

Sleep quality in hospitalized patients with advanced cancer: an observational study using self-reports of sleep and actigraphy

Gunnhild Jakobsen^{1,2} · Morten Engstrøm^{3,4} · Morten Thronæs^{1,2} · Erik Torbjørn Løhre^{1,2} · Stein Kaasa^{1,5} · Peter Fayers⁷ · Marianne Jensen Hjermsstad^{5,6} · Pål Klepstad^{1,8,9}

Received: 28 February 2019 / Accepted: 16 July 2019
© Springer-Verlag GmbH Germany, part of Springer Nature 2019

Abstract

Purpose Although patients with advanced cancer report poor sleep quality, few studies have assessed sleep quality with a combination of subjective and objective measures. We aimed to examine sleep quality in hospitalized patients with advanced cancer by combining patient-reported outcome-measures (PROMs) and polysomnography (PSG) or actigraphy.

Methods A one-night prospective observational study of sleep in hospitalized patients with metastatic cancer using WHO step III opioids was conducted. Total sleep time, sleep onset latency, number of awakenings, and wake after sleep onset were assessed by PROMs and actigraphy. Sleep quality was assessed by the Pittsburgh Sleep Quality Index (PSQI) (range; 0–21), where higher scores indicate worse sleep quality.

Results Forty patients were monitored. Median age was 70, median oral morphine equivalent dose was 80 mg/24 h (10–1725), median Karnofsky Performance Score was 50 (20–90), and median time to death from inclusion was 38 days (4–319). Mean PSQI score was 6.5 (SD ±3.4). PROMs and actigraphy of mean (SD) sleep onset latency were 46 (±64) and 35 min (±61), respectively, while mean time awake at night was 37 (±35) and 40 min (±21). PROMs and actigraphy differed on number of awakenings (mean 2 (±1) vs. 24 (±15), $p < 0.001$). Bland-Altman plots showed large individual differences between PROMs and actigraphy. PSG was not feasible.

Conclusions PROMs and actigraphy documented poor sleep quality, but a lack of agreement across methods. The study demonstrates a need to improve assessment of sleep quality and treatment of sleep disturbance in hospitalized patients with advanced cancer near end of life.

Keywords Sleep · Advanced cancer · Sleep diary · Actigraphy · Polysomnography

Electronic supplementary material The online version of this article (<https://doi.org/10.1007/s00520-019-04998-5>) contains supplementary material, which is available to authorized users.

✉ Gunnhild Jakobsen
gunnhild.jakobsen@ntnu.no

Morten Engstrøm
morten.engstrom@ntnu.no

Morten Thronæs
morten.thrones@ntnu.no

Erik Torbjørn Løhre
erik.t.lohre@ntnu.no

Stein Kaasa
stein.kaasa@medisin.uio.no

Peter Fayers
p.fayers@abdn.ac.uk

Marianne Jensen Hjermsstad
mariajhj@medisin.uio.no

Pål Klepstad
pal.klepstad@ntnu.no

Extended author information available on the last page of the article

31 **Introduction**

32 Patients with advanced cancer often report sleep disturbances
 33 [1, 2], with frequent sleep-related problems such as insomnia,
 34 restless legs, hypersomnolence, and sleep apnea [3]. Poor
 35 sleep decreases the tolerability of other symptoms and impairs
 36 quality of life (QoL) [4, 5].

37 Clinical sleep research should include composite sleep as-
 38 sessments with a combination of objective registrations such
 39 as polysomnography (PSG) and actigraphy as well as objec-
 40 tive (self-report) patient-reported outcome measures
 41 (PROMs) to give detailed information on sleep disturbances
 42 [5–7]. Moreover, monitoring of sleep should yield informa-
 43 tion about a number of relevant metrics, including sleep onset
 44 latency, wakefulness after sleep onset, total sleep time, sleep
 45 efficiency (percent of time asleep out of amount of time spent
 46 in bed), and sleep quality, reflecting a subjective global ap-
 47 praisal of each night’s sleep [8].

