/hypothesis

The primary objective of this RCT is to reduce pain intensity of patients with cancer. The secondary objectives are to improve knowledge of the guideline to increase pain reporting by patients and professionals, to increase systematic pain measurement by medical specialists and nurses working at oncology outpatient clinics, and increase quality of life of patients.

It is hypothesized that this innovative implementation strategy—which includes use of technical tools, training of professionals, and patient involvement—may increase the use of the guideline for pain management in patients with cancer, and consequently reduce pain intensity (individual level and cluster level) and increase pain management. SMS-IVR alerts may serve as a tool to support self-management of patients.

Time frame

This study will be conducted from 2011 to 2015.

Study design

A non-blinded cluster RCT, will be performed in six oncology outpatient clinics of hospitals in the south-eastern region of the Netherlands, with hospital as cluster. Stratified randomisation will be performed based on pairs of two comparable hospitals regarding number of beds and number of medical oncologists. For each pair, one hospital will be randomly allocated to the intervention condition and the other to the control condition. Allocation to the intervention or control condition will be done before start of the intervention period by asking a statistician to select three closed envelopes (Figure 1). The allocation was generated by an independent statistician.

Chosen implementation strategies are:

1. Training of oncologists and nurses involved in cancer care on the most important aspect of the CPG comprising of three one-hour sessions, one main session at baseline, session two at month six, and the final session at month twelve (intervention arm).
2. Patients will receive SMS-IVR and personal advice by phone on how to reduce their pain if their pain rating is 5 or higher on a numeric rating scale (NRS) of 0 (no pain at all) to 10 (worst pain you can imagine) (intervention arm).
3. Patients will receive a leaflet on cancer pain of the Dutch Cancer Society (in both arms).
4. Oncologists and nurses will receive a leaflet for professionals on pain treatment of the Comprehensive Cancer Centre organisation (VIKC) (both arms).
5. GPs in the Netherlands will be offered a web-based training on the most important aspects of the CPG (intervention arm).

Figure 1 Flowchart cluster randomisation of clinics

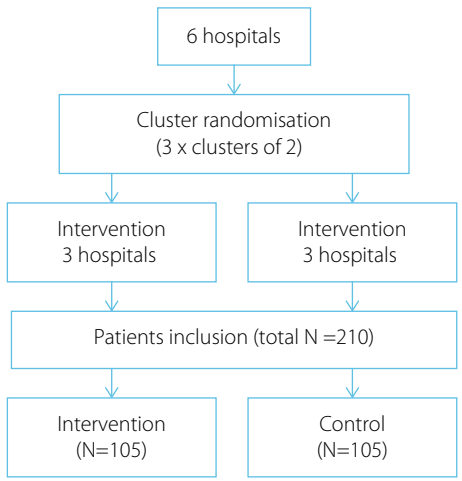


Figure 1 shows the cluster randomisation of clinics. A cluster RCT with two arms will be performed in six oncology outpatient clinics of hospitals, with three hospitals in the intervention and three in the control condition. Clusters of hospitals will be determined based on number of beds and number of medical oncologists. We require 35 patients per hospital, a total of 210 patients.

Follow-up measurements in all hospitals will be conducted to study the long-term effect of the intervention. Regarding the patients recruited in this study, the intention to treat principle will be used (Figure 2).

Furthermore, four times, during a period of one week, transversal measurements will be performed in outpatient clinics of all six hospitals. Pain intensity of all patients who visit the oncology outpatient clinic during that week will be measured.

Participant recruitment and inclusion- and exclusion criteria

To recruit hospitals, a letter was sent to hospital boards. If the board was willing to cooperate, a meeting with the oncologists and nurse practitioners in oncology was arranged to introduce the study. All hospitals are recruited from the south-eastern region of the Netherlands. Via the hospital boards, professional caregivers, oncologists, and nurses involved in cancer care of the six participating hospitals will be invited to take part. Patients who visit the oncology outpatient clinic will be screened for possible inclusion. Patients will be invited to take part by their medical oncologist or research nurse if they start to experience cancer-related pain.

Figure 2 Overall time chart of the study and per patient (M = month)

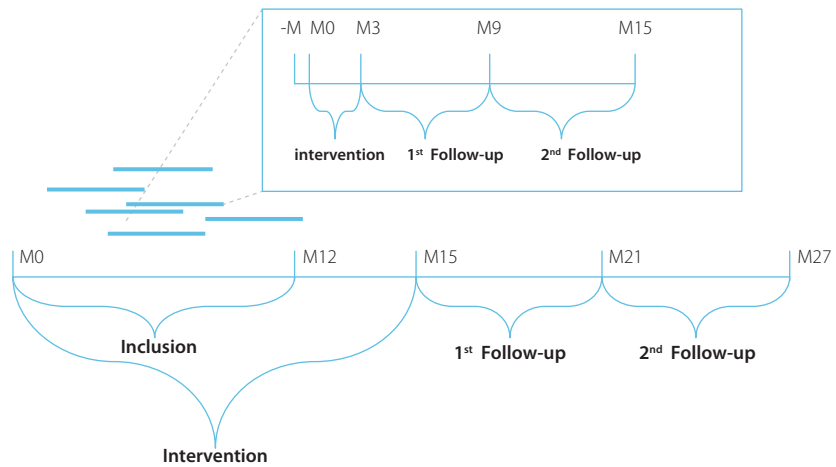


Figure 2 shows the overall time-chart of the study and per patient. Each hospital has a period of twelve months to include 35 patients in the study. The total intervention period of hospitals is fifteen months (per patient twelve weeks). The first follow-up period is six months after the intervention period (M15) and the second, twelve months after the intervention period (M27). Each patient will be included in the study for 15 months.

Overall inclusion criteria for patients are: diagnosed with cancer; aged 18 years or older; pain intensity of 3 or more on an NRS for the worst pain experienced in the last 24 hours; and having and being familiar with the use of a mobile phone. Overall exclusion criteria are: dementia and other severe cognitive disorders; no informed consent; and non-Dutch speaking and writing.

Intervention

The intervention was based on a pilot study with 13 patients, performed from November 2009 to January 2010, to test feasibility of SMS-IVR. The mean response rate was 62%. A significant reduction of highest pain intensity was found between pre- and post-test ($p = 0.018$). Pain fluctuated more in patients included in this pilot study than would be expected in patients who will be included in the present study, because only patients in palliative care were included in the pilot study.

Next, we developed a multifaceted intervention with hospital as cluster. Multifaceted interventions are proven to be more effective than single interventions[66,67].

Oncologists and nurses in the hospitals allocated to the intervention condition will be trained in-person, and GPs of patients that take part in the study will be offered a web-based training on the most important aspects of the CPG.

Patients in the intervention condition will get SMS-IVR and will receive an advice by phone how to reduce their pain if their pain rating is 5 or higher on a NRS (0 =no pain at all to 10 =worst pain you can imagine). The research nurse of the hospital, specialised in pain treatment and trained for this project, will provide the personal advice.

The training for oncologists and nurses consists of three one-hour sessions, all given in-person; one main session at baseline, session two at six months, and the final session at 12 months. The first session will include the aim of the study, the main aspects of pain treatment in patients with cancer, pain measurement, and an instruction of the SMS-IVR system in detail. The next two sessions aim to summarise the first session and discuss problems associated with the implementation of the guideline.

Figure 3 shows the workflow of the SMS-IVR intervention. Patients receive SMS-IVR minimal once a week (Tuesdays), twice a day, during 12 weeks (Figure 2). SMS alerts are used as a reminder for patients that they will receive an automatic telephone call in 15 minutes. SMS alerts will be received at 09:45 a.m. and at 2:45 p.m. At 10 a.m. and at 3 p.m. the patients will be called and invited to rate their pain on a scale of 0 (no pain) to 10 (worst pain imaginable). In the morning patients were asked to rate their pain by choosing a number that best describes their WORST pain in the last 24 hours. In the afternoon patients were asked to rate their pain at this moment.

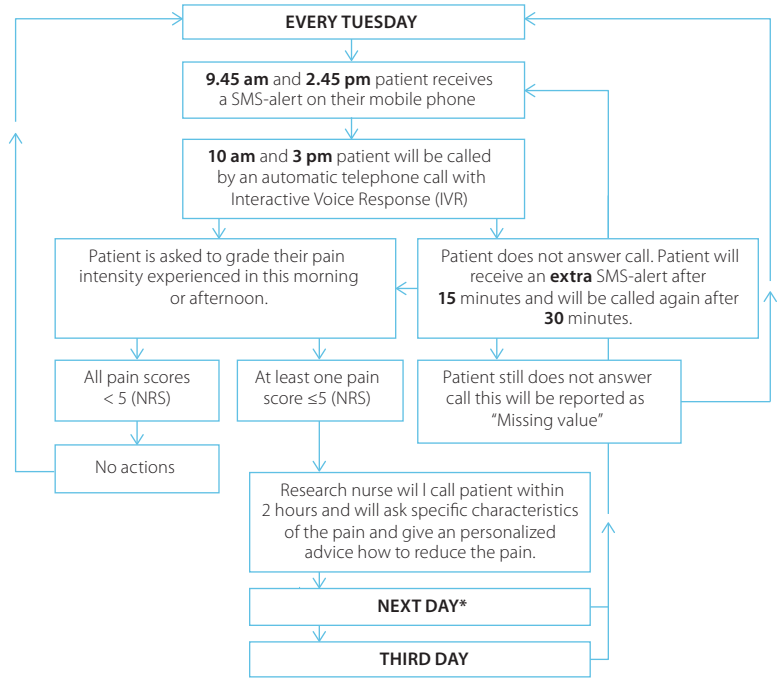
If the highest pain score is 5 or higher, the research nurse will contact the patient and will ask: 'at what time/period the patients experienced the worst pain and whether the pain limited daily activities?'

Any patient with a pain intensity of 5 or higher on an NRS on Tuesday will again receive two SMS alerts the next day (Wednesday); the procedure will be repeated. For those who still have a pain score of 5 or higher on Wednesday, the procedure will be repeated again at Thursday.

The whole procedure of the SMS-IVR system is described in figure 3. For the days without SMS, patients will follow the instructions of the research nurse.

Figure 3 shows the workflow of the SMS-IVR intervention. Patients receive SMS-IVR minimal once a week (Tuesdays), twice a day, during 12 weeks. SMS alerts are used as a reminder that they will receive an automatic telephone call 15 minutes later with IVR. SMS alerts will be received at 09.45 a.m. and at 2.45 p.m. At 10.00 a.m. and at 3.00 p.m. the patients will be called and invited to rate their pain on a scale of 0 (no pain) to 10 (worst pain imaginable). If the highest pain score is 5 or more, the research nurse will contact the patient. If a patient has five or higher on an NRS on Tuesday he/she will again receive two SMS alerts the next day (Wednesday); the procedure will be repeated. For those who still have a pain score of five or higher on Wednesday, the procedure will be repeated again at Thursday. The whole procedure of the SMS-IVR system described in figure 1 will start again the next week at Tuesday.

Figure 3 Workflow SMS alerts



*If the next day pain is graded as ≥ 5 the oncologists will be informed.

In addition, both patients in the intervention and the control condition will fill in a pain diary on Tuesdays for 12 weeks; twice each Tuesday, once between 8:00 and 12:00 a.m., and once between 12:00 a.m. and 17:00 p.m.. However, there should be a minimum of five hours between the morning and afternoon measurement. The pain diary reports pain intensity with an NRS, the use of pain medication, and any side effects of the medication. Patients will also receive a leaflet on cancer pain of the Dutch Cancer Society. In addition, oncologists and nurses will receive a leaflet for professionals on pain treatment of the VIKC.

Control

Patients in the control condition will also receive a leaflet on cancer pain. These patients will complete a pain diary on Tuesdays during the 12-week period in the same way as the patients in the intervention condition. In addition, professionals will be offered a leaflet on pain treatment as a summary of the pain management guideline.

Outcomes and measurement instruments

The primary outcomes of this implementation study include: the first primary outcome is the percentage of all patients that visits the medical oncology outpatient clinic with adequate pain therapy/medication. Pain treatment adequacy will be calculated with both the Cleeland's Pain Management Index (PMI)[68] and Ward's variation of the PMI[33]. It is the most used measure for adequate pain treatment[33]. Cleeland's PMI compares the most potent analgesic prescribed, with patient's reported worst pain level on the Brief Pain Inventory (BPI).

In addition, Ward's variation of the PMI compares the most potent analgesic used by a patient with that patient's reported worst level of pain on the BPI.

The worst score on the BPI will be determined (1 to 3, mild pain; 5 to 6, moderate pain; and 7 to 10, severe pain), where the absence of pain will be defined as 0, mild pain as 1, moderate pain as 2 and severe pain as 3. The worst pain score on the BPI is used because it is often used clinically as an indicator for treatment[69]. PMIs will be computed by subtracting the pain level from the analgesic level, ranging from -3 (a patient with severe pain receiving or using no analgesic drug) to +3 (a patient with no pain receiving or using a strong opioid or equivalent). PMI-scores of 0 or higher are considered to be a reflection of adequate pain treatment, whereas negative PMI-scores are considered to reflect inadequate pain treatment.

The second primary outcome is the mean pain intensity of patients with cancer, measured with an NRS (SMS alerts and pain diary). The NRS is the most appropriate choice to use in practice for pain intensity (see Table 1)[70,71]. The pain diary is used to obtain additional information (medication use, side effects of medication) and to report pain intensity in the control group.

The secondary outcomes of this study include:

1. Percentage of medical records in which pain of new patients in the outpatient oncology clinic is registered with a validated instrument, such as the NRS or visual analogical scale (VAS). These data will be collected retrospectively via medical records.
2. Quality of life of patients assessed with The European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ-C30) questionnaire[72].
3. Knowledge of medical oncologists and nurses of the content of the guideline with a self-developed and pilot-tested knowledge questionnaire and vignette study. This knowledge questionnaire and vignette study are based on the recommendations in the guideline, with input from specialists in pain treatment and GPs.
4. Pain intensity and impact of pain on daily activities will be measured with the Brief Pain Inventory Short Form (BPI-SF)[73]. This questionnaire consists of four questions in which pain intensity is rated on an 11-point numerical scale (NRS) from 0 (no pain) to 10 (worst pain ever).

5. Insight in the multidimensional aspects of pain with the Short-form McGill Pain Questionnaire[74]. To measure sensory, affective, and evaluative qualities of pain the McGill Pain Questionnaire Dutch version (MPQ-DV) will be used[75].
6. Performance status of patients will be measured with the Karnofsky scale[76]. It is based on the assessment by the oncologist of the patient`s ability to perform usual daily activities.
7. We will identify neuropathic pain characteristics by using the two first questions of the Douleur Neuropathic 4 questionnaire, short form (DN4-SF)[77].
8. To assess multidimensional problems (work, family, *et al.*) related to cancer the distress thermometer (DT) will be used[78].
9. Prevalence of anxiety and depression will be measured with the Hospital Anxiety Depression Scale HADS[79].
10. Patients` experiences with the SMS-IVR system will be assessed with semi-structured interviews.
11. Self-efficacy for communicating about pain with oncologists will be assessed with the mean response to the five items in the Perceived Efficacy in Patient-Physician Interactions scale (PEPPI-5), with the wording of the items modified to refer to communication about pain with oncologists (Table 1)[80].

Sample size

Sample size calculations of the present study with three clusters of two hospitals, are based on the expected effect of the intervention on the PMI. However, the present study is the first investigating the effects of using an SMS-IVR system in cancer pain management. Several studies show that adequate pain relief can be achieved in 70 to 90% of patients with cancer[44-47]. To achieve this, the present study aims to find out whether our implementation strategy reduces the negative PMI from 42%[6] to 20%[44-47] of all patients with cancer visiting the outpatient clinic. To detect a difference with 80% power (alpha = 0.05), we need 90 patients per condition.

Accounting for clustering resulted in an intraclass correlation coefficient (ICC) of 0.05. Based on the ICC and three hospitals per condition, we need 30 patients per hospital. Taking into account a dropout rate of 15%, we need 35 patients per hospital, for a total of 210 patients.

Cluster randomisation of clinics

Clusters of hospitals will be determined based on number of beds and number of medical oncologists to increase comparability of hospitals and to reduce contamination[64]. Of each pair, one hospital will be randomly allocated to the intervention condition and the other to the control condition. Randomisation took place after all hospital boards and medical oncologists had agreed to participate. Next, an independent statistician allocated to the intervention or control condition based on clusters by selecting three closed envelopes (Figure 1). Patients will be invited to take part by their medical oncologist or research nurse.

Table 1 Patient questionnaires/scales

Measurement	Validated questionnaires	Time points (M=month)
Pain intensity	A. Numeric Rating Scale (NRS) B. Brief Pain Inventory Short form (BP-SF)	A. M0-M3/ M9/ M15 B. M0/M3/ M9/ M15
Multidimensional aspects of pain	McGill pain questionnaire (MPQ)	M0/M3/M9/ M15
Pain interference with function	Brief Pain Inventory Short form (BP-SF)	M0/M3/M9/ M15
Adequate pain treatment	Ward`s Pain Management Index (PMI-revised)	M0/M3/M9/ M15
Quality of life	European Organization for Research and Treatment of cancer Quality of Life Questionnaire- C30 (EORTC QLQC30)	M0/M3/M9/ M15
Neuropathic pain	Neuropathic Pain Diagnostic Questionnaire (DN4-SF) (first two questions)	M0/M3/M9/ M15
Problems in daily life associated with cancer	Distress Thermometer (DT)	M0/M3/M9/ M15
Emotions related to cancer	Hospital Anxiety and Depression Scale (HADS)	M0/M3/M9/ M15
Performance status	Karnofsky Performance Scale (KPS)	M0/M3
Self-efficacy for communication about pain with oncologist	Perceived Efficacy in Patient-Physician Interactions (PEPPI-5)	M0/ M3

Statistical analysis

To measure the effect of the implementation the PMI and NRS will be used and tested with general linear model analysis of variances (GLM ANOVA) repeated measures. Qualitative content analysis will be used to analyse the results of the focus group discussions and to analyse the interviews to evaluate the SMS alert intervention. Qualitative analysis will be supported by the use of the Atlas.ti software programme.

Data collected via SMS-IVR will be analysed for descriptive data: how did pain scores change and fluctuate in the whole period, what actions were taken by the research nurse, and did this intervention help the patients to manage pain? Subgroup analysis will be conducted. Differences in subgroups of the effectiveness of the intervention are expected. Subgroups will be classified by: age, gender, race, education, performance status, and classification of malignant tumours (TNM stage). The most recent version of SPSS will be used to perform the statistical analysis.

Qualitative data collection

Many studies explored barriers in pain management of patients with cancer and professional caregivers in different countries. However, this has never been done in the Netherlands. Therefore, four focus group interviews will take place to explore barriers and incentives about cancer pain management with respectively: patients with cancer, oncologists, nurses and GPs. Focus groups offer an opportunity to obtain significant insight regarding the experiences, observations, and opinions of members of that group[81].
In addition, semi-structured interviews by phone focused on patient empowerment will be used to evaluate the SMS-IVR intervention.

Ten randomly selected participating patients per hospital will be interviewed. The aim of these interviews is to shed light on the results of the intervention and the effect on patient empowerment.

Retrospective analysis

To investigate how and how frequently pain has been reported in medical records retrospective analysis will be performed for the year 2010 (two years after the guideline has been published). Thirty-six medical records per hospital (the first three of each month) of oncology patients who came for their first consultation at the outpatient clinic will be obtained. Retrospective analysis of medical records will be repeated after the intervention period.

Additional data

Data on patients characteristics will be obtained from medical records: patient identification code, date of diagnosis, gender, age, postal code, marital status, primary cancer type, secondary cancer, history of cancer treatment, present treatment, cancer exact location, TNM stage cancer, and pain medication. Retrospective data of surgery and other cancer treatment during intervention period, and hospital admission(s) (number, length and indication) will also be analysed.

Other data will be obtained via a patient questionnaire including questions about: SMS use, education level, and experiences with present pain treatment.

Ethical considerations

The study has been approved by the Medical Ethics Committee (CMO) of the Radboud University Nijmegen Medical Centre (METC protocol number 2011/020). The Dutch Cancer Society (KWF) approved the research protocol, which has been registered by the Dutch Trial Register (NTR2739). This study has also been registered by the local ethical committees of each hospital. Anonymity of every patient is guaranteed. Patients have to sign an informed consent before start of the intervention.

Discussion

This implementation study will be the first RCT to study the use of SMS- IVR to collect data on cancer pain. Furthermore, this study is innovative in the active involvement of oncologists, nurses, GPs, and patients with cancer from guideline development to the implementation of the guideline. SMS and/or IVR have never been used before to assess pain in patients with cancer. Using SMS-IVR as a reminder and as a tool to collect data on pain scores is an innovative and promising method[55]. It does not interfere with the patient's daily activities, because SMS has become part of daily life[59]. Pain can be measured systematically at any location with SMS-IVR, the patient can prepare himself (reminder before the actual call), can grade his pain two times a day without much effort and time investment, and, if necessary, can be treated earlier than in usual care.

The use of SMS alerts and mobile phones in the present study may be a way to encourage patient empowerment, because the patient's role in their pain management becomes more active. Another way to describe this is that it may increase patient participation.

Whether the use of SMS alerts and mobile phones with IVR to report pain in patients with cancer may increase patient empowerment or patient participation can be questioned. Patient empowerment is a commonly used term within healthcare, but there is little consensus regarding its definition.[82] In this intervention, the patient is not able to report pain at any time. However, the SMS alert may increase the feeling of having control. Therefore, the SMS alert intervention increases patient-participation and may increase the feeling of having control over one`s life. In this way the SMS alert intervention may encourage patient empowerment.

In addition, our study will show possible barriers in SMS-IVR use for pain reporting in patients with cancer. This has never been done before. One of the possible barriers accounted for in the present study is asking too often about cancer pain and this could be experienced as a confrontation with their disease.

However, nothing is known about a proper frequency to ask patients about their pain with IVR. In the present study, patients will receive a weekly SMS alert twice a day. In the pilot study, patients received SMS alerts four times a week for four weeks. To achieve a similar response rate and compliance as was achieved in the pilot study, the frequency of SMS alerts has been reduced in the present study. It has been reduced to once a week if there is no pain and to maximal three times a week if pain remains present because the intervention period is three times as long. Asking patients about pain improves insight in pain intensity of professionals and it increases registration of pain[83,84]. Asking about pain in itself can reduce pain intensity[84]. Therefore, using SMS-IVR as a way to systematically measure pain is expected to reduce pain intensity.

Apart from the SMS-IVR, a pain diary is necessary to obtain data on pain intensity in the control group and additional information in both control and intervention group.

Asking about pain by measuring pain intensity with a pain diary in itself can reduce pain intensity[84]. Therefore, we expect that pain intensity difference between the intervention and the control group will be smaller. However, the possibility of earlier treatment is restricted to the intervention group.

We expect an increase in motivation of patients to take part in the control condition and higher compliance during the study than without the pain diary. However, because patients are expected to be more motivated to participate when SMS alerts are offered to them, this may cause selection bias. However, it was not possible to randomise at patient level, because of the multifaceted intervention. Oncologists and nurses should be trained before inclusion of patients.

This study protocol shows that the present study is the first to use SMS alerts as a reminder in patients with cancer and mobile phones with IVR to collect data on cancer pain. Furthermore, this study is innovative in the active involvement of oncologists, nurses, GPs, and patients with cancer from guideline development to the implementation of the guideline. If the implementation proves to be effective, it can be considered for use in other hospitals to increase percentage of patients with cancer that receive adequate pain therapy and to reduce pain intensity in patients with cancer. If SMS-IVR proves to be an acceptable and useful method to report pain for patients with cancer and medical professionals, it can be considered for use of data collection to report pain. Therefore, the SMS alert intervention increase patient participation and may increase the feeling of having control over one`s life. In this way the SMS alert intervention may encourage patient-empowerment.

Competing interests

The authors declare that they have no competing interests.

Authors' contribution

All authors contributed to the design of the study. NtB and TB are the principal researchers. NtB was responsible for writing this paper. All other authors scrutinized the manuscript. YE coordinates the study. KV and MVD supervise this study. All authors have read and approved the final manuscript.

Authors information

NtB is the principal investigator in this study. YE combines experience in quality of care research (indicator development and implementation, improving quality of care, changing behaviour of professionals) with experience in research in pain and palliative care. TB, an anesthesiologist and pain therapist, was involved in the development of the guideline and is also a principal investigator in this study.

KV is head of the Knowledge Center Of Pain And Palliative Medicine, and a medical specialist in pain control and palliative medicine. He was chairman of the developmental process of the guideline 'pain in patients with cancer', and has a national and international respected knowledge and experience in the field of pain diagnosis and therapy. MVD has an extensive record of experience in research in palliative care, quality of care research, and in implementation research.

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6

The effect of patient monitoring using the interactive distance alert system (MIDAS 4 Cancer Pain) on cancer pain treatment: a cluster randomised controlled trial

Nienke te Boveldt
Kris Vissers
Jan Hendriks
Myrra Vernooij-Dassen
Yvonne Engels

Submitted

Abstract

Background. Cancer pain is still undertreated in more than 50% of the patients. We monitored patients to assess the effect using the interactive distance alert system (MIDAS 4 Cancer Pain) on the reduction of the percentage of inadequate cancer pain treatment. **Methods.** In a cluster randomised controlled trial, eight hospitals were randomly assigned to the MIDAS 4 Cancer Pain (M) or control (C) groups (4:4). Primary outcome was the Pain Management Index (PMI) at week 12. Secondary outcomes included pain intensity, interference with daily activities, neuropathic pain characteristics, pain descriptors, quality of life, emotional distress, and self-efficacy regarding communication about pain. **Results.** 111 patients with cancer and pain participated in this study (M 72: C 39). At week 12, the percentage of patients with a negative PMI in the MIDAS 4 Cancer Pain group was not significantly lower than in the control group (16%; 95%CI -3 to 35; P=0.12). Pain-related interference with daily activities and depressed mood score were significantly lower in the MIDAS 4 Cancer Pain group. In the subgroup of patients with moderate to severe pain (NRS 5-10) at baseline, the percentage of patients with a negative PMI was significantly lower in the MIDAS 4 Cancer Pain than in the control group (35%; 95% CI 7 to 62; p=0.03). **Conclusion.** The reduction in inadequate pain treatment was not significantly higher in the total group of patients compared to controls. Results for the subgroup of patients with moderate to severe pain revealed that the intervention was significantly more effective in reducing inadequate pain treatment. Our data are therefore promising when defining subgroups for which the intervention might be effective. In addition, our results demonstrate the positive effects of Midas 4 Cancer Pain on pain-related interference with daily activities and depressed mood.

Introduction

In our aging society, cancer prevalence is steadily on the rise. In 2012, the 10-year prevalence of cancer in the Netherlands was 454,388, with 101,864 patients newly diagnosed; in 2013, the 10-year prevalence was 468,939, with 101,848 patients newly diagnosed[1]. Trends from 1989 to 2011 show an average annual increase in incidence of 3%[2].

Pain is one of the most prevalent symptoms of patients with cancer[3], with a prevalence ranging from 27%[4] to 60%[5]. Undertreatment of cancer pain is associated with anxiety, depression, and sleep disturbances[6,7]; it hampers daily activities[8], and therefore affects the quality of life. The aim of pain treatment is to reduce pain intensity to an acceptable level with minimal side-effects[9]. Despite the availability of evidence-based clinical practice guidelines (CPGs), pain treatment in patients with cancer is still inadequate in 31%[10] to 65%[4] of the patients, whereas adequate pain relief is considered feasible in 71%[11] to 86%[12] of the patients. The Pain Management Index (PMI) considers pain treatment to be adequate if there is congruence between the patient`s reported level of worst pain and the prescribed analgesics[13].

The Dutch CPG "Pain in patients with cancer", developed in 2008, is one of the most recent guidelines on this subject in Europe[14]. However, publishing a guideline alone is insufficient[15]; an implementation strategy is also needed. This strategy should address patient and physician related barriers in cancer pain management. Key barriers in pain management are the reluctance of many patients to discuss pain with their doctor or to ask for pain medication, and the absence of systematic assessment and registration of pain by medical professionals[16].

A promising method for lowering these barriers is pain monitoring using interactive voice response (IVR) with short message service (SMS)-alerts.

IVR/SMS enables patients to communicate with health care professionals outside the consultation room. Patients hear a recorded message on their phone and respond to queries using their keypad. SMS-alerts are text messages used to alert health professionals when symptom scores need follow-up. SMS-alerts have been successfully used for collecting weekly symptom data, and have been shown to improve health outcomes in patients with asthma[17], irritable bowel syndrome[18], and diabetes[19].

A pilot test using IVR-SMS alerts to collect prospective and follow-up data on pain intensity in patients with cancer gave positive results and was considered acceptable[20]. These results encouraged us to set up a study to assess the effect of using the interactive distance alert system (MIDAS 4 Cancer Pain) to monitor a possible reduction in the percentage of patients with a negative Pain Management Index (PMI). We hypothesized that the MIDAS 4 Cancer Pain treatment would be more effective in reducing the percentage of patients with a negative PMI than usual care. In addition, we expect that patients with moderate to severe pain (NRS 5-10) at baseline would benefit most from the MIDAS 4 Cancer Pain intervention.

Method

Participants

We performed a multicenter, cluster randomised controlled trial. The trial protocol, approved by the Medical Ethics Committee (protocol number 2011/020), has been outlined in a previous study[21]. All participants provided written informed consent.

Patients were eligible for inclusion if they had been diagnosed with cancer, were 18 years or older, and experienced pain related to cancer or to anti-cancer treatment with an intensity of > 0 on a Numeric Rating Scale (NRS).

In the original protocol patients with a pain intensity of ≥ 3 on an NRS were eligible; the protocol amendment to include all patients with pain was approved. Patients with severe cognitive disorders and those who were not able to speak or write Dutch were excluded (n=0). Figure 1 shows the flow diagram for this study; the RCT follows the CONSORT reporting guidelines.

Randomisation and masking

Eight hospitals were randomised in a 4:4 ratio to the MIDAS 4 Cancer Pain or the control group based on hospital size.

Departments in these hospitals with an outpatient clinic treating oncology patients were asked to participate. Although complete masking of groups was not possible, patients were asked to participate in their own study condition without being informed of the existence of another condition. Patients were recruited from 16 September 2011 to 31 December 2014 by health care professionals responsible for cancer care (oncologists, urologists, gynaecologists, and nurses).

Procedures

The MIDAS 4 Cancer Pain treatment protocol requires medical professionals to be trained in using the guideline 'pain in patients with cancer'[14] and patients' pain was monitored with IVR-SMS-alerts. In the control hospitals no training took place, and patients completed a pain diary.

In both groups, patients were asked to report pain on an NRS twice daily, once a week, for 12 weeks. As part of the MIDAS 4 Cancer Pain treatment, an automatic alert (by SMS and email) was sent to the study nurse when a patient reported a pain score of 5 or higher. The study nurse then contacted the patient within two hours and, after having explored the problem, advised the patient or adjusted pain medication.

In addition, the study nurse activated IVR and SMS-alerts for the next two days to monitor the clinical impact of the advice or medication change[21].

Primary outcome

The primary outcome was defined as a negative PMI[13] score suggests inadequate analgesic pain treatment[13]. The PMI is calculated based on the most potent analgesic drug therapy actually used and the patient's worst pain level. The levels of analgesic treatment are scored as 0, no analgesic; 1 a non-opioid analgesic; 2 a weak opioid; and 3 a strong opioid. The levels of worst pain are scored as 0, absence of pain; 1, mild pain; 2, moderate pain; and 3, severe pain. The PMI score is determined by subtracting the pain level from the analgesic level and can range from -3 to +3.

Pain- related secondary outcomes

Pain- related outcomes were assessed in 5 ways: 1)Pain intensity using the Brief Pain Inventory Short Form (BPI-SF); 2) neuropathic pain characteristics (≥ 3 out of 7) (NPC) with the Douleur Neuropathic 4 questionnaire short form (DN4-SF); 3) the pain severity index was calculated as the sum of worst pain, least pain, average pain, obtained from the BPI-SF; 4) pain-related interference with daily activities using the BPI-SF; and 5) pain descriptors were obtained from the short- form McGill Pain Questionnaire (MPQ) (references see appendix).

Quality of life related secondary outcomes

Quality of life(QoL) related secondary outcomes were assessed in 4 ways: 1) QoL was assessed using the European Organization for Research and Treatment of Cancer Care Quality of life Questionnaire (EORTC QLQ-C30); 2) anxiety and depression scores were measured with the Hospital Anxiety Depression Scale (HADS); 3) self-efficacy for communicating about pain with the medical oncologist using the Perceived Efficacy in Patient-Physician Interactions scale (PEPPI-5) and 4) experiences of patients with the MIDAS 4 Cancer Pain intervention were collected. (references see appendix)

Statistical methods

The power calculation, as reported in our protocol[21], was updated based on new insights[28]. We aimed to reduce the percentage of patients with a negative PMI at week 12 to 20% in the MIDAS 4 Cancer Pain group compared to 62%[28] in the control group. Twenty-four patients are needed in each group to obtain a power of 80%, using a Fisher-exact test (two-sided alpha =0.05). To account for clustering (ICC = 0.05) and to allow for an additional dropout rate of 15%, 39 patients in each group were needed in our study.

Descriptive statistics were used to present patient characteristics in each group. The Fisher exact test was used to test the difference in the primary outcome (PMI < 0) at week 12 between the intervention and control groups.

As patients with moderate to severe pain (NRS 5-10) at baseline would benefit most from the MIDAS 4 Cancer Pain intervention, and as clinical practice guidelines recommend treating this subgroup of patients[14], we were specifically interested in the effect of the MIDAS 4 Cancer Pain treatment in these patients. In addition, in the IVR-SMS-alert procedure, nurses only take action for patients that report an NRS ≥ 5. We therefore decided to perform a subgroup analysis of patients with an NRS ≥ 5 at time of inclusion. The Fisher exact test was also used for all dichotomous secondary outcomes.

We used linear mixed models with adjustment for baseline values to study the influence of the intervention on the continuous secondary outcomes at 12 weeks. The dependent variable was the outcome measure of interest. The independent fixed variables were group (intervention, control) and the baseline score.

Hospital was treated as a random variable. We present the baseline adjusted mean difference between the groups at 12 weeks with the 95% CI. Analyses were done using the principle of intention-to-treat. Statistical analyses were performed using SAS 9.2 for Windows and IBM SPSS statistics 20 for Windows.

Results

Participant characteristics

A total of 111 patients signed the informed consent form; 72 were placed in the MIDAS 4 Cancer Pain group (M) and 39 in the control group (C). Of the original 111 patients, 62 and 29 per group respectively completed the baseline measurements. (Figure 1, Table 1)

Table 1 presents the patient demographics. In the MIDAS 4 Cancer Pain group, less men (MIDAS 50.0%: Control 65.5%) and less patients with lung tumours participated (MIDAS 4.8%: Control 20.7%) than in the control group. Gastrointestinal tumours were more common in the MIDAS 4 Cancer Pain group (MIDAS 30.6%: Control 13.8%) compared to the control group. In addition, 91.7% of the patients underwent palliative care in the MIDAS 4 Cancer Pain group, and 75.0% in the control group.

Response rate to IVR calls

The response rate to the IVR calls was 1334 of the 1398 calls (95.4%). Of these responses, 1029 (77.1%) were correct. Incorrect responses were caused by technical requirements of the system used. The hash symbol needed to switch from the introduction section to the question, resulted in incorrect use of the system in 288 of the 1398 IVR calls (20.6%); in these cases the call was disconnected, and in 17 of the 1398 IVR calls (1.2%) the system did not function.

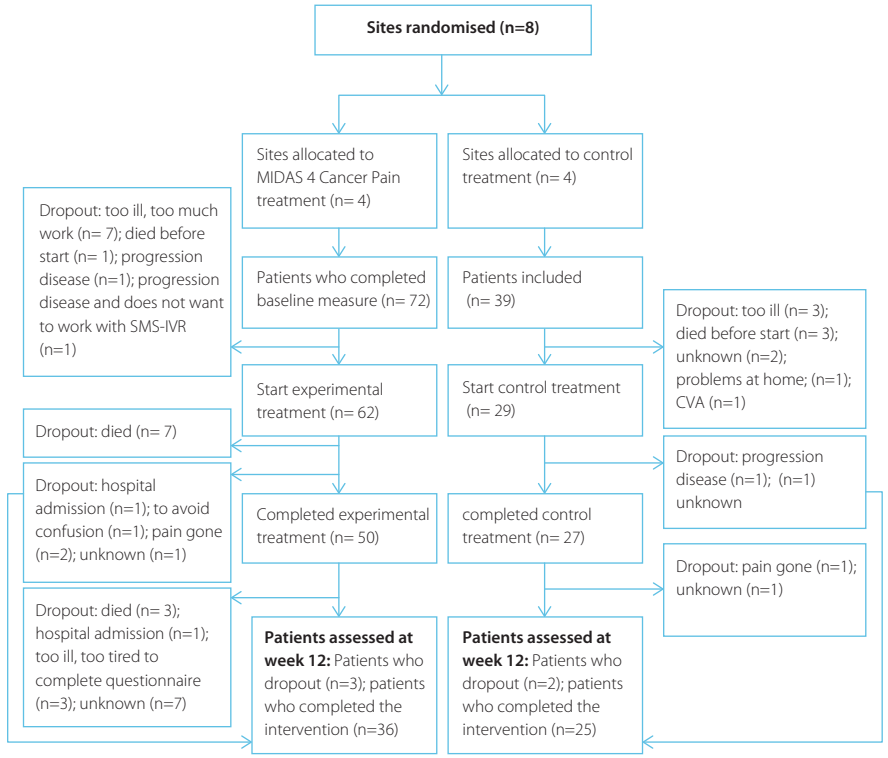
Primary outcome: negative PMI at week 12

Data of 60 and 28 patients for the M and C groups respectively were analysed for primary outcome. At week 12, the percentage of patients with a negative PMI in the MIDAS 4 Cancer Pain group was not significantly lower than in the control group(16%; 95%CI -3 to 35; P=0.12).(Table 2)

Pain- related secondary outcome

Mean pain- related interference with daily activities in the MIDAS 4 Cancer Pain group was significantly lower than in the control group at week 12 (7.9; 95% CI 1.0 to 14.9; p=0.03). (Table 2)

Figure 1 Flow diagram



Quality of life related secondary outcomes

At week 12, mean symptom scores related to QoL were significantly lower in the MIDAS 4 Cancer Pain group than in the control group for nausea and vomiting(14.1; 95% CI 4.5 to 23.5), appetite loss (20.6; 95% CI 1.6 to 39.7),and financial difficulties (8.3; 95% CI 0.0 to16.6). (Table 2)

In addition, the mean score for depressed mood was significantly lower in the MIDAS 4 Cancer Pain group than in the control group (2.0; 95% CI 0.1 to 3.8; p=0.04). (Table 2)

Table 1 Demographics of the participants

	MIDAS 4 Cancer Pain group n=62		**Control group** n=29	
	Median or n/N	(IQR) or (%)	Median or n/N	(IQR) or (%)
Individual level				
Age (years)	63.0	(56.8-68.0)	64.0	(54.0-72.0)
Male	31/62	(50.0)	19/29	(65.5)
Education level				
Secondary school or less	19/61	(31.1)	11/29	(37.9)
Lower vocational education	11/61	(18.0)	2/29	(6.9)
Middle vocational education	22/61	(36.1)	8/29	(27.6)
Higher professional education/ academic	9/61	(14.8)	8/29	(27.6)
Tumour type [a]				
Head and neck	1/62	(1.6)	0/29	(0.0)
Gastrointestinal	19/62	(30.6)	4/29	(13.8)
Lung	3/62	(4.8)	6/29	(20.7)
Breast	17/62	(27.4)	10/29	(34.5)
Prostate	13/62	(21.0)	7/29	(24.1)
Urogenital other	2/62	(3.2)	2/29	(6.9)
Gynaecological	4/62	(6.5)	0/29	(0.0)
Haematological	1/62	(1.6)	0/29	(0.0)
Other	1/62	(1.6)	0/29	(0.0)
Unknown tumour	1/62	(1.6)	0/29	(0.0)
Karnofsky performance scale (%)[b]	80.0	(70.0-80.0)	80.0	(70.0-90.0)
Treatment type				
Curative	2/60	(3.3)	2/28	(7.1)
(neo-) adjuvant	3/60	(5.0)	5/28	(17.9)
Palliative	55/60	(91.7)	21/28	(75.0)
Cluster level[c]	Mean	Range	Mean	Range
Mean number of patients	20.7	(12-35)	7.3	(3-14)
Mean number of male	10.3	(4-19)	4.8	(2-12)
Mean number of patients with palliative care	18.3	(11-33)	5.3	(2-11)

Data are median (IQR) or n/N (%) [a] Adapted from van den Beuken et al. [b] Karnofsky performance scale is missing in 14 patients in the control group and in 4 in the MIDAS 4 Cancer Pain. [c] mean (range).

Table 2 Proportions and medians of outcome and adjusted difference between groups at week 12

	Observed **Baseline**			**Week 12**			**Estimated difference between groups at 12 weeks (M-C)**		
	N	*%*	*(n/N)*	*N*	*%*	*(n/N)*	*Δ %*	*(95% CI)*	*P value*
Pain Management Index: PMI <0									
MIDAS	60	21.7	(13/60)	48	12.5	(6/48)	16.1	(-3.1 to 35.2)*	0.12
Control	28	42.6	(12/28)	28	28.6	(8/28)	Ref		
Brief Pain Inventory: Worst pain intensity ≥ 5 NRS (yes/no)									
MIDAS	61	59.0	(36/61)	36	30.6	(11/36)	-8.3	(-30.1 to 13.4)	0.57
Control	29	44.8	(13/29)	27	22.2	(6/27)	Ref		
Douleur Neuropathique 4: Neuropathic pain characteristics ≥ 3 out of 7 (yes/no)									
MIDAS	60	23.3	(14/60)	37	16.2	(6/37)	22.3	(0.1 to 44.4)	0.08
Control	29	41.4	(12/29)	26	38.5	(10/26)	Ref		
	N	*Median*	*(IQR)*	*N*	*Median*	*(IQR)*	*Mean*	*(95% CI)*	*P value*
Pain Management Index for adequacy of analgesic pain treatment (-3, -2, -1, 0, 1, 2, 3)[a,b]									
MIDAS	60	1.0	(0.0-1.0)	48	1.0	(0.0-2.0)	0.4	(-0.1 to 0.8)	0.09
Control	28	0.0	(-1.0-1.0)	28	0.0	(-1.0-1.0)	Ref		
Brief Pain Inventory: Pain severity index (0-40)									
MIDAS	60	16.0	(10.0-21.0)	36	10.0	(6.0-16.0)	1.8	(-1.9 to 5.5)	0.33
Control	29	11.0	(7.0- 16.5)	27	8.0	(2.0-12.0)	Ref		
Brief Pain Inventory: Interference with daily activities total (0-70)									
MIDAS	61	28.0	(20.0-39.0)	37	18.0	(1.0-33.0)	7.9	(1.0 to 14.9)	**0.03**
Control	28	20.0	(14.0-32.8)	27	18.0	(1.0-33.0)	Ref		
McGill Pain Questionnaire for pain experience: number of words chosen (0-20)									
MIDAS	62	8.0	(5.0-11.0)	38	7.0	(4.0-11.0)	0.5	(-2.1 to 3.0)	0.71
Control	26	8.0	(5.8-12.3)	26	7.0	(5.0-9.0)	Ref		

Table 2 Continued

	Observed								
	Baseline			**Week 12**			**Estimated difference between groups at 12 weeks (M-C)**		
	N	*Median*	*(IQR)*	*N*	*Median*	*(IQR)*	*Mean*	*(95% CI)*	*P value*
McGill Pain Questionnaire for pain experience: Intensity rank score (0-63)									
MIDAS	62	12.0	(9.8-19.0)	38	12.0	(5.0- 20.0)	1.2	(-4.4 to 6.7)	0.68
Control	26	12.5	(6.8-18.0)	26	9.0	(7.0-14.3)	Ref		
EORTC QLQ-C30: Physical functioning (0-100)[b]									
MIDAS	62	55.8	(46.7-73.3)	37	60.0	(43.3-66.7)	-9.4	(-20.1 to 1.4)	0.09
Control	28	70.0	(40.0-80.0)	26	70.0	(46.7-86.7)	Ref		
EORTC QLQ-C30: Role functioning (0-100)[b]									
MIDAS	62	33.3	(16.7-66.7)	38	50.0	(16.7-66.7)	-5.7	(-21.1 to 9.7)	0.46
Control	28	50.0	(33.3-66.7)	26	50.0	(29.2-83.3)	Ref		
EORTC QLQ-C30: Emotional functioning (0-100)[b]									
MIDAS	62	75.0	(47.9-91.7)	38	70.8	(50.0-91.7)	-2.6	(-13.4 to 8.2)	0.63
control	28	75.0	(58.3-83.3)	26	75.0	(64.6-91.7)	Ref		
EORTC QLQ-C30: Cognitive functioning (0-100)[b]									
MIDAS	62	66.6	(50.0-83.3)	38	66.7	(50.0-100.0)	-1.2	(-12.2 to 9.7)	0.82
Control	28	75.0	(66.7-100.0)	26	66.7	(62.5-100.0)	Ref		
EORTC QLQ-C30: Social functioning (0-100)[b]									
MIDAS	62	66.7	(50.0-83.3)	38	66.7	(45.8-83.3)	-11.0	(-23.4 to 1.4)	0.08
Control	28	66.7	(33.3-83.3)	26	66.7	(62.5-100.0)	Ref		
EORTC QLQ-C30: Fatigue (0-100)									
MIDAS	62	44.4	(33.3-66.7)	38	44.4	(22.2-66.7)	-5.3	(-8.6 to 19.1)	0.45
Control	28	44.4	(25.0-66.7)	26	44.4	(22.2-58.3)	Ref		
EORTC QLQ-C30: Nausea and vomiting (0-100)									
MIDAS	62	16.7	(0.0-16.7)	38	16.7	(0.0-33.3)	14.1	(4.5 to 23.5)	**0.00**
Control	28	0.0	(0.0-16.7)	26	0.0	(0.0-16.7)	Ref		
EORTC QLQ-C30: Pain (0-100)									
MIDAS	62	66.7	(33.3-83.3)	38	50.0	(33.3-66.7)	3.0	(-9.5 to 15.5)	0.63
Control	28	50.0	(33.3-66.7)	26	33.3	(29.2-66.7)	Ref		
EORTC QLQ-C30: Dyspnoea (0-100)									
MIDAS	62	33.3	(0.0-33.3)	38	16.7	(0.0-33.3)	0.24	(-13.6 to 14.1)	0.97
Control	28	0.0	(0.0-33.3)	26	33.3	(0.0-41.7)	Ref		
EORTC QLQ-C30: Insomnia (0-100)									
MIDAS	62	33.3	(0.0-66.7)	38	33.3	(0.0-66.7)	11.3	(-3.3 to 25.8)	0.13
Control	28	33.3	(0.0-66.7)	26	16.7	(0.0-33.3)	Ref		
EORTC QLQ-C30: Appetite loss (0-100)									
MIDAS	62	33.3	(0.0-41.7)	38	33.3	(0.0-66.7)	20.6	(1.6 to 39.7)	**0.03**
Control	28	0.0	(0.0-33.3)	26	0.0	(0.0-33.3)	Ref		
EORTC QLQ-C30: Constipation (0-100)									
MIDAS	62	0.0	(0.0-33.3)	38	0.0	(0.0-33.3)	9.1	(-4.3 to 22.5)	0.18
Control	28	0.0	(0.0-33.3)	26	0.0	(0.0-0.0)	Ref		
EORTC QLQ-C30: Diarrhoea (0-100)									
MIDAS	62	0.0	(0.0-33.3)	38	0.0	(0.0-33.3)	4.5	(-8.4 to 17.3)	0.49
Control	28	0.0	(0.0-33.3)	26	0.0	(0.0-0.0)	Ref		
EORTC QLQ-C30: Financial difficulties (0-100)									
MIDAS	62	0.0	(0.0-33.3)	38	0.0	(0.0-33.3)	8.3	(0.0 to 16.6)	**0.05**
Control	28	0.0	(0.0-33.3)	26	0.0	(0.0-0.0)	Ref		
EORTC QLQ-C30: Global health status (0-100)[b]									
MIDAS	62	50.0	(39.6-66.7)	37	50.0	(33.3-66.7)	-4.0	(-21.0 to 12.9)	0.64
Control	28	50.0	(41.7-64.6)	27	58.3	(50.0-66.7)	Ref		
Hospital Anxiety and Depression Scale: Anxiety (0-21)[c]									
MIDAS	62	7.0	(3.0-10.0)	37	5.0	(2.0-11.0)	0.1	(-1.5 to 1.6)	0.93
Control	29	8.0	(4.5-9.5)	27	7.0	(4.0-10.0)	Ref		
Hospital Anxiety and Depression Scale: Depression (0-21)[c]									
MIDAS	62	7.0	(4.0-9.0)	37	6.0	(4.0-11.0)	2.0	(0.1 to 3.8)	**0.04**
Control	29	7.0	(4.0-10.0)	27	7.0	(2.0-10.0)	Ref		
Perceived Efficacy in Patient Physician Interactions : communication about pain total (5-25)[b]									
MIDAS	56	23.0	(20.0-25.0)	35	23.0	(20.0-25.0)	-0.7	(-1.9 to 0.5)	0.24
Control	28	22.5	(19.3-25.0)	26	25.0	(20.8-25.0)	Ref		

Difference between groups: MIDAS 4 Cancer Pain (M) – Control (C) * Primary outcome. For all measures, unless otherwise stated, a decrease in score over time suggests improvement. Group differences were estimated using linear mixed models with adjustment for baseline values. [a]If PMI was missing in the week 12 questionnaire, the PMI has been calculated from the last reported pain score and pain medication in the pain diary.[b] an increase in score over time suggests improvement. [c]Patients screened positive for anxiety or depression with a score of ≥ 8 on a subscale (for references see appendix).

Subgroup patients with moderate to severe pain

Findings from the subgroup analysis in patients with moderate to severe pain (NRS 5-10) at baseline showed that the percentage of patients with a negative PMI was significantly lower in the MIDAS 4 Cancer Pain at week 12 (35%; 95% CI 7 to 62; p=0.03 N=39).

In addition, the secondary outcomes in the subgroup showed a significantly higher mean PMI score in the MIDAS 4 Cancer Pain group than in the control group (0.8; 95% CI 0.21 to 1.29; p=0.01).

Table 3 Patient experiences with treatment and study design

	MIDAS 4 Cancer Pain group n=35		**Control group** n=24		**Difference between groups**
	n/N	(%)	n/N	(%)	P-value (2-sided)*
My pain control improved					
Agreed	14/32	43.8	10/23	43.5	0.98
Did not know	15/32	46.9	3/23	13.0	**0.01**
Disagreed	3/32	9.4	10/23	43.5	**0.00**
Time investment was acceptable					
Agreed	27/35	77.1	21/24	87.5	0.50
Did not know	7/35	20.0	1/24	4.2	0.13
Disagreed	1/35	2.9	2/24	8.3	0.56
Frequency of IVR calls or filling in pain diary was acceptable					
Agreed	28/35	80.0	20/23	87.0	0.73
Did not know	7/35	20.0	2/23	8.7	0.30
Disagreed	0/35	0.0	1/23	4.3	0.40
I would participate in this study again if I were asked					
Agreed	19/30	63.3	12/23	52.2	0.41
Did not know	9/31	29.0	6/23	26.1	0.81
Disagreed	3/30	10.0	5/23	21.7	0.21
I reported lower NRS scores than the real pain scores to avoid that the nurse would call : Yes	8/34	23.5	n/a	-	-

*Chi-square or Fischer's Exact test.

Patients' experiences

Table 3 presents the patient experiences with treatment. The percentage of patients who agreed that their pain control improved during treatment was the same for both groups (43%). Eight of the 34 patients (23.5%) in the MIDAS 4 Cancer Pain group noted that they reported lower NRS scores to avoid the nurse calling them.

Discussion

This cluster RCT shows that reduction in inadequate pain treatment was not significantly higher in the MIDAS 4 Cancer Pain group than in the control group. Yet, in the subgroup of patients with moderate to severe pain at baseline, MIDAS 4 Cancer Pain was significantly more effective in reducing inadequate pain treatment.

In this subgroup analysis, patients were excluded who had a mild pain intensity at baseline as for this group pain treatment could not or hardly improve.

Patient recruitment was difficult because of pain related barriers; oncologists do not systematically ask patients about their pain and patients are reluctant to talk about their pain. Due to these recruitment issues, we adapted the inclusion criteria for pain intensity from ≥ 3 on an NRS to 'all patients with pain'. As a result, patients with mild pain were also included which may have resulted in increased medicalization due to the extra focus on pain. However, this adaptation also became a strength, as it enabled a subgroup analysis to determine who would most benefit from MIDAS 4 Cancer Pain.

Although we aimed to include patients in all cancer stages, the majority of our study population consisted of palliative patients, particularly in the MIDAS 4 Cancer Pain group. This inclusion bias is possibly due to the higher prevalence of pain in patients with an advanced disease stage, for whom the treatment focus changes from curative treatment to symptom management. This inclusion bias caused a higher number of missing values and dropout than expected.

Despite recruitment difficulties, most patients in the MIDAS 4 Cancer Pain group (77%) considered the total time investment to be acceptable, and an equal percentage agreed that the frequency of the IVR calls was acceptable. However, 24% percent of patients reported lower NRS scores to avoid the nurse calling them.

This shows that to achieve patient-centred care, the need or wish of patients to report their pain level or to be contacted by the study nurse should be taken into account.

Yet, of those patients that participated in the study, almost all in the MIDAS 4 Cancer Pain group adequately responded to the weekly IVR-SMS-alerts (95%). This is in line with results from a recent study in which IVR completion rates were also high[25]. These figures suggest that patients with an advanced stage of cancer are able to use IVR for symptom management[23,25].

Although IVR completion rates were generally high, the drop-out rate in our study was also high. In the MIDAS 4 Cancer Pain group, 42% of patients dropped out, whereas in the control group 14% of patients dropped out. Reasons for dropout were death, being too ill/too tired, or hospital admission. The high drop-out rate in the MIDAS 4 Cancer Pain group may have influenced the results.

Our study has several strengths. Firstly, as far as we are aware, our study is the first RCT on inadequate cancer pain treatment to assess the effects of IVR/SMS versus a pain diary. Secondly, we performed a multicentre, real time, multidisciplinary RCT which is uncommon in cancer pain management[26].

However, we also noted a number of limitations. To improve patient recruitment, a protocol amendment was required. Therefore patients with mild pain were included, may have resulted in increased medicalization due to the extra focus on pain. Secondly, as a result of the cluster randomisation at hospital level, the number of included patients at inclusion differed between both conditions. Yet, randomisation at patient level would have caused contamination.

Our results are important for health care professionals, patients and future research, as they show that MIDAS 4 Cancer Pain has the potential to reduce inadequate pain treatment in patients with moderate to severe pain. Results from a recent multicentre RCT with 253 patients with advanced lung cancer, monitoring with IVR and symptom alerts, appeared to be no more effective in reducing symptom burden than monitoring alone[23]. Similar to our study, patients with a low symptom burden may have attenuated the effects on the entire group, as they may not have required treatment.

To conclude, the reduction in inadequate pain treatment was not significantly higher in the total group of patients compared to controls. Results for the subgroup of patients with moderate to severe pain revealed that the intervention was significantly more effective in reducing inadequate pain treatment. Our data are therefore promising when defining subgroups for which the intervention might be effective. In addition, our results demonstrate the positive effects of Midas 4 Cancer Pain on pain-related interference with daily activities and depressed mood.

Contributors

NtB was principal investigator; all authors contributed to the design of the study. NtB was responsible for data collection and writing the manuscript. NtB and JH conducted the statistical analysis, and all authors contributed to the data interpretation. YE, KV and MVD scrutinised the manuscript. A physician (pain specialist and palliative care consultant) was involved in this study (KV).

Declaration of interests

The authors declare no conflicts of interest.

Ethical considerations

This study has been approved by the Medical Ethics Committee.

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Appendix Secondary outcomes

Pain and pain- related secondary outcomes

1) Brief Pain Inventory Short Form (BPI-SF)[1]
2) Douleur Neuropathic 4 questionnaire short form (DN4-SF)[2]
3) Short- form McGill Pain Questionnaire[3,4]

Quality of life and quality of life-related secondary outcomes

1) European Organization for Research and Treatment of Cancer Care Quality of life Questionnaire (EORTC QLQ-C30)[5]
2) Hospital Anxiety Depression Scale (HADS)[6,7] Patients screened positive for anxiety or depression with a score of ≥ 8 on a subscale[7-9]
3) Perceived Efficacy in Patient-Physician Interactions scale (PEPPI-5).[10]

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7

Patient empowerment in cancer pain management: an integrative literature review

Nienke te Boveldt
Myrra Vernooij-Dassen
Irene Leppink
Han Samwel
Kris Vissers
Yvonne Engels

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Abstract

Background. More than 50% of patients with cancer experience pain. Patient empowerment has been highlighted as central to success in pain management. Up to now, no clear model for this patient group exists, yet several strategies to empower patients have been used in clinical practice. This review examines how empowerment or related concepts have been described in relation to pain management in patients with cancer. With the help of a conceptual model recommendations for clinical practice are provided. **Methods.** An integrative review was conducted, using the databases PubMed, CINAHL and PsycINFO. We evaluated papers discussing empowerment or related concepts in relation to pain management in patients with cancer. We analysed the term 'empowerment' semantically. **Results.** From a total of 5984 identified papers, 34 were included for analysis. Empowerment has been described with the concepts self-efficacy, active patient participation, increasing abilities, and control of life. Most papers focus on pain treatment induced by the professional caregiver or on the active involvement of the patient, and not on the combination of both. The following elements of empowerment could be discriminated: role of the patient, role of the professional, resources, self-efficacy and active coping, shared decision-making. **Conclusions.** Based on the findings we propose a conceptual model to empower patients in controlling cancer pain. We recommend focusing on pain treatment given by the professional, on the active involvement of the patient, and on the interaction of both. Our model might also be useful for other patient groups or specific contexts, especially in symptom management.

Introduction

In Europe, in 2006 about 3.2 million patients were diagnosed with cancer[1] and in 2012 this number increased to 3.5 million[2]. As a result of the ageing population, this number is expected to increase further in the next decades[1]. Pain is one of the most prevalent symptoms of patients with cancer; more than 50% of them suffer from it[3].

Since cancer pain hampers daily activities[4], quality of life[5-7] and is also associated with anxiety, depression and sleep disturbances[5-7], cancer pain strongly influences patients' quality of life and wellbeing. Although adequate pain relief up to 86% of patients with cancer is considered feasible[8], inadequate pain treatment ranged from 31%[9] to 65%[10]. Thus, cancer pain is still undertreated.

Multi-disciplinary pain management, in which medical, behavioral and cognitive aspects are combined, has been found to be more effective than single pharmacological treatments[11]. Patient empowerment could be one of these aspects, as it has been highlighted as central to success in pain management[12].

Since 1988, patient empowerment has gained more attention in healthcare[13]. The European Network on Patient Empowerment (ENOPE 2012), defined patient empowerment as "a process to help people gain control, which includes people taking the initiative, solving problems, and making decisions"[14]. Patient empowerment is a growing trend; models of patient-doctor relationships are making way for empowered patient models with patients as active partner[15]. The concept empowerment in healthcare might get increasing interest in the next decades, because of the requirement to reform healthcare systems[16]. Healthcare systems should deliver healthcare in a way that meets the increasing health demands in a cost-effective manner[16]. An empowered patient probably self-manages his cancer pain to a larger extent than a non-empowered patient.

Self-management might be an alternative for the traditional patient-physician hierarchy, which might increase cost-effectiveness[15].

Up to now, no clear patient empowerment model exists that can guide cancer pain management, although several strategies to empower patients are currently used in clinical practice[17]. Such a model might be useful to implement empowerment in a more consistent way in clinical practice. Therefore, this review examines how empowerment or related concepts have been described in relation to pain management in patients with cancer in order to provide recommendations and to define a conceptual model.

Method

We performed an integrated review. Whittemore and Knafl defined an integrative review as 'a specific review method that summarizes past empirical or theoretical literature to provide a more comprehensive understanding of a particular phenomenon or healthcare problem'[18]. As this paper examines how empowerment or related concepts have been

described, both empirical and theoretical data were needed. Therefore, an integrative review based on the guidelines suggested by Whittemore and Knafl was the first choice[18]. We evaluated papers discussing empowerment or empowerment-related concepts in relation to pain management in patients with cancer. As other constructs, like self-efficacy and shared decision-making (SDM), have shown to be essential in cancer pain management[19,20] and also show overlap with empowerment, these were included too. Therefore, to get insight in the concept empowerment, related concepts should be taken into account. Studies included in this review have varying methodological quality, but all were included in this review in accordance with the integrative review approach[18].

Search strategy

Databases PubMed, CINAHL and PsycINFO were searched. Detailed search strategies are presented in Appendix 1. The search was limited to studies published between 1990 and October 2012. Studies on children (<18 years of age) were excluded.

Key words and/or MESH terms used were empowerment, self-efficacy, mastery, self-control, self-esteem (obtained from Samoocha et. al[21]), self-concept, self-perception, internal-external control, decision-making and self-regulation. These key words and/or MESH terms were combined with pain management, pain measurement, analgesia, pain therapy, pain prevention, pain control and pain assessment. The search strategy was not limited to cancer, since papers may discuss patients with cancer without mentioning it in the abstract or title.

Reference lists of selected publications as well as major relevant journals (Pain, Anaesthesiology, CA: A Cancer Journal for Clinicians, Nature Review Cancer) were hand-searched to check for missing publications.

In- and exclusion criteria

Papers that studied or discussed empowerment or empowerment related concepts in relation to pain management or pain management/control were included. Papers were excluded when empowerment/ empowerment related concepts or pain management/ control were not related to cancer or were not separately discussed for cancer; when empowerment or related concepts were not discussed in relation to pain management/ control; when empowerment or related concepts were only related to professional caregivers; when the study population consisted of patients with a psychiatric or cognitive disorder/impairment or depression; and finally, when the paper was not written in English.

Data extraction

One of the authors (NtB) initially identified and reviewed citations on title. Two authors (IL and NtB) independently reviewed the papers remaining after title selection on abstract and they selected papers for full text reading. Discrepancies were discussed and a third reviewer (YE) was consulted when necessary. Data were extracted on study design and descriptions, definitions and theories on empowerment related concepts.

Results

Included studies

We initially identified a total of 5984 articles; 5839 citations by database searching and 145 citations by hand searching. After correction for duplicates, 4987 citations were reviewed on title. The remaining 490 papers after title selection were reviewed on abstract and 155 papers were selected for full text reading. An assessment of full text excluded 121 papers. The remaining 34 papers were 22 studies with empirical data, three case reports, one systematic review with meta-analysis, two theoretical papers, two opinion papers, one study protocol, two validation studies and finally one invited commentary. The detailed selection process is described in Figure 1.

Empowerment in relation to cancer pain management

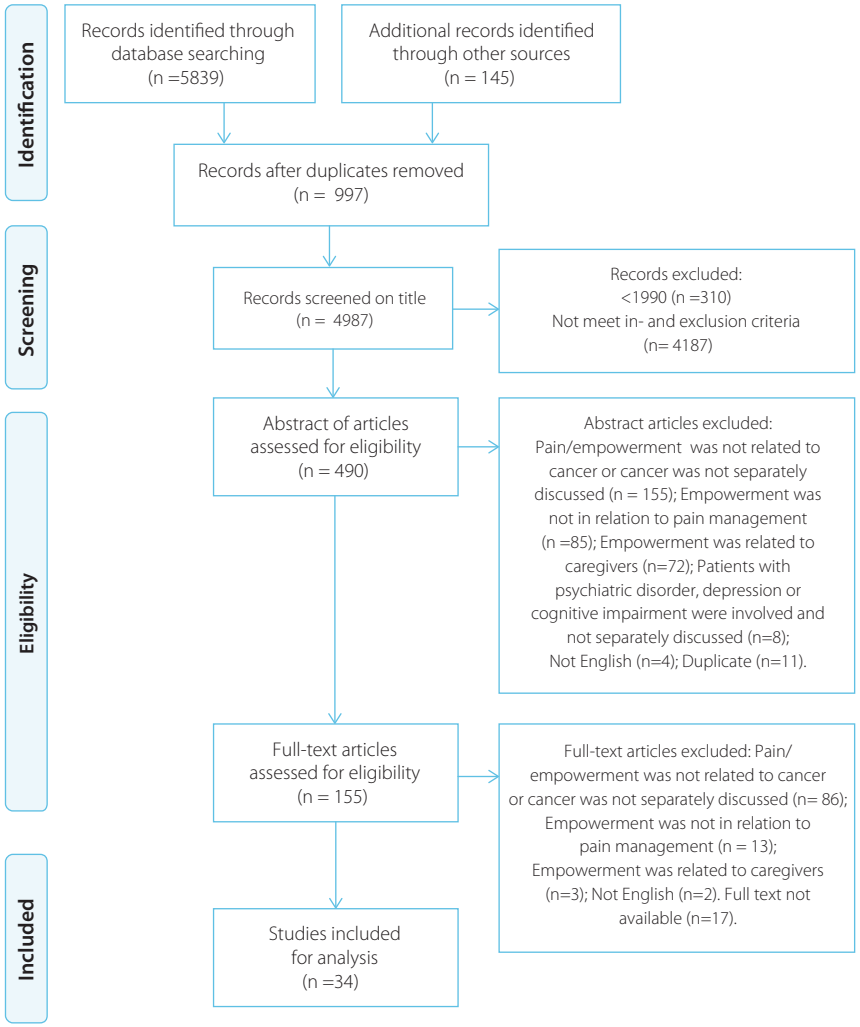
Seven papers out of 34 described or defined empowerment in pain management in patients with cancer. They focused on a limited number of aspects of empowerment in pain management (see table 1). Some papers focus on the professional caregiver and others on the active involvement of the patient, however both should be discussed. Although Kravitz et al[22,23] described their intervention as 'Cancer Health Empowerment for Living without Pain intervention' (Ca-HELP), they measured and discussed empowerment as self-efficacy for pain control and for patient-physician communication. Whereas Lasch[24] and Thomas[25] described empowerment as active patient participation in pain management, Tse et. al.[26], McNeill[27], González Barón[28] described the empowerment concept itself.

Lasch[24], Thomas[25], González Barón[28] and McNeill et al. [27] addressed that access to resources are essential in empowerment to control pain (e.g. enjoy themselves, plans for the future, information, access to support). Tse[26] defined empowerment as increasing patients abilities to take control of their life and McNeill[27] as a feeling of control, making patients active participants in pain management. González Barón[28] defined empowerment as the belief that patients with cancer could do something to feel better by empowering resources (enjoy themselves, plans for the future) and that empowering resources of patients with cancer and pain might help them to give a new sense to their lives. Both Tse[26] and McNeill[27] note that the feeling of control over their pain can empower patients (see table 1).

Related concepts of empowerment

Eighteen out of 34 papers discussed the concept of self-efficacy in pain management. Self-efficacy has been well defined and these definitions show strong similarities with the descriptions of empowerment in the previously mentioned papers. Self-efficacy has been defined in pain management as 'the patient`s confidence, perception or belief in his or her ability to perform a specific behaviour, task or to achieve a desired goal'[22,23,29-36].

Figure 1 Search flow diagram: Preferred Reporting Items of Systematic reviews and Meta-Analysis (PRISMA)



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097
For more information, visit www.prisma-statement.org.

It has been defined as a cognition[22,23,29-36], whereas empowerment has been described as an action or/and as a cognition (table 1). Self-efficacy is task-specific[22,23,29,30]. Patients with high communication self- efficacy may still have low confidence for performing pain self-care behaviors. Others do refer to self-efficacy but do not define or describe it[37-44].

Other related concepts of empowerment discussed are coping strategies and/or locus of control, self-esteem and mastery. Although these concepts have been discussed in four out of 34 papers[51-54] they do not describe or define it. Büssing and authors[51] analysed which coping strategies refer to the concept 'locus of control'. They found that patients with cancer often have a strong reliance on external sources (e.g. trust in God`s help). Büssing et al described external resources of control, however they also reported internal resources[55]. These external resources might not be seen as true factors of empowerment because they are often used as passive strategies, while the internal strategies are in most cases active processes (e.g. abilities).

Finally, a concept related to locus of control is mastery. Kurtz defined mastery as sense of control, as the extent to which a person feels in control over his/her environment[56].

Conceptual model to empower patients in controlling cancer pain

Based on these findings, we suggest a conceptual model to empower patients in controlling cancer pain. A cyclical model seems most appropriate, as pain and other characteristics might change over time and sometimes the patient and professional caregiver have to start all over again to empower the patient. Previous research focussed only on pain treatment provided by the clinician or on the active involvement of the patient, but not on the combination of both. However, both are essential to empower the patient in controlling their cancer pain. Patient empowerment could improve pain management and pain control might result in improved empowerment and this might result in more pain control.

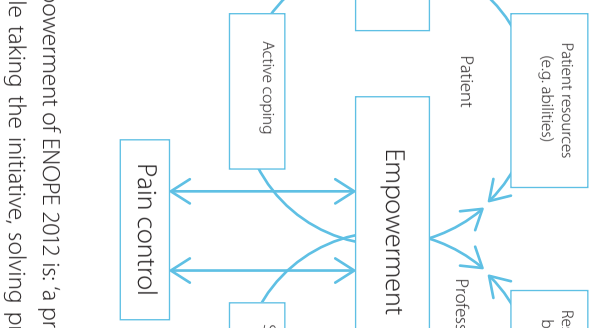
Therefore, we suggested a model with both the patient as the clinician as well as their interaction. Self -efficacy has been shown essential in both elements of empowerment. In relation to empowerment it has been described as a core cognition. In this model e.g. communication self-efficacy, and self-efficacy for shared decision-making are essential. Another essential element of empowerment is having resources.

A professional caregiver can induce external resources (e.g information on pain management, pain treatment) and use strategies to empower the patient. However, the patient needs to be involved to become empowered and to manage his pain. External and internal resources have been described. Internal resources are related to the patient, like his abilities, his attitude. Yet, external resources can be introduced by the professional caregiver e.g. information or access to support. Resources and self-efficacy are a prerequisite to be able to cope actively. Yet, resources and self-efficacy are not enough to achieve pain control. The patient also needs to be involved, needs to become an active patient.

Table 1 Definitions and descriptions of empowerment in cancer pain management

Author, Year [ref]	Study design	N	Professional field	How empowerment was defined/ described and its assessment	Definition empowerment or definition related concept
Kravitz, 2009 [22]	Study protocol	265	Oncology	Empowerment is described and assessed as self-efficacy	Self-efficacy is the confidence in the ability to achieve control over one`s pain.
Kravitz, 2011 [23]	RCT	258	Oncology	Empowerment is described and assessed as self-efficacy	None
Lasch, 2000 [24]	Qualitative data analysis	None	Nursing	Empowerment is described as effective communication/ participation	None
Thomas, 2000 [25]	Opinion paper	n/a	Oncology, Psychosocial	Empowerment is described as active participation	None
McNeill, 2007 [27]	Case report	n/a	Nursing	Empowerment is defined as a control and active participation	Empowerment is a feeling of control, making patients active participants
Tse, 2012 [26]	Randomised clinical trial (without control)	38	Nursing	Empowerment is defined as control and increasing abilities, however it was not assessed	Empowerment should involve increasing the patients` abilities to take control of their life.
González Barón, 2006 [28]	Cross-sectional	73	Oncology	Empowerment is described as resources to relief the suffering	Empowerment is the belief that they could do something to feel better by empowering resources (enjoy themselves, plans for the future)
Common concepts discussed in relation with empowerment				Self-efficacy, locus of control, coping, active participation	

Figure 2 A conceptual model to empower patients in controlling their cancer pain



The definition of empowerment of ENOPE 2012 is: 'a process to help people gain control, which includes people taking the initiative, solving problems, and making decisions'[14]. This definition includes both the help of the clinician and the active involvement of the patient. Strategies to empower the patients are also essential in this model. These strategies can be either induced by the professional caregiver (collaboration; shared-decision making; education/coaching; communication) or induced by the patient (becoming a partner in decision-making; choose resources according to his/her needs; ask questions and obtains information (communication).

Discussion

With the help of an integrative literature review, we examined how empowerment or related concepts have been described in relation to pain management in patients with cancer, and recommendations on how to improve patient empowerment were made, illustrated by a conceptual model. Elements in this two-cycle model, with central roles for the patient as well as the clinician, are resources (external and internal), self-efficacy, shared decision-making and active patient participation/coping.

Our results are in agreement with the definition of empowerment of ENOPE 2012[14]. Like in our conceptual model, this definition includes both the help of the professional caregiver and the active involvement of the patient. Previous research focussed only on pain treatment induced by professional caregiver or active involvement of the patient and did not combine these elements.

Studies that did not explain the term empowerment used it as a synonym of self-efficacy active participation in decision making or access to resources (table 1). It is noteworthy that papers presented their own descriptions of empowerment with little overlap and they focused on a limited number of aspects. Only one paper described a limited model of cancer pain management including empowerment[26]. They described a pain management model with empowerment as an element of the model. Our model is an empowerment model in pain management, including pain treatment, clinician as well as patient involvement.

Nevertheless, the articles included in this review provided insight in aspects essential for empowerment and related concepts in cancer pain management to suggest an empowerment model for cancer pain management. Both the confidence in the ability to perform a task (self-efficacy) and the access to internal and external resources[24,25,27,28] have shown to be the most important aspects of empowerment.

Self-efficacy appeared to be strongly related to empowerment and often used as empowerment outcome. Self-efficacy is needed to achieve empowerment, whereas empowerment is not needed for self-efficacy.

The present study has some strengths. First, until now there was no systematic review on empowerment in cancer pain management. Second, our model might also be useful for other patient groups or contexts. We expect that the elements of our model (resources, self-efficacy and active patient participation) are also essential in other diseases. The symptom and the resources may differ, but the framework of the model stays the same. Finally, as other constructs, like self-efficacy and shared decision-making (SDM), have shown to be essential in cancer pain management[19,20] and also show overlap with empowerment, these were included too.

However, there were also some limitations. First, the suggested model needs to be tested before it can be widely used in clinical practice[57]. As well professionals involved in cancer pain management as patients with cancer and pain should be involved in such a pilot. Finally, only papers in English were included. As this review aimed to describe/define a concept, translation might change the meaning. Cultural differences should be taken into account in future studies.

Conclusion

Based on the findings we propose a conceptual model to empower patients in controlling cancer pain. We recommend focusing on pain treatment induced by the professional, on the active involvement of the patient, and on the interaction of both. Both elements are needed to empower the patient to control their cancer pain. The model should be tested in future research. Our model might also be useful for other patient groups or specific contexts, especially in symptom management.

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8

General discussion

In the past 40 years adequacy of pain treatment in patients with cancer has not improved[1]. Today, both healthcare professionals and decision makers clearly recognize that patient centered care is important[2]. Telemedicine, bridging as well the time gap as the geographical gap between professional caregivers and patients, can support them to achieve patient centered care, because it might encourage patients to become a partner in their own pain management.

Although pain in patients with cancer had already been well studied[1,3-5], pain management and strategies to improve adequacy of pain treatment in these patients were poorly understood. For those reasons, **the objective of this thesis was to increase awareness and to provide recommendations for clinical practice to improve cancer pain management.**

Pain is still a significant problem in outpatients with cancer

In our cross-sectional study in which 428 medical oncology outpatients participated, pain prevalence and interference of pain with daily activities were assessed. More than one third of all participants reported pain (39%). Eighty-three patients (20%) had moderate to severe pain (NRS 5-10). Analgesic treatment was inadequate in more than half of the patients with pain (62%). Interference of pain with daily activities increased with increased intensity, yet even 10%-33% of patients suffering mild pain reported high interference with daily activities. High current pain intensity and high interference with general daily activities predicted moderate to severe pain.

The pain prevalence rates we found fall within the range of earlier studies (27%[3] to 60%[4]) and prevalence of pain treatment inadequacy ranged from 31%[5]to 65%[3].

As adequate pain relief for up to 86%[6] of patients with cancer is considered feasible, our results show that pain in patients with cancer is still undertreated.

In earlier studies, a mild pain intensity in patients with cancer (NRS 1-4), usually not treated with opioids, has been shown to hardly interfere with daily activities[7,8]. However, we found that some patients with mild pain (NRS 1-4) and even some patients with an NRS 1-2 experienced moderate to severe interference with daily activities. Although Serlin and colleagues[7] established cut-off points for pain intensity based on its interference with daily activities already 18 years ago, there is still no consensus on how to categorize pain intensity. Often pain is categorized as mild pain (NRS 1-4), moderate pain (5-6) and severe pain (7-10)[7,8]. Based on our findings we conclude that pain intensity alone is not enough to determine whether a patient with cancer and pain needs treatment. Interference of pain with daily activities and patients' needs should also be taken into account(Chapter 2).

Pain is not systematically registered in medical records

In our multicentre retrospective study in which pain registration in medical records of 380 outpatients with cancer was studied, we found that in 23% of all 987 visits at the outpatient

clinic, pain or absence of pain was registered, and in an additional 15%, a nonspecific symptom description was given(e.g. is doing well, no complaints). Regarding all other visits, (62%) pain or absence of pain was not documented at all. Pain measurement using a VAS or NRS was documented in only one visit. Pain was more often registered in medical records of patients with metastasis, as well as in those of patients with urogenital tumours.

Although pain measurement using a VAS or NRS at each visit is a key recommendation of the Dutch CPG on cancer pain, it was documented in only one visit. No recent other data on cancer pain registration have been published. In 1999, Weber et al analysed medical records of outpatients with cancer and severe pain and found that only three out of 12 physicians registered pain severity in more than 15% of their consultations[9].

In our study we did not only analysed medical records of patients known with pain, but of all outpatients with cancer. Weber et al analysed the number of physicians documenting pain severity, whereas we analysed the percentage of visits in which pain was reported, which makes comparing findings of these studies difficult[9]. Another study by Rhodes et al[10] found that healthcare providers and healthcare assistants at the radiation and medical oncology outpatient clinic did not routinely assess pain[10]. Additionally, Rhodes et al. showed that, before training, physicians never documented quantitative pain assessment in their medical records. They found a higher percentage of qualitative pain registration in medical and radiation oncology (54% medical and 73% radiation oncology vs. 23% in our study)[10]. We made a distinction between quantitative, qualitative and nonspecific symptom registration. Since 2001, pain registration has not improved although systemic pain documentation has shown to be feasible in a busy outpatient oncology practice and is sustainable over time[10] (Chapter 3).

Pain assessment needs more attention in CPGs

In our cross-sectional case vignette survey describing a patient with intractable pancreatic cancer and pain, 63 of 268 medical oncologists (24%) completed the survey. Adherence to the different recommendations of the guideline ranged from 18 to 100%.

Confidence for treatment choice ranged from 5.6 to 9.5 on a Numeric Rating Scale (0–10). Most of the responding oncologists (94%) adhered to prescribing paracetamol as first-line pain treatment, and all prescribed a laxative in combination with opioids to prevent constipation. However, only 24% of the respondents adhered to the guideline when first-line treatment had insufficient effect. Additionally, only 35% adhered to the recommendation for insomnia treatment providing psychosocial support or using a multidimensional pain questionnaire besides pharmacological treatment. Finally, only 18% adhered to the recommendation to perform a multidimensional pain assessment when disease worsens and pain increases.

A possible explanation for this low adherence might be that in the Dutch CPG, the recommendations for pain assessment are not specified: when, why and how pain should be assessed is not mentioned. Our study was the first to assess medical oncologists` intention to act in congruence with an evidence-based cancer pain CPG.

An Australian survey among oncologists to identify barriers and facilitators to cancer pain assessment and management showed that only 22% of the respondents reported to use pain CPGs[11]. In agreement with our findings, they addressed that particular attention should be paid to promoting the use of validated pain assessment scales[11] (Chapter 4).

MIDAS 4 Cancer Pain was effective in patients with moderate to severe pain in reducing inadequate cancer pain treatment

We monitored patients to assess the effect using the interactive distance alert system (MIDAS 4 Cancer Pain) on the reduction of the percentage of inadequate cancer pain treatment. In a cluster randomised controlled trial, eight hospitals were randomly assigned to the MIDAS 4 Cancer Pain (M) or control (C) groups (4:4).111 patients with cancer and pain participated in this study (M 72: C 39).

At week 12, the percentage of patients with a negative PMI in the MIDAS group was not significantly lower than in the control group (16%; 95%CI -3 to 35; P=0.12). Pain-related interference with daily activities and depressed mood score were significantly lower in the MIDAS group. In the subgroup of patients with moderate to severe pain (NRS 5-10) at baseline, the percentage of patients with a negative PMI was significantly lower in the MIDAS group than in the control group (35%; 95% CI 7 to 62; p=0.03).

The reduction in inadequate pain treatment was not significantly higher in the total group of patients compared to controls. Results for the subgroup of patients with moderate to severe pain revealed that the intervention was significantly more effective in reducing inadequate pain treatment.

Our data are therefore promising when defining subgroups for which the intervention might be effective. In addition, our results demonstrate the positive effects of Midas 4 Cancer Pain on pain-related interference with daily activities and depressed mood.

In the subgroup analysis, patients were excluded who had a mild pain intensity at baseline as for this group pain treatment could not or hardly improve. Patient recruitment was difficult because of pain related barriers; oncologists do not systematically ask patients about their pain and patients are reluctant to talk about their pain. Due to these recruitment issues, we adapted the inclusion criteria for pain intensity from ≥ 3 on an NRS to 'all patients with pain'. As a result, patients with mild pain were also included which may have resulted in increased medicalization due to the extra focus on pain. However, this adaptation also became a strength, as it enabled a subgroup analysis to determine who would most benefit from MIDAS 4 Cancer Pain.

Our results are important for health care professionals, patients and future research, as they show that MIDAS 4 Cancer Pain has the potential to reduce inadequate pain treatment in patients with moderate to severe pain.

Results from a recent multicentre RCT with 253 patients with advanced lung cancer, monitoring with IVR and symptom alerts, appeared to be no more effective in reducing symptom burden than monitoring alone[12]. Similar to our study, patients with a low symptom burden may have attenuated the effects on the entire group, as they may not have required treatment (Chapter 6).

Conceptual model to empower patients in controlling cancer pain

Our integrative literature review to examine how empowerment or related concepts have been described in relation to pain management in patients with cancer, resulted in a total of 5984 identified papers and 34 were included for analysis. Empowerment has been described with the concepts self-efficacy, active patient participation, increasing abilities, and control of life. Most papers focus on pain treatment induced by the professional caregiver or on the active involvement of the patient, and not on the combination of both. The following elements of empowerment could be discriminated: role of the patient, role of the professional, resources, self-efficacy, active coping, and shared decision making.

We found that empowerment has been poorly defined and described regarding cancer pain management. Many other concepts were used to describe empowerment. Self-efficacy appeared to be strongly related to empowerment and often used as an empowerment outcome. Yet, self-efficacy is needed to achieve empowerment, whereas empowerment is not needed for self-efficacy. Our results are in agreement with the definition of empowerment of ENOPE 2012[13].

Like in our conceptual model, this definition includes both the help of the professional caregiver and the active involvement of the patient. Previous research focused only on pain treatment induced by professional caregiver or active involvement of the patient and did not combine these elements. Only one previously conducted study described a limited model of cancer pain management with empowerment as element of the model[14] (Chapter 7).

Methodological considerations

I will reflect on the strengths and limitations of the methods used in this thesis. One of the prominent strengths of this thesis is that the studies described in chapter 2,3,6 were multi-centre, including as well academic as peripheral hospitals, which increases generalizability.

In addition, in these chapters all patients with cancer (and cancer-related pain in chapter 6) were invited to participate, there was no selection on tumour type or disease stage. In chapter 4 and 6 medical oncologists were involved. They play a key role in planning, delivering, and coordinating cancer care and pain management in these patients. Another prominent strength in this thesis is that we tested a telemedicine tool that allows patients to communicate with clinicians outside the consultation without time delay and irrespective of distance, using a mobile phone or landline telephone in chapter 6.

Almost all patients have a mobile phone or landline telephone and are familiar with its use. Finally, in chapter 7 we proposed a conceptual model how to empower patients with cancer in pain management based on our integrative review. This model is the first step towards patient centered care in cancer pain management, because to become real partners in their own care, patients need to be empowered.

Some limitations of the research should also be considered. One of the prominent limitations is that we were not able to obtain characteristics of the non-participants in chapter 2 and 6. Another limitation is that in chapter 4, our case-vignette study, the response rate was only 24%. Yet, this appeared to be equal to other surveys on cancer pain in medical oncologists. This relatively low response rate raises concerns whether the results can be generalized to the entire Dutch medical oncologists' population. The responding medical oncologists probably were more interested in cancer pain management than non-respondents. For this reason, the low response rate will not have influenced our conclusion that pain assessment needs further implementation.

A limitation in the study described in chapter 6 is the overrepresentation of palliative patients, although we aimed to include patients in our cluster RCT in all cancer stages. This inclusion bias might be explained by the higher prevalence of pain in patients in an advanced stage of the disease, in which the treatment focus changes from curative to symptom management.

This inclusion bias increased the number of missing values and dropout as compared to what we expected. Secondly, due to recruitment issues, we adapted the inclusion criteria for pain intensity from ≥ 3 on an NRS to 'all patients with pain'. As a result, patients with mild pain were also included which may have resulted in increased medicalization due to the extra focus on pain. However, this adaptation also became a strength, as it enabled a subgroup analysis to determine who would most benefit from MIDAS 4 Cancer Pain.

Recommendations for policy makers

This thesis adds that cancer pain management is still a problem, partly due to the lack of systematic pain registration and proper pain assessment. In cancer pain management, it is not only essential to assess pain but also to register pain. Therefore, in order to facilitate pain diagnosis, evaluation and documentation of cancer pain we recommend to implement a quality indicator for assessing cancer pain. Although pain physicians often like to think of pain management as a human right, organisations generally do not define pain management as a specific duty of the physician[15]. An obligatory quality indicator for standardised postoperative pain assessment is already implemented in Dutch practice. The need for a cancer pain quality indicator in clinical practice might be as urgent as the quality indicator for postoperative pain, because cancer pain management is complicated by many barriers.

An obligatory quality indicator might help to overcome a few of these barriers. In addition, we would recommend to include in the revised version of the CPG pain in patients with cancer, clear recommendations for pain assessment and registration; how pain should be assessed and registered and who is responsible should be specified. Finally, to facilitate assessment and registration of pain with a validated pain assessment scale, we recommend to give it more attention in education for medical and nursing students and for professionals (see box 1).

Box 1 Recommendations/considerations

Policy makers

3. Implement a quality indicator for assessing cancer pain.
4. Include clear recommendations for pain assessment and registration in the revised version of the CPG for cancer pain.
5. Invest in the development and improvement of pain educational programs for medical and nursing students and for professionals.

Practice

1. Assess and register pain in patients with cancer each visit with a validated pain assessment scale (VAS/NRS).
2. Use pain-specific questions, because patients are reluctant to report pain.
3. Document also the absence of pain to facilitate evaluation of pain treatment.
4. Use IVR and SMS-alerts to monitor pain in patients with cancer and moderate to severe pain.

Future research

1. Only include patients with moderate to severe pain in future research using IVR and SMS-alerts to report pain as they benefit most.
2. Personal needs of patients should be taken into account in future research. Not all patients might experience a pain intensity of ≥ 5 as unacceptable.
3. Test our conceptual model to empower patients in controlling cancer pain. As well professionals involved in cancer pain management as patients with cancer and pain should be involved in such a pilot.

Recommendations for practice

The findings of this thesis have important implications for daily practice. Because patients with cancer are reluctant to talk about pain, we would recommend health professionals to systematically assess and register pain in oncology outpatients at each visit with a validated pain assessment scale (VAS/NRS). Using pain-specific questions might help patients to talk about pain. General questions as "how are you doing?" might not be useful, because patients are reluctant to report pain. In addition, we recommend to document also absence of pain to facilitate evaluation of pain treatment.

Another consideration for daily practice might be shifting the responsibility for pain management of the oncologist to another profession e.g. the nurse. Finally, we would recommend to use IVR and SMS-alerts to monitor pain in patients with cancer and moderate to severe pain (see box 1).

Recommendations for future research

As described in chapter 6, telemedicine can support caregivers and patients to achieve patient centred care, because it might encourage patients to become a partner in their own pain management. As shown in this thesis pain monitoring with IVR-SMS in patients with cancer is feasible and it reduced inadequate pain treatment in patients with moderate to severe pain compared to the pain diary. IVR in combination with SMS-alerts might be suitable for more symptoms besides pain. Therefore, it would be interesting in future research to monitor more symptoms related to cancer or cancer related treatment.

Other recommendations for future research are based on our recruitment difficulties in the RCT. The effect of the protocol amendments on patient recruitment was small.

Besides, it resulted in the inclusion of patients that already had a low pain intensity at baseline, and consequently their pain treatment could not improve. Because IVR-SMS was effective in those patients with moderate to severe pain (NRS 5-10) we recommend future studies to only include patients with moderate to severe pain as they benefit the most from the intervention (chapter 6).

As 24% of patients in the IVR-SMS condition reported lower NRS scores than was really the case to avoid that the nurse would call them, personal needs of patients should be taken into account in future research. Not all patients might experience a pain intensity of ≥ 5 as unacceptable. Therefore, to achieve patient-centred care it might be interesting to assess whether or not patients experience their pain intensity as acceptable (chapter 6).

Patients need to be empowered to become real partners in their own care. In chapter 7, we describe a conceptual model to empower patients in controlling their cancer pain. This model might be useful to meet the requirements of future care with increasing demands in a cost-effective manner. An empowered patient probably self-manages his cancer pain to a larger extent than a non-empowered patient. This might improve cost-effectiveness. Patients who ask questions, express concerns, and state preferences about pain-related matters can change pain management, which in turn may lead to better pain control. The next step would be testing our conceptual model to empower patients in controlling cancer pain. As well professionals involved in cancer pain management as patients with cancer and pain should be involved in such a pilot (see box 1).

General conclusion

Adequacy of pain treatment in patients with cancer at the outpatient clinic has not improved, partly due to the lack of systematic pain registration and proper pain assessment. Today, both healthcare professionals and administrators clearly recognize that patient centered care is important.

As shown in this thesis pain monitoring with IVR-SMS in patients with cancer is feasible and reduces inadequate pain treatment in patients with moderate to severe pain. It facilitates systematic pain assessment and registration with a validated pain assessment scale and supports caregivers and patients to achieve patient centered care.

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Summary

In this thesis we monitored patients to assess the effect using the interactive distance alert system on the reduction of inadequate cancer pain treatment, we discussed active involvement of the patient with cancer in their own pain management and provided recommendations for current practice. The overall objective was **to increase awareness and to provide recommendations for clinical practice to improve cancer pain management**. Firstly, we assessed pain prevalence, pain intensity, its interference with daily activities and the adequacy of analgesic pain treatment in patients with cancer at the outpatient clinic. Secondly, we explored pain registration in medical records of these patients by medical oncologists. Thirdly, we assessed medical oncologists` reported adherence to evidence-based guidelines in cancer pain management. Fourthly, we monitored patients to assess the effect using the interactive distance alert system on the reduction of inadequate cancer pain treatment. Finally, we examined how empowerment or related concepts have been described in relation to pain management in patients with cancer.

In **chapter 1**, we provided the background of this thesis with epidemiologic data, definitions, the role of clinical practice guidelines, the theoretical background, the rationale for the use of IVR and SMS-alerts to monitor pain and finally, the outline of this thesis.

In **chapter 2**, we describe a cross-sectional study in which 428 medical oncology outpatients participated. Pain prevalence and pain-related interference with daily activities were assessed using the Brief Pain Inventory questionnaire.

Adequacy of analgesic treatment was determined by calculating the Pain Management Index (PMI). More than one third of all participants reported pain (39%). Eighty-three patients (20% of all) had moderate to severe pain (NRS 5-10). Analgesic treatment was inadequate in more than half of the patients with pain (62%). Pain-related Interference with daily activities increased with increased intensity, yet even 10%-33% of patients suffering mild pain reported high interference with daily activities.

Based on our findings we conclude that pain remains a significant problem in medical oncology outpatients, and often pain is insufficiently managed. Patients with a high pain intensity were more at risk to experience pain related interference with daily activities, but even quite some patients suffering from only mild pain, experienced high interference with daily activities. As adequate pain relief is considered feasible in 86% of patients with cancer, pain in medical oncology outpatients is still undertreated. Taking into account pain-related interference with daily activities and predictors of pain will facilitate cancer pain management.

In **chapter 3**, we described the results of a multi-centre study in six Dutch hospitals, in which data were extracted from medical records of 380 outpatients with cancer. Data of the first three visits at the outpatient clinic were studied. In 23% of all 987 visits at the outpatient clinic pain or absence of pain was registered and in an additional 15% a non-specific symptom description was given. Regarding all other visits (62%) pain or absence of pain was not documented at all. Pain measurement using a VAS or NRS was documented in only one visit. Pain was more often registered in medical records of patients with metastasis, as well as urogenital tumours. To conclude, pain in medical oncology outpatients is not systematically registered in their medical records. Pain was not registered with a VAS or NRS.

Registration and assessment of pain in order to monitor pain are essential to evaluate and adapt pain treatment over time. Apparently, since 2001 pain registration has not improved. Therefore, implementation of recommendations regarding systematic monitoring of pain is needed.

The study described in **chapter 4** is based on the results of a cross-sectional case vignette survey describing a patient with pancreatic cancer and pain. This survey was sent to all 268 medical oncologists registered at the Netherlands Association of Internal Medicine. Sixty-three of 268 medical oncologists (24%) completed the survey. Adherence to the different recommendations of the guideline ranged from 18 to 100%. Confidence for treatment choice ranged from 5.6 to 9.5 on a Numeric Rating Scale (0–10). Most of the responding oncologists (94%) adhered to prescribing paracetamol as first-line pain treatment, and all prescribed a laxative in combination with opioids to prevent constipation. However, only 24% of the respondents adhered to the guideline when first-line treatment had insufficient effect. Additionally, only 35% adhered to the recommendation for insomnia treatment providing psychosocial support or using a multidimensional pain questionnaire besides pharmacological treatment. Finally, only 18% adhered to the recommendation to perform a multidimensional pain assessment when disease worsens and pain increases. To conclude, the recommendations of the guideline have been partly adopted in cancer pain practice by medical oncologists. Particularly pain assessment is not applied in the recommended manner. Therefore, implementation strategies should focus on adequate pain assessment in patients with cancer.

In **chapter 5**, we described the protocol of a cluster randomised controlled trial with three hospitals in the intervention and three in the control condition. The intervention included training of professionals and IVR with SMS-alerts (MIDAS 4 Cancer Pain) to report pain in patients with cancer. The objective was to improve pain reporting by patients and pain management by medical oncologists and nurses. This implementation strategy with technical tools might encourage patients active involvement in their pain management and may enhance the use of the guideline 'pain in patients with cancer' for pain management.

MIDAS 4 Cancer Pain may serve as a tool to support self-management of patients.

In **chapter 6**, we reported the results of a clustered randomised controlled trial. We monitored patients to assess the effect using the interactive distance alert system (MIDAS 4 Cancer Pain) on the reduction of the percentage of inadequate cancer pain treatment. In this cluster randomised controlled trial, eight hospitals were randomly assigned to the MIDAS 4 Cancer Pain (M) or control (C) groups (4:4). Primary outcome was the Pain Management Index (PMI) at week 12. Secondary outcomes included pain intensity, pain-related interference with daily activities, neuropathic pain characteristics, pain descriptors, quality of life, emotional distress, and self-efficacy regarding communication about pain. Hundred-eleven patients with cancer and pain participated in this study (M 72: C 39). At week 12, the percentage of patients with a negative PMI in the MIDAS group was not significantly lower than in the control group (16%; 95%CI -3 to 35; P=0.12). Pain-related interference with daily activities and depressed mood score were significantly lower in the MIDAS group.

In the subgroup of patients with moderate to severe pain (NRS 5-10) at baseline, the percentage of patients with a negative PMI was significantly lower in the MIDAS group than in the control group (35%; 95% CI 7 to 62; p=0.03).

The reduction in inadequate pain treatment was not significantly higher in the total group of patients compared to controls. Results for the subgroup of patients with moderate to severe pain revealed that the intervention was significantly more effective in reducing inadequate pain treatment. Our data are therefore promising when defining subgroups for which the intervention might be effective. In addition, our results demonstrated the positive effects of Midas 4 Cancer Pain on pain-related interference with daily activities and depressed mood.

Our integrative literature review to examine how empowerment or related concepts have been described in relation to pain management in patients with cancer has been described in **chapter 7.** We used the databases PubMed, CINAHL and PsycINFO. We evaluated papers discussing empowerment or related concepts in relation to pain management in patients with cancer.

We analysed the term "empowerment" semantically. From a total of 5984 identified papers, 34 were included for analysis. Empowerment has been described with the concepts self-efficacy, active patient participation, increasing abilities, and control of life. Most papers focus on pain treatment induced by the professional caregiver or on the active involvement of the patient, and not on the combination of both. The following elements of empowerment could be discriminated: role of the patient, role of the professional, resources, self-efficacy and active coping, and shared decision-making. Based on the findings we propose a conceptual model to empower patients in controlling cancer pain.

We recommend focusing on pain treatment given by the professional, on the active involvement of the patient, and on the interaction of both. Our model might also be useful for other patient groups or specific contexts, especially in symptom management.

In **chapter 8**, the most important findings and conclusions are discussed. Besides, methodological issues are discussed and recommendations for policy makers, clinical practice and future research were provided.

This thesis adds that adequacy of pain treatment in patients with cancer at the outpatient clinic has not improved, partly due to the lack of systematic pain registration and proper pain assessment. Today, both healthcare professionals and administrators clearly recognize that patient centred care is important.

As shown in this thesis pain monitoring with MIDAS 4 Cancer Pain in patients with cancer is feasible and it reduced inadequate pain treatment in patients with moderate to severe pain. It facilitates systematic pain assessment and registration with a validated pain assessment scale and supports caregivers and patients to achieve patient centred care.

Samenvatting

In dit proefschrift hebben we bij patiënten met kanker het effect onderzocht van het monitoren van pijn met telemedicine op het percentage patiënten met een inadequate pijnbehandeling en de actieve betrokkenheid van de patiënt bij zijn eigen pijnbehandeling bediscussieerd. Met telemedicine wordt bedoelt de technologie die gebruikt wordt om informatie uit te wisselen tussen patiënt en zorgverlener. Daarnaast worden er in dit proefschrift aanbevelingen gedaan voor de klinische praktijk. De doelstelling van dit proefschrift is: **bewustwording voor de omvang van het probleem en aanbevelingen formuleren om pijnmanagement bij patiënten met kanker te verbeteren.**

Ten eerste, hebben we de pijnprevalentie, pijnintensiteit, de belemmering bij het uitvoeren van dagelijkse activiteiten onderzocht en we hebben vastgesteld bij hoeveel patiënten de pijnbehandeling adequaat was. Ten tweede, hebben we de pijnregistratie van oncologen in medische dossiers bij patiënten met kanker geëvalueerd. Ten derde, zijn we met behulp van een casus nagegaan of medisch oncologen de intentie rapporteren dat zij deze patiënt zouden behandelen volgens de aanbevelingen van de richtlijn pijn bij kanker. Daarnaast, hebben we het effect van het monitoren van pijn met telemedicine onderzocht op inadequate pijnbehandeling bij patiënten met kanker. Tenslotte, hebben we met behulp van een literatuuronderzoek onderzocht hoe empowerment of gerelateerde termen beschreven worden in relatie tot pijnmanagement bij patiënten met kanker.

In **hoofdstuk 1,** hebben we de achtergrond van dit proefschrift beschreven met epidemiologische data, definities, het doel van klinische richtlijnen, de theoretische achtergrond, de onderbouwing voor het gebruik van IVR-SMS om pijn mee te monitoren en ten slotte de opzet van dit proefschrift.

In **hoofdstuk 2**, beschrijven we de resultaten van een onderzoek waaraan 428 patiënten met kanker uit de polikliniek deelnamen. De pijnprevalentie en de belemmeringen in het uitvoeren van dagelijkse activiteiten zijn onderzocht met de Brief Pain Inventory vragenlijst. Of de pijnbehandeling adequaat was is berekend met de Pain Management Index (PMI). Meer dan een derde van alle patiënten had pijn (39%). Drieëntachtig patiënten (20% van alle patiënten) gaf aan gemiddeld tot ernstige pijn te hebben (NRS 5-10). De pijnbehandeling was inadequaat in meer dan de helft van de patiënten met pijn (62%). De mate waarin een patiënt belemmeringen ervaart bij het uitvoeren van dagelijkse activiteiten nam toe als de pijnintensiteit ook toe nam. Zelfs 10%-33% van de patiënten met milde pijn gaf aan veel belemmering te ervaren bij het uitvoeren van dagelijkse activiteiten. We kunnen concluderen dat de pijn behandeling nog steeds een probleem is in de polikliniek bij patiënten met kanker. Omdat pijnverlichting bij 86% van de patiënten haalbaar is, blijkt uit onze studie dat pijn bij kanker vaak nog niet voldoende behandeld wordt.

In **hoofdstuk 3**, beschrijven we de resultaten van een studie in zes Nederlandse ziekenhuizen, waar we data hebben verzameld uit medische dossiers van 380 patiënten die de polikliniek bezoeken. Data van de eerste drie consulten op de polikliniek zijn bekeken.

Bij 23% van alle 987 consulten op de polikliniek was pijn of de afwezigheid van pijn gedocumenteerd en daarnaast is in 15% van de consulten een niet specifieke symptoom beschrijving gedocumenteerd (geen klachten, gaat goed). Van alle consulten was in 62% pijn of de afwezigheid van pijn niet gedocumenteerd. Een pijnmeting met een VAS of NRS was maar in één consult gedocumenteerd. Pijn werd vaker gedocumenteerd door medisch oncologen bij patiënten met uitzaaiingen en bij patiënten met urogenitale tumoren. We kunnen concluderen dat pijn door medisch oncologen niet systematisch gedocumenteerd wordt in medische dossiers en dat pijn niet gedocumenteerd wordt met een VAS of NRS. Het meten en documenteren van pijn is essentieel om te kunnen evalueren wat het effect is van de ingestelde behandeling en om op tijd de behandeling aan te kunnen passen als dat nodig is.

Sinds 2001 is de documentatie van pijn in medische dossier bij patiënten met kanker niet verbeterd. Daarom is implementatie van het systematisch monitoren van pijn nodig.

In **hoofdstuk 4** is een cross-sectioneel onderzoek beschreven, waarbij een vragenlijst wordt gebruikt met een casus van een patiënt met pancreaskanker en pijn. Deze vragenlijst is gestuurd naar alle 268 medisch oncologen die geregistreerd zijn bij de Nederlandse internisten vereniging (NIV). Drieënzestig van de 268 oncologen (24%) hebben de vragenlijst ingevuld en teruggestuurd. De intentie dat zij deze patiënt zouden behandelen volgens de aanbevelingen van de richtlijn pijn bij kanker varieerde van 18-100% voor verschillende aanbevelingen. De meeste respondenten (94%) rapporteerden de intentie te handelen volgens de richtlijn door het voorschrijven van paracetamol als eerstelijns pijnbehandeling.

Vierentwintig procent van de respondenten rapporteerden de intentie te handelen volgens de richtlijn bij de vervolgbehandeling die nodig is als de eerstelijns behandeling onvoldoende werkt. Ten slotte rapporteerde maar 18% van de oncologen de intentie om een multidimensionale pijnmeting uit te voeren bij progressie van de ziekte en toename van de pijn. We kunnen concluderen dat de aanbevelingen van de richtlijn deels bekend zijn en naar verwachting deels worden gebruikt door oncologen. Vooral de aanbevelingen in de richtlijn met betrekking tot het meten van pijn worden niet altijd toegepast.

In **hoofdstuk 5**, beschrijven we het protocol van een cluster gerandomiseerde studie met drie ziekenhuizen in de controle conditie en drie in de interventie. De interventie bestaat uit een training voor oncologen en verpleegkundigen en het monitoren van pijn met IVR-SMS bij patiënten met kanker. Deze interventie heeft als doel het rapporteren van pijn te verbeteren en het verbeteren van de pijnbehandeling bij patiënten met kanker.

In **hoofdstuk 6**, bespreken we de resultaten van een cluster gerandomiseerde gecontroleerde studie. Onze doelstelling was onderzoeken wat het effect is van het monitoren van pijn bij kanker op afstand met automatische telefoontjes (MIDAS 4 Cancer Pain). Acht ziekenhuizen zijn cluster gerandomiseerd. Ziekenhuizen werden toegewezen aan de MIDAS 4 Cancer Pain interventie of een pijndagboekje. De primaire uitkomst was inadequate pijnbehandeling bij week 12. Secundaire uitkomsten waren pijnintensiteit, neuropatische pijn karakteristieken, belemmering in dagelijkse activiteiten, determinanten van pijn, kwaliteit van leven, angst, depressie en self-efficacy met betrekking tot het communiceren over de pijn. 111 patiënten met kanker en pijn hebben deelgenomen aan deze studie.

Het percentage patiënten met een negatieve PMI (inadequate pijnbehandeling) in de MIDAS 4 Cancer Pain groep was niet significant lager dan in the controle groep (16%; 95%CI -3 tot 35; P=0.12). Pijn gerelateerde belemmering in dagelijkse activiteiten en de score voor depressie waren significant lager in de MIDAS 4 Cancer Pain groep. In de subgroep van patiënten met matig tot ernstige pijn (NRS 5-10) bij baseline, was het percentage van patiënten met een negatieve PMI significant lager in the MIDAS 4 Cancer Pain groep dan de controle groep (35%; 95% CI 7 tot 62; p=0.03). De resultaten van de subgroep patiënten met matig tot ernstige pijn liet zien dat de interventie significant effectiever was in het reduceren van inadequate pijnbehandeling dan de controle. Onze resultaten zijn daardoor veelbelovend bij het definiëren van subgroepen voor wie de interventie effectief zou zijn. Daarnaast laten onze resultaten positieve effecten zien van MIDAS 4 Cancer Pain voor pijn gerelateerde belemmeringen in dagelijkse activiteiten en voor depressie.

Onze literatuurstudie (integrative review) hebben we in **hoofdstuk 7** beschreven. De databases PubMed, CINAHL and PsycINFO zijn gebruikt voor deze studie. We evalueerden artikelen die empowerment of een gerelateerde term beschreven in relatie tot pijnmanagement bij patiënten met kanker. We analyseerden de term "empowerment" op basis van betekenis. Van de 5984 geïdentificeerde artikelen, zijn er 34 geïncludeerd voor de analyse. Empowerment is beschreven met de concepten self-efficacy, actieve participatie van de patiënt, vergroten van mogelijkheden, en gevoel van controle over het leven. De meeste artikelen over pijnmangement focussen op de behandeling geïnduceerd door de zorgverlener of de actieve betrokkenheid van de patiënt en niet de combinatie van beide.

De volgende elementen van empowerment kunnen worden onderscheiden: de rol van de patiënt, de rol van de professional, benodigdheden (resources), self-efficacy, actieve coping en gedeelde besluitvorming (shared-decision making). Gebaseerd op deze resultaten, hebben we een conceptueel model beschreven om de patiënt te empoweren bij het onder controle krijgen van de pijn. Dit model zou ook bruikbaar kunnen zijn voor andere patiëntgroepen of in een andere context vooral voor symptoommanagement.

In **hoofdstuk 8**, worden de belangrijkste bevindingen en conclusies bediscussieerd. Daarnaast worden de gehanteerde methodes bediscussieerd en worden er aanbevelingen gedaan voor beleidsmakers, de klinische praktijk en voor toekomstig onderzoek.

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Curriculum Vitae

Nienke Faber- te Boveldt werd geboren op 22 mei 1986 in Winterswijk en ze groeide op in Bredevoort, waar ze de basisschool doorliep. In 2004 haalde ze haar havo-diploma aan het Christelijk college Schaersvoorde in Aalten. Daarna studeerde ze Voeding en Diëtetiek in Nijmegen aan de Hogeschool van Arnhem en Nijmegen en behaalde haar propedeuse in 2005. In de zomer van 2005 heeft ze pre-universitair onderwijs gevolgd aan de Wageningen universiteit in wiskunde en scheikunde en heeft met succes de examens afgerond. In 2005 startte ze met de opleiding Voeding en Gezondheid aan de Wageningen universiteit en haalde in 2008 haar Bachelor of Science diploma. Direct aansluitend is ze begonnen aan de Master of Science opleiding Voeding en Ziekte ook aan de Wageningen universiteit en behaalde in 2010 haar Master of Science diploma. In 2010 heeft ze stage gelopen bij het VU Medisch centrum in Amsterdam op de afdeling Voeding en diëtetiek en dit leverde de volgende publicatie op: Dietician-delivered intensive nutritional support is associated with a decrease in severe postoperative complications after surgery in patients with esophageal cancer. Diseases of the Esophagus 2013, 26: 587-593. Hier ontstond haar interesse in oncologisch klinisch onderzoek. In 2010 is ze gestart met het promotie onderzoek “pijnsein” op de afdeling Anesthesiologie, pijn en palliatieve Geneeskunde aan de Radboud Universiteit onder leiding van prof. Kris Vissers, prof Myrra Vernooij-Dassen en Yvonne Engels.