Is it possible to detect an improvement in cancer pain management? A comparison of two Norwegian cross-sectional studies conducted five years apart.

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Original article

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Abstract

Is it possible to detect an improvement in cancer pain management? A comparison of two Norwegian cross-sectional studies conducted five years apart.

Purpose: Cancer pain (CP) management is challenging. In recent years, efforts were undertaken to achieve better CP management, e.g. clinical research, new treatment modalities, development of guidelines, education, and focus on implementation. The aim of the present study was to compare the prevalence and characteristics of pain and breakthrough pain (BTP) between cross-sectional studies conducted in 2008 and 2014. It was hypothesized that an improvement in pain control would be observed the years in-between.

Methods: Two cross-sectional studies were conducted where adult cancer patients answered questions from Brief Pain Inventory and the Alberta Breakthrough Pain Assessment Tool for cancer patients. Physicians reported socio-demographic and medical data. Regression models were applied for analysis.

Results: In total, 168 inpatients, 92 in 2008 and 76 in 2014, and 675 outpatients, 301 in 2008 and 374 in 2014, were included. The patient characteristics of the samples were comparable. Prevalence of CP among inpatients was 55% in 2008 and 53% in 2014, and among outpatients 39% and 35%, respectively. Inpatients reported average pain intensity (0-10 NRS) of 3.60 (SD 1.84) (2008) and 4.08 (SD 2.11) (2014), prevalence of BTP was 52% (2008) and 41% (2014). For outpatients, average pain intensity was 3.60 (SD 2.04) (2008) and 3.86 (SD 2.20) (2014), prevalence of BTP was 43% (2008) and 37 % (2014). None of the differences were statistically significant.

Conclusion: Unexpectedly, no improvement in pain control was observed. Efforts are still needed to improve cancer pain management.

Introduction

The World Health Organization (WHO) pain ladder has since the 1980`s been the basic recommendation for cancer pain management (1). Trials evaluating the efficacy of the WHO pain ladder have indicated pain relief in approximately 80-90% of cancer patients if managed according to this approach (2, 3). However, several trials report prevalence of cancer pain in about 50% of patients (4). Improved pain control is important as pain may lead to significant burden for patients and their relatives (5).

Proper classification and systematic assessment is essential for adequate cancer pain management. To evaluate pain, localization, pain intensity, breakthrough pain (BTP), neuropathic pain, and depressive symptoms has been recommended as a minimum (6). For evaluation of these domains, different assessment tools are available, such as the Edmonton Classification System for Cancer Pain (ESC-CP) (7), the Brief Pain Inventory (BPI) (8), the Leeds assessment of Neuropathic Symptoms and Signs (LANSS) (9), and the Patient Health Questionnaire (PHQ) 9 (10, 11). Pain is also one of the symptoms in the Edmonton Symptom Assessment Scale (ESAS) (12) and the European Association for Palliative Care (EAPC) basic dataset (13).

BTP is present in 40%-80% of cancer patients with pain (14) and has been associated with increased pain intensity, psychological distress, sleep disturbance, longer time to achieve pain control and as a predictor of more complex pain (6, 7, 15, 16). Despite that classification, assessment and treatment of BTP are fundamental in cancer pain management; still no consensus is achieved on a common definition of BTP or an international recommendation for which assessment tool to use (17).

The following significant barriers to adequate pain control have been identified in a recent review; inadequate pain assessment, lack in use of guidelines, reluctance to administer opioids, lack of knowledge, patients concerns regarding addiction and side effects, and suboptimal education of health care providers (18). Several efforts have been conducted during the last decade to overcome some of these barriers, creating expectations of a potential improvement in cancer pain management. International (19) and national pain guidelines (20) have been published and new medication for the treatment of BTP have been introduced (21).

The Norwegian guidelines recommend prescribing opioids for cancer pain (20). In Norway, structural changes in the health care system have been introduced in recent years. The main principle of the Norwegian health care coordination reform (22) is that all treatment and follow-up should be offered at the lowest possible level at the health care system. Symptom management has been prioritized in these structural changes. Education in pain management is mandatory in medical school and for residents in oncology departments. Locally, more education on cancer pain management has been provided to health care employees.

Hypothesizing that an improvement in cancer pain control would be observed, two cross-sectional studies evaluating prevalence and characteristics of cancer pain and BTP were conducted in 2008 (the 2008 sample) and 2013/14 (the 2014 sample). The aim of the present study was to compare the prevalence and characteristics of pain and BTP among cancer patients between the 2008 sample and the 2014 sample. The research questions were:

1. What were the differences in prevalence and intensity of pain among cancer patients between the 2008 sample and the 2014 sample?
2. What were the differences in prevalence and characteristics of BTP among cancer patients between the 2008 sample and the 2014 sample?

Methods

Study design

A cross-sectional study was conducted at a university hospital and a local hospital in mid-Norway in 2008. The study was repeated at both hospitals in 2014. The university hospital is responsible for about 300.000 inhabitants (approximately 800 beds). The local hospital is responsible for about 100.000 inhabitants (approximately 250 beds). Both hospitals have an oncology department (36 and 16 beds for the university and the local hospital, respectively), departments of internal medicine, surgery and gynaecology. At both hospitals cancer patients are managed at various departments according to cancer diagnosis and treatment modalities. The inpatients were in both studies seen by both oncologists and specialists in internal medicine and surgery, while the outpatients in both studies were seen by oncologists.
The cancer patients received pain treatment according to existing guidelines, including adjuvant analgesics, opioids, and anti-cancer treatment. Only in the 2014 study information regarding medication was recorded.

Intervention

In the five years between the two studies, efforts have been made to improve cancer pain management. Internationally, new guidelines in opioid treatment have been published (19) and rapid acting fentanyl formulations for the treatment of BTP have been launched (21). Nationally, new guidelines in palliative care were developed (20) including cancer pain management and a special focus on palliative radiotherapy. In mid-Norway, a general educational programme has been offered to health care providers (physicians, nurses and other professions related to palliative care) in community and specialist care. Cancer pain assessment and classification, opioid guidelines, new drugs and radiotherapy have been key areas covered in the lectures. Additionally a weekly video-conference has been offered all palliative care teams from autumn 2012 with lectures covering evidence-based topics in palliative care with special focus on symptom management.

The access to specialized palliative care and specialized pain services, as well as formal regulatory practice are considered unchanged in the time period from before 2008 until after the 2014 study.

Patients

Eligible inpatients with cancer admitted to the two hospitals were included at predefined days in November 2008 and in August/ September 2013. In addition, eligible outpatients at the oncological department of the university hospital were included at predefined days in November 2008 (23) and in January 2014. Patients that were inpatient the day of the study were asked to participate, regardless of how many days they had stayed in the hospital. Outpatients with an appointment at the outpatient clinic at the day of the study were asked to participate, independent of primary referral or follow-up. The sample of in- and outpatients in 2008 was named "the 2008 sample" while the sample of inpatients in 2013 and outpatients in 2014 was named "the 2014 sample". Inclusion criteria in both cross-sectional trials were: adult cancer patients, able to read and write Norwegian, with adequate cognitive function, clinically assessed by the responsible physician. Exclusion criterion was surgical procedure the last 24 hours before inclusion. Each patient was included only once.

Data collection and assessment

A questionnaire that was similar for the 2008 sample and the 2014 sample was distributed to all patients who fulfilled the inclusion criteria. Questions regarding pain from the Brief Pain Inventory (BPI) (8) and questions regarding BTP from the Alberta Breakthrough Pain Assessment Tool for cancer patients (ABPAT) (24) were applied. A confirmative response of one screening question (pain yes/no) qualified for additional questions from the BPI and a screening question for BTP. Yes-responders were asked additional questions from the ABPAT. All patients were first asked the following question from the BPI; "Throughout our life, most of us have had pain from time to time (such as minor headache, sprains, toothaches). Have you had pain other than these everyday kinds of pain the last 24 hours?" Yes-response to this item was used to calculate the prevalence of pain. Yes-responders were then asked for average pain intensity and worst pain intensity the last 24 hours.

A question from ABPAT; ''Breakthrough pain can be defined as a brief flare-up of pain. It can be a flare-up of the usual, steady pain you always experience (your baseline pain) OR it can be a pain that is different from your baseline pain. Have you had breakthrough pain in the last 24 hours?" was asked all pain-responders and used to calculate the prevalence of BTP. Yes-responders to this question were then asked additional questions from ABPAT about frequency and intensity of their BTP.

Physicians at participating departments recorded the following data: patient demographics, cancer diagnosis, comorbidity, extent of cancer disease (localized, metastatic or "other") and performance status (25). Performance status was classified into three groups according to the work of Buccheri et al (26); Group 1 Karnofsky status >70 or WHO-PS-status 0-1, Group 2 Karnofsky status >50 and ≤ 70 or WHO-PS-status 2, Group 3 Karnofsky ≤ 50 or WHO-PS-status 3-4. The stage of solid cancers was classified as localized or metastatic disease. Lymphomas and haematological cancers were defined as "others" due to different classification systems for these diagnoses. To be included in the analysis, questionnaires completed both by the staff and by the patients were needed.

Statistical analysis

Inpatients and outpatients are clinically different cohorts and previous studies have shown different prevalence-rates of BTP in these cohorts (14). Thus, inpatients and outpatients were analysed separately. Descriptive statistics were applied to describe clinical and demographic data of the two study samples. Comparison of the prevalence of pain and BTP between the 2008 sample and the 2014 sample were performed applying simple logistic regression models (binary outcome), while a simple linear regression model was applied for pain intensity (continuous outcome). Multiple regression models (both logistic and linear) were applied to adjust for independent variables such as gender, age, presence of metastases and comorbidity. Statistical analyses were performed using SPSS statistical software, IBM SPSS statistics version 21.

Ethics

The study was approved by the Regional Committee for Medical Research Ethics, Health Region Central Norway. The principles of the Helsinki declaration were followed and informed consent was obtained from all individual participants included in the study.

Results

Inpatient population

A total of 258 inpatients were screened in the two cross-sectional studies. Ninety-two and 76 patients were eligible for inclusion in the 2008 and 2014 samples, respectively (figure 1). There were no statistical significant differences between the two samples on age, gender, diagnosis, stage, and performance status. However, more patients with comorbidity were included in the 2014 sample compared to the 2008 sample (76 vs 59%, p= 0.02) (table 1).

Outpatient population

In the outpatient setting, 883 patients were screened for these studies. 301 in the 2008 sample and 374 in the 2014 sample were included (figure 1).
The differences in age, gender, performance status and comorbidity in the 2008 sample and the 2014 sample were not statistically significant. More patients with lymphomas and hematological cancer (20% vs 12%, p=0.01) and fewer patients with localized disease (41% vs 55%, p= 0.01) were included in the 2014 sample compared to the 2008 sample (Table 1).

Pain prevalence and pain intensity in the inpatient population

Pain was reported by 55% and 53% of the inpatients in the 2008 and 2014 samples respectively (Fig 2) The difference was not statistically significant (p=0.72)
In the subsample of inpatients with pain, the mean “average pain intensity last 24 h” was 3.60 (SD 1.84) and 4.08 (SD 2.11) (p=0.26), while “worst pain intensity last 24 h” was 4.96 (SD 2.58) and 5.35 (SD 2.70) (p= 0.49) in the 2008 and 2014 sample respectively (Table 2a). The differences were not statistically significant between the two samples.

Pain prevalence and pain intensity in the out-patients population

Among the outpatients 39% and 35% reported pain in the 2008 and 2014 sample, respectively. (Fig 2) The difference was not statistically significant (p=0.29)
In the subsample of patients that reported pain, the average pain intensity (0-10 NRS) for was 3.60 (SD 2.04) and 3.86 (SD 2.20) in the 2008 sample and the 2014 sample. The difference was not statistical significant (p=0.34). In the 2014 sample, worst pain intensity (11-point

NRS) was reported as 4.63 (SD 2.30) compared to 4.03 (SD 2.35) in the 2008 sample which was a statistically significant difference (p=0.04) (Table 2b).

BTP in the in-patient population

In the inpatient population, there was no statistically significant difference in the prevalence of BTP between the 2008 sample and the 2014 sample (table 2a). In the sample of inpatients with BTP, no difference in BTP intensity or BTP frequency was shown in the two periods (2008 vs 2014) (Table 3). For those who had pain, BTP was reported by 52% and 41% in the 2008 sample and 2014 sample, respectively (p= 0.31). Average pain intensity of the BTP episodes were 7.3 (SD 2.0) and 7.6 (SD 1.8) (0-10 NRS) (p=0.66), while mean frequency of BTP episodes was reported as 3.5/ 24 h (SD 3.1) and 3.6/ 24 h (SD 1.7) (p=0.85) in the 2008 sample and the 2014 sample, respectively.

BTP in the out-patient population

For the prevalence of BTP and the intensity of BTP among outpatients, there were no statistically significant differences between the 2008 sample and the 2014 sample (Table 2b and 3). For patients who reported pain in the outpatient population, BTP was reported by 43% in the 2008 sample and 37% in the 2014 sample (p=0.37) . For patients with BTP, the intensity of the BTP episodes were reported as 6.6 (SD 2.0) and 6.6 (SD 2.5) (11-point NRS) in the 2008 sample and the 2014 sample, respectively (p=0.99). Higher frequency of BTP episodes was reported in the 2014 sample compared to the 2008 sample, 4.9/ 24 h (SD 3.0) vs 2.3/ 24 h (SD 2.1). The difference was statistically significant (p=0.01).

Adjusted difference estimation

When adjusting for gender, age, presence of metastases and comorbidity, no statistically significant difference between the 2008 sample and the 2014 sample was shown for pain prevalence (p= 0.64), average pain intensity (p= 0.32), worst pain intensity (p= 0.54), or the presence of BTP (p= 0.46) among inpatients. The same results occurred in the outpatients for pain prevalence (p= 0.47), average pain intensity (p= 0.23), and the presence of BTP (p=0.55). Worst pain intensity among outpatients was reported higher in the 2014 sample compared to the 2008 sample also when adjusting for independent variables (p=0.02).

Discussion

Two cross-sectional symptom prevalence studies in cancer patients were performed at one university hospital and one local hospital in Mid-Norway; one in 2008 and one in 2014. Improvement in cancer pain management in this time period was expected due to education, new guidelines and new treatment opportunities. However, no improvement in cancer pain management between 2008 and 2014 was shown when measuring the difference in prevalence rates of pain, pain intensity scores, and the prevalence rates of BTP. No statistically significant improvements, neither for inpatients nor for outpatients even when adjusting for potentially confounding factors were identified. The prevalence rates of pain and BTP in the two studies did not differ significantly from other studies of cancer patients (4, 27) (14). Characteristics of pain and BTP were also similar to results from other studies (28-30).

There are several explanations for this probable lack of improved pain control in the time period from 2008 to 2014. The study samples may not be directly comparable. However, when adjusting for independent variables such as gender, age, setting and comorbidity, no differences were demonstrated either. There might have been variables not measured in this study that could have influenced the results such as presence of neuropathic pain, substance abuse, and opioid use. Furthermore, prevalence rates might not be an optimal measurement to explore change in cancer pain management. Changes in pain intensity might be more sensitive. However, no improvement was identified for pain intensity scores either. In addition, information about the degree of implementation of cancer pain guidelines could have given valuable insight, however, guideline adherence among physicians was not assessed.

Other explanations for the lack of improvement might have been: not optimal teaching of health care providers, the cancer pain guidelines may not have been followed due to lack of proper implementation into all providers of cancer care, and the content of the guidelines may not be completely appropriate. Our results may indicate that implementation of new findings and guidelines might be challenging. Preconditions to succeed with pain control may be that classification systems, assessment tools and clinical guidelines are available, that patients and health care providers are offered proper education, and that the health care is properly organized.

Barriers to improve cancer pain management might be divided into patient related, health care provider-related and health care system-related barriers (18). Several patient related barriers to achieve pain control have been described (18). For example concerns for disease progression, addiction and side effects, psychological distress, and non-adherence to pain medication prescriptions. A systematic patient and family education might reduce some of these barriers. In a systematic review a reduction in average pain intensity of more than one point on an 0-10 NRS was demonstrated by employing patient education (31). A recent review explored the importance of patient education for improving cancer pain management (32). Four core principles were presented as important: pain education, the integration of patient education in the health professional-patient communication, empowering the patient, and incorporating patient education as an integral part of standard care.

For health care providers, education and focus on implementation are important. A recent case vignette study demonstrated that a clinical practice guideline in cancer pain is adopted only partly by medical oncologists in the Netherlands (33). Lack of use of guidelines in clinical practice and lack of assessment have been considered as significant barriers in cancer pain management (18). In an Australian study lack of access to non-pharmacologic pain management strategies, lack of coordination between providers, lack of consensus and knowledge about pain management, and the lack of educational resources were identified as barriers to optimal pain management. Additionally, patient comorbidity was a barrier. The importance of guidelines and implementation strategies of these were highlighted (34). Staff culture is also described as an important factor for successful implementation of evidence-based medicine (EBM) into evidence-based practice (EBP) (35). Resistance to alter practice, conflict with competing priorities, lack of time and resources may be important barriers.

Implementation of guidelines on pain management has been shown to reduce pain intensity among cancer patients (36). Additional improvement in cancer pain management was achieved if an educational intervention using the guidelines was applied (37). In the present study, a structured education program for health care providers using results from the studies presented above might have led to improved cancer pain management in the time period. The health care system itself could be a barrier to achieve improved cancer pain management. Sanders et al. (35) reported that agency culture might be an important barrier for implementing EBM into EBP. A standardized care pathway (SCP) might be an effective method to improve implementation (38, 39) (40, 41). Several studies recommend SCPs as one

way to overcome the shift from EBM to EBP (40). The SCP should advice the provider in routine assessments, patient reported outcome measures (PROMs), classification and re-classification, treatment, and follow-up while an implementation strategy should make sure that the SCP is followed and applied. Health care authorities should facilitate the process of implementing new knowledge and the use of SCP (41). Strategies to implement clinical guidelines for the management of chronic disease at primary care level have been explored in a systematic review (42). In a total of 21 studies, the implementation strategy was fully effective in only four of them, describing the difficulty in implementing EBM into EBP. Multifaceted intervention strategies were slightly better than single interventions. Four strategies have been identified to increase the use of research in clinical practice: audit and feedback, computerized decision support, the use of opinion leaders, and multifaceted interventions (43). Also in this study, a combination of several interventions was superior single interventions. Guidelines, feedback and educational interventions achieved small to moderate effects alone while combining them gave increased effect. The importance of support in the organizations and of the health care authorities has been underlined, and creating implementation teams to promote the change from EBM to EBP has been suggested (44). The use of computerized decision support systems has been explored in several studies. In a recent meta-analysis of 162 randomized trials, the authors concluded that systems providing advice to patients and practitioners and systems requiring reasons when over-riding advices were most likely to be successful (45).

We suggest applying standardized care pathways integrated in a computerized decision support system as an approach to improve cancer pain management in the future.

Conclusion

No change in cancer pain management was possible to detect when comparing two cross-sectional studies done five years apart. The outcomes chosen might have been suboptimal. However, these results might indicate that improving cancer pain management is challenging despite existing guidelines, available treatments, and efforts in educating health care providers in cancer pain management. Further efforts should be made to improve cancer pain management.

Disclosure and acknowledgement

The research group was given a grant from the Cancer Foundation, St. Olavs Hospital, Trondheim University Hospital, Trondheim, Norway to conduct this study. BC received training grant from the Floriani Foundation - Milan (del.CDA 22/11/12).

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

A special thanks to Professor Dagny Faksvåg Haugen for support and advice during the analysis and writing of the manuscript and to Jorunn Brekke Fjeldheim for including patients at Aalesund Hospital in this study.

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Figure 1 Flowchart

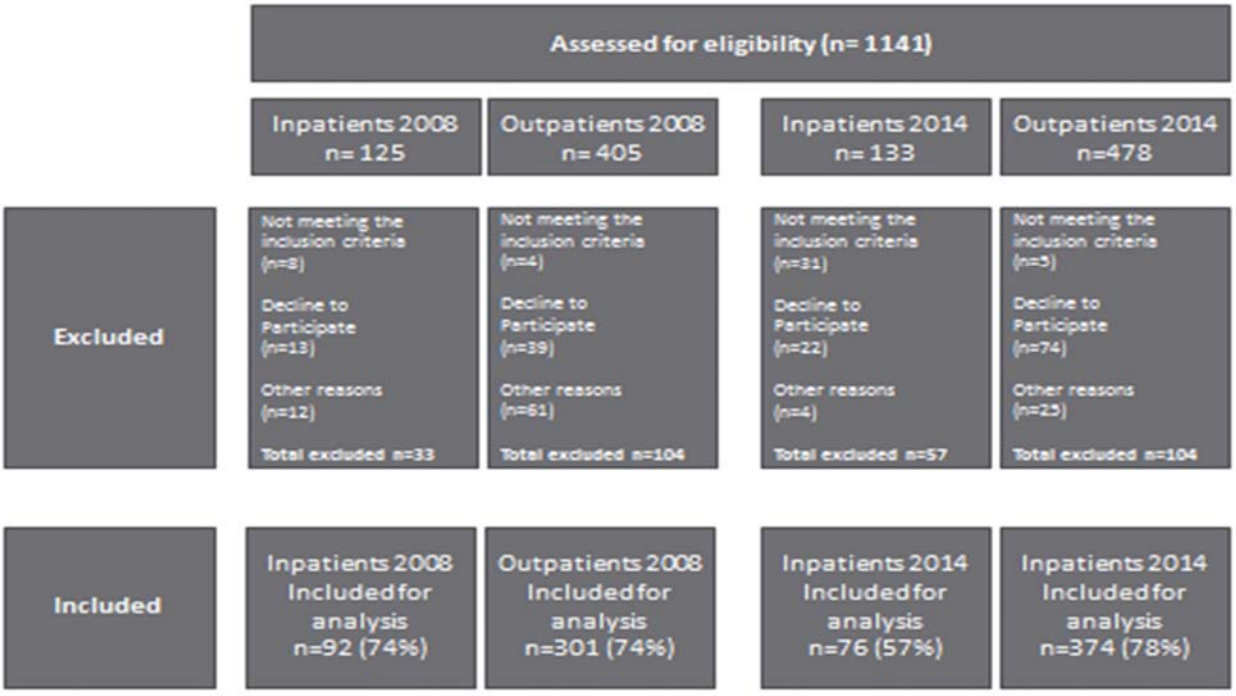
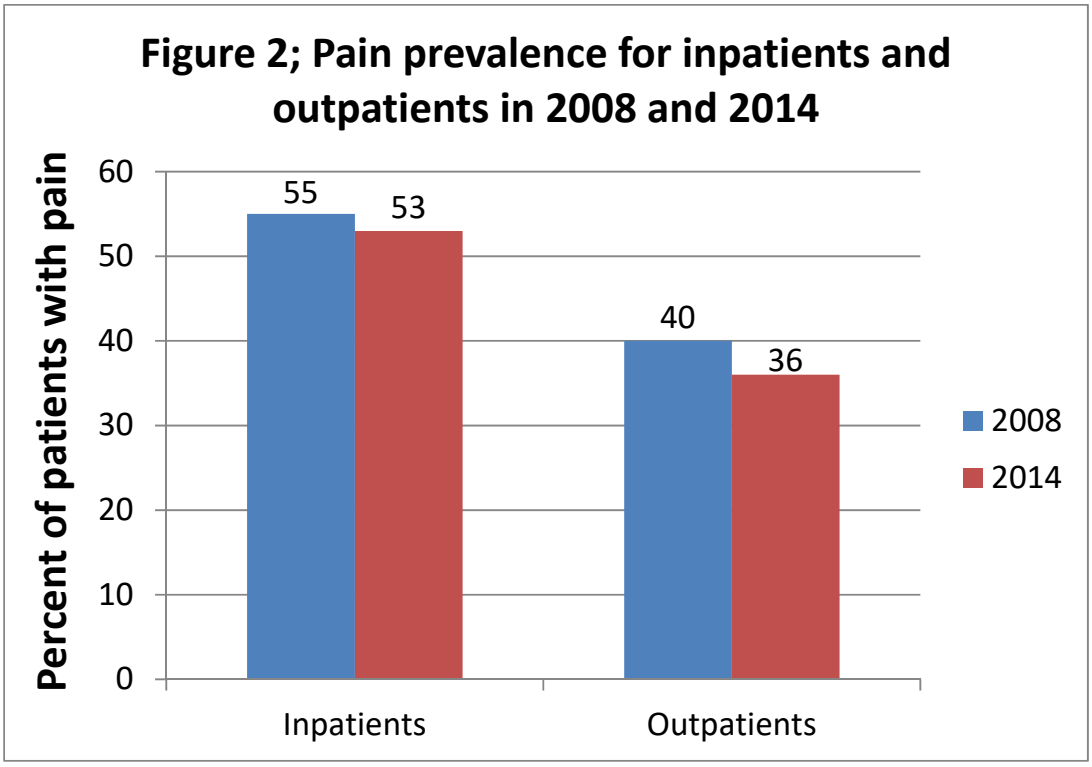


Figure 1 shows the flowchart of the patients in the two cross-sectional studies



Pain prevalence in percent for inpatients in 2008 and 2014, the difference was not statistical significant, p = 0.72,
Pain prevalence in percent for outpatients in 2008 and 2014, the difference was not statistical significant, p= 0.29

Table 1 Clinical and demographic characteristics of patients

	Inpatients		*p-value*	*Outpatients*		*p-value*
	2008	2014		2008	2014	
No of patients	92	76		301	374	
Age, mean, (SD)	66 (14.5)	67 (13.1)	0.63	60 (13.1)	61(13.6)	0.19
Gender						
Female	45 (49 %)	29 (38 %)	0.16	161 (53 %)	182 (49 %)	-
Male	47 (51 %)	47 (62 %)	-	140 (47 %)	192 (51 %)	0.21
Cancer diagnosis						
Gastro-intestinal	20 (22%)	22 (29%)	0.23	67 (22%)	72 (19%)	0.68
Urological	14 (15%)	13 (17%)	0.27	53 (18%)	74 (20%)	0.13
Gynecological	10 (11%)	4 (5%)	0.71	0	0	N.A.
Lung	9 (10%)	11 (14%)	0.19	19 (6%)	15 (4%)	0.57
Lymphomas and Hematological cancer	21 (23%)	16 (21%)	0.34	37 (12%)	73 (20%)	0.01
Breast	4 (4%)	1 (1%)	-	94 (31%)	92 (25%)	-
Others	14 (15%)	9 (12%)	0.43	29 (10%)	48 (13%)	0.06
Missing				2 (1%)		
Stage						
Localized	29 (32 %)	28 (37 %)	0.58	166 (55 %)	154 (41 %)	0.01
Metastatic	42 (46 %)	29 (38 %)	0.81	98 (33 %)	147 (39 %)	0.25
Unable to classify	21 (22 %)	16 (21 %)	-	37 (12 %)	73 (20 %)	-
missing		3 (4 %)				
Performance status (*)						
1	42 (46 %)	39 (51 %)	0.25	280 (93 %)	324 (87 %)	0.01
2	22 (24 %)	20 (26 %)	0.33	19 (6 %)	43 (11 %)	-
3(**)	27 (29 %)	16 (21 %)	-	0	7 (2 %)	N.A.
Missing	1 (1 %)	1 (1 %)		2 (1 %)	0	
Comorbidity						
No	38 (41%)	18 (24%)	0.02	100 (33 %)	138 (37 %)	0.32
Yes	54 (59 %)	58 (76 %)	-	201 (67 %)	236 (63 %)	-
Missing	0	0		0	0	

Inpatients of 2008 compared to inpatients of 2014, outpatients of 2008 compared to outpatients of 2014, statistical significant differences demonstrated by p-value.

Female, breast cancer, stage- unable to classify, performance status group 3 (inpatients) and group 2 (outpatients), and comorbidity (yes) used as constants in the multinomial logistic regression model.

(*) Performance status classified according to Buccheri (table 1) (25)
(**) For outpatients the 7 patients in PS group 3 were classified as Karnofsky status ≥ 50 For inpatients, one were in WHO 4 (2008), 5 and 3 patients in Karnofsky status 40% and 30%, respectively (2014)

Table 2a Pain characteristics inpatients 2008-2014

Inpatients	2008	2014	Effect size (95% CI) (*)	unadjusted p-value (**)	adjusted p-value (***)
Pain					
N	92	76			
Prevalence of pain	55%	53%	0.89 (0.49-1.64)	0.72	0.64
Average pain intensity					
N	51	40			
Mean (SD)	3.60 (1.84)	4.08 (2.11)	0.48 (-0.36-1.31)	0.26	0.32
Median (range)	3.5 (8)	4.0 (8)			
Worst pain intensity					
N	52	40			
Mean (SD)	4.96 (2.58)	5.35 (2.70)	0.39 (-0.72-1.49)	0.49	0.54
Median (range)	5.0 (10)	5.0 (10)			
BTP					
N	48	39			
Prevalence of BTP	52%	41%	0.64 (0.27-1.50)	0.31	0.46

Pain intensity, average pain (0-10 NRS), worst pain intensity (0-10 NRS) and breakthrough pain among inpatients in the 2008 sample and the 2014 sample. N= number of patients, SD = Standard deviation, BTP= Breakthrough pain

(*) un-adjusted mean difference between 2008 - 2014 for pain average and worst pain intensity, un-adjusted Odds Ratio for presence of pain and BTP in the two time periods.
(**) p-values calculated from simple regression analysis (linear for pain intensities, logistic for presence of pain and BTP) to test the hypothesis of no difference between the 2008 and 2014 cohorts.
(***) p-values calculated from multivariable regression analysis to test the hypothesis of no difference between the 2008 and 2014 cohorts, adjusting for age, gender, setting and comorbidity.

Table 2b Pain characteristics outpatients 2008-2014

Outpatients	2008	2014	Effect size (95% CI)(*)	p-value unadjusted (**)	p-value adjusted (***)
Pain					
N	301	374			
Prevalence of pain	39%	35%	0.84 (0.62-1.15)	0.29	0.47
Average pain intensity					
N	118	126			
Mean (SD)	3.60 (2.04)	3.86 (2.20)	0.26 (-0.27-0.80)	0.34	0.23
Median (range)	3.0 (9)	3.5 (10)			
Worst pain intensity					
N	118	124			
Mean (SD)	4.03 (2.35)	4.63 (2.30)	0.6 (0.02-1.19)	0.04	0.02
Median (range)	4.0 (10)	5.0 (10)			
BTP					
N	110	127			
Prevalence of BTP	43%	37%	0.8 (0.47-1.33)	0.37	0.55

Pain intensity, average pain (0-10 NRS), worst pain intensity (0-10 NRS) and breakthrough pain among outpatients in the 2008 sample and the 2014 sample. N= number of patients, SD = Standard deviation, BTP= Breakthrough pain

(*) un-adjusted mean difference between 2008 - 2014 for pain average and worst pain intensity, un-adjusted Odds Ratio for presence of pain and BTP in the two time periods.
(**) p-values calculated from simple regression analysis (linear for pain intensities, logistic for presence of pain and BTP) to test the hypothesis of no difference between the 2008 and 2014 cohorts.
(**) p-values calculated from multivariable regression analysis to test the hypothesis of no difference between the 2008 and 2014 cohorts, adjusting for age, gender, setting and comorbidity.

Table 3 Breakthrough pain (BTP) characteristics, all patients with BTP (n= 135)

	Inpatients		*p-value (*)*	*Outpatients*		*p-value (*)*
BTP	2008	2014		2008	2014	
N	25	16		47	47	
Intensity (**)						
Intensity of BTP episodes						
Mean(SD)	7.3 (2.0)	7.6 (1.8)	0.66	6.6 (2.0)	6.6 (2.5)	0.99
Median (range)	8 (7)	8 (6)		7 (7)	7 (10)	
Frequency						
BTP episodes last 24 h,						
mean (SD)	3.5 (3.5)	3.6 (1.7)	0.85	2.3 (2.1)	4.9 (3.0)	0.01
median (range)	2.0 (12)	4.0 (5)		2.0 (8)	4.5 (11)	

Intensity and frequency of breakthrough pain (BTP) among inpatients and outpatients in the 2008 sample and the 2014 sample measured by 0-10 NRS.
SD= standard deviation.

(*) p-value calculated from simple linear regression analysis to test the hypothesis of no difference between 2008 and 2014 cohorts.
(**) 0-10 NRS