48 Most studies of sleep in patients with advanced cancer
 49 use self-report. Self-reports reflect not only the quantitative
 50 sleep variables such as total sleep but also the patients’ ex-
 51 perience of sleep. Self-report is also more feasible than ob-
 52 jective registrations. However, the use of objective mea-
 53 surements of sleep are increasing [4]. Good et al. recently
 54 applied PSG in patients with advanced cancer in a study that
 55 documented sleep and respiratory patterns [9]. Moreover,
 56 Bernatchez et al. applied actigraphy in advanced cancer
 57 outpatients and observed that both PROMs and actigraphy
 58 detected disturbed sleep [10]. In a large sample of 237 pa-
 59 tients with metastatic colorectal cancer, Palesh et al. com-
 60 bined actigraphy and patient-reported subjective sleep and
 61 found sleep problems in 63% [11]. However, available stud-
 62 ies that use subjective and objective measures of sleep usu-
 63 ally include patients with early-stage cancer [12–15], with
 64 performance status of at least 60% [9, 11, 16–19], or outpa-
 65 tients [10, 20]. Thus, assessment of sleep by a combination
 66 of PROMs and objective measures, such as PSG or
 67 actigraphy, in hospitalized patients with advanced cancer
 68 approaching end of life, is scarcely investigated.

69 There are several reasons why we should examine sleep
 70 quality with both subjective and objective assessment in hos-
 71 pitalized patients with advanced cancer. These patients are
 72 often vulnerable, experience a high and fluctuating symptom
 73 burden [21], may be too weak to report sleep due to the dis-
 74 ease, or are cognitively impaired [22]. Moreover, patients with
 75 advanced cancer use multiple drugs, including strong opioids
 76 [23]. Opioids might alter psychomotor function, mood, con-
 77 centration, and other mental capabilities [24]. Thus, PROMs
 78 may not give an entirely representative assessment of sleep in
 79 patients with advanced cancer using strong opioids, due to the
 80 reliance on cognitive capacity to self-report sleep quality and
 81 symptoms. For these patients, objective sleep measures can
 82 supplement important information about sleep.

The aim of this study was to examine sleep quality by 83
 combining PROMs and objective measures (PSG or 84
 actigraphy) in hospitalized patients with advanced cancer. 85

Methods 86

Study design and patients 87

88 A one-night observational study of sleep quality in adult patients
 89 hospitalized for symptom control at a specialized inpatient unit
 90 was conducted at the Department of Palliative Medicine, St.
 91 Olav’s hospital, Trondheim University Hospital, Norway. This unit
 92 has approximately 550 admissions a year with a median hospital
 93 stay of 7 days. Inclusion criteria for the present study were verified
 94 malignant metastatic disease, regularly scheduled WHO step III
 95 opioid treatment [25], and ability to comply with study procedures
 96 including at least one, preferably both, of the objective assessments
 97 PSG and actigraphy. A one-night assessment was chosen to reduce
 98 the burden on the patients in a setting with inpatients with an
 99 expected short survival. Patients were asked to wear the sleep
 100 equipment overnight (4 pm–9 am, a total of 17 h). Exclusion
 101 criteria were severe cognitive impairment as evaluated by the at-
 102 tending physician and inability to answer Norwegian question-
 103 naires (Clinical [Trials.gov](https://www.clinicaltrials.gov) identifier: NCT02585609).

**Assessment of sleep quality with PROMs, 104
 polysomnography, and actigraphy** 105

106 The primary purpose of this study was to explore sleep quality
 107 using objective (actigraphy and PSG) and subjective
 108 (PROMs) measures. The five sleep quality outcomes assessed
 109 by each measure were total sleep time (TST, i.e., the actual
 110 time slept in minutes); sleep onset latency (SOL, i.e., how
 111 many minutes it takes to fall asleep starting from the moment
 112 of intention to fall asleep); number of awakenings during the
 113 night (NWAK); wake after sleep onset (WASO, i.e., total
 114 amount of time awake during the night in minutes); and sleep
 115 efficiency (SE, i.e., percent of time in bed spent asleep) [26].

116 PROMs of sleep during the observation night were report-
 117 ed in a sleep diary [8, 26]. Patients were asked to record time
 118 to falling asleep, duration of sleep, and wake after sleep in a
 119 sleep diary. In the morning, total subjective sleep quality was
 120 assessed by one question on a numerical rating scale (NRS) 0–
 121 10, where 0 = best sleep and 10 = worst possible sleep, from
 122 the European Association for Palliative Care (EAPC) basic
 123 dataset [27], while sleepiness was assessed by the
 124 Karolinska Sleepiness Scale (KSS). The KSS is a 9-point
 125 Likert scale assessing the patient’s perception of sleepiness.
 126 The nine answer categories range from 1 = very alert to 9 =
 127 very sleepy [28]. Patients also reported events that may have
 128 affected sleep/wake patterns during the observation night, e.g.,
 129 symptoms or taking medications.

130 Sleep quality during the previous month was measured by
 131 the Pittsburgh Sleep Quality Index (PSQI), a self-rating ques-
 132 tionnaire for measuring subjective sleep quality [29]. The PSQI
 133 consists of 19 questions, which assess seven sleep components:
 134 subjective sleep quality, sleep latency, sleep duration, habitual
 135 sleep efficiency, sleep disturbances, use of sleep medications,
 136 and daytime dysfunction. Seven component scores on 0 to 3
 137 scales are summarized to yield a global PSQI score between 0
 138 and 21; higher scores indicate worse sleep quality. A global
 139 score > 5 is generally indicating poor sleep [29]. In addition, a
 140 score > 8 is suggested as more relevant to cancer patients [30].

141 Patients were asked to do a sleep polysomnography (PSG)
 142 test using the ambulatory equipment SOMNOscreen TM plus
 143 [31] to score sleep stages, awakenings, and respiratory param-
 144 eters during one afternoon and a full night [17].
 145 Supplementary Fig. 1 illustrates the clinical setup of PSG.

146 An actigraph is a small wristwatch-size device
 147 (Supplementary Fig. 2) which is used to assess sleep-wake
 148 cycles. It measures the degree and intensity of motion by
 149 means of a multidirectional piezoelectric accelerometer [32,
 150 33]. In the present study, Actiwatch 2 (Philips Respironics,
 151 Inc., Murrysville, PA, USA) and Actiware software (version
 152 6.0.7) were used to collect and analyze actigraphy data. Sleep
 153 estimates were automatically calculated by the Actiware soft-
 154 ware using the digital integration method [34]. The data were
 155 recorded with an epoch length (i.e., the period of time over
 156 which the actigraphy data is averaged) of 30 s and scored as
 157 wake or sleep by the use of medium sensitivity threshold,
 158 corresponding to 40 activity counts per epoch. A 10-min in-
 159 activity threshold for sleep onset was chosen as a default set-
 160 ting. All patients wore the actigraph around the wrist of their
 161 choice. The period of interest was sleep/wake during one night
 162 in the hospital. Based on differences in movement intensity,
 163 the software automatically defines rest intervals. In the present
 164 study, an initial visual examination of the actograms identified
 165 periods assessed as sleep despite apparent activity, and vice
 166 versa. Therefore, manually scored rest intervals were deter-
 167 mined by a researcher (GJ) and a specialist in clinical neuro-
 168 physiology (ME) following previously published criteria for
 169 rest interval onset (significant sustained decrease in activity,
 170 the patient-reported "lights off"), rest interval (significant
 171 sustained decrease in activity > 3 h), and rest interval termina-
 172 tion (significantly sustained increase in activity, patient-
 173 reported "lights on") [32, 35].

174 Symptom burden and demographic variables

175 Cancer-related symptoms were measured by NRS in the EAPC
 176 basic dataset [27]. Overall QoL and pain during the last week
 177 were measured by the European Organisation for Research and
 178 Treatment of Cancer Core questionnaire for Quality of Life in
 179 palliative care patients (EORTC QLQ-C15-PAL) [36].

Sociodemographic and medical characteristics were ob- 180
 tained from the medical records. Morphine daily equivalent 181
 doses were calculated based on established definitions [25]. 182
 The treating physicians independently assessed performance 183
 status by the Karnofsky Performance Status Scale (KPS) [37]. 184
 KPS ranges from 0 (i.e., dead) to 100 (i.e., normal activity). 185
 Status of survival and date of death were obtained from the 186
 medical record 6 months after inclusion. 187

Statistical considerations 188

The sample size calculation was based on the expected preci- 189
 sion of the observed mean of total sleep time, in minutes, 190
 measured by PSG. We estimated an expected standard devia- 191
 tion (SD) for total sleep time to be 60 min and assumed a 192
 normal distribution. We accepted an expected 95% confidence 193
 interval of 120 min (± 1 h). An estimation using these condi- 194
 tions, a significance level of 5%, and a power of 90% con- 195
 firmed that 40 observations would ensure an acceptable (\pm 196
 1 h) precision of the primary variable total sleep time. 197

Descriptive statistics were used for the sleep quality and 198
 demographic variables. Independent sample *t* tests were used 199
 to explore whether sleep quality in patients with a lower func- 200
 tional status (i.e., KPS ≤ 50) was different from sleep quality 201
 in patients with higher functional status (i.e., KPS > 50). Three 202
 approaches were used in the examination of agreement be- 203
 tween PROMs of sleep quality and actigraphy. First, to evalu- 204
 ate possible relationships between PROMs and actigraphy, 205
 we calculated Spearman's rank correlation coefficient for the 206
 sleep parameters: total sleep time, sleep onset latency, number 207
 of awakenings, wake after sleep onset, and sleep efficiency. 208
 Second, after visual inspection, we concluded that the mean 209
 differences had normal distributions, and that the mean values 210
 of the abovementioned sleep parameters were compared using 211
 two-tailed paired *t* tests. Bland-Altman plots [38] were used to 212
 explore the agreement between actigraphy and PROMs. In 213
 this analysis, where A = actigraphy and B = PROMs, we 214
 calculated the difference between actigraphy and PROMs (A 215
 minus B), average $[(A + B)/2]$, mean difference, and standard 216
 deviation of the differences. Mean difference between 217
 actigraphy and PROMs is the estimated bias, which is the 218
 systematic difference between the methods. The 95% limits 219
 of agreement were obtained (mean difference ± 1.96 SD) and 220
 data from the sleep parameters were examined visually by 221
 plotting differences between the actigraphy and PROMs (dif- 222
 ference score = actigraphy minus PROMs) against their indi- 223
 vidual means in the Bland-Altman plots. To examine whether 224
 any of the observed discrepancies between the measurements 225
 could be accounted for by performance status, independent 226
 sample *t* tests were used. The KPS group ≤ 50 was compared 227
 with the KPS group > 50. Associations between actigraphy 228
 and PROMs on total sleep quality were examined by 229
 Spearman's rank correlations (r_s). There were no imputations 230

231 for missing values on the PROMs. A significance level of
 232 $p < 0.05$ was used for all analyses. Data were analyzed by
 233 IBM SPSS Statistics version 20.0 for Windows (IBM
 234 Corporation, Armonk, USA).

235 **Results**

236 From January 2016, to March 2017, 41 of 128 screened inpa-
 237 tients were eligible (Fig. 1). Due to ongoing symptoms or poor
 238 condition, only two of the 41 included patients could use PSG.
 239 This method was therefore excluded from the study. However, all
 240 41 patients entered a one-night assessment with actigraphy and
 241 PROMs of sleep. One patient died from cancer disease during the
 242 study night. For two patients, it was not possible to generate sleep
 243 parameters from the Actiware software. Supplementary Fig. 3
 244 includes the actograms for these two patients.

245 **Sample characteristics**

246 All patients used step III opioids for cancer pain with a median oral
 247 daily morphine equivalent dose of 80 mg/24 h (range 10–1725).
 248 Median age was 70 years (range 41–91) and 40% were female.

249 Median KPS was 50 (range 20–90). All had metastatic cancer and
 250 33 of the patients (83%) died within 6 months. Median time to
 251 death from inclusion date was 38 days (range 4–319, interquartile
 252 range = 60.5, 25th percentile = 17.5; 75th percentile = 78). Other
 253 patient characteristics are given in Table 1.

254 The mean value on the overall QoL scale (0–100) was 51.8
 255 (SD ± 25.4; 0–83.3) (Table 2). The mean pain intensity assessed
 256 in the morning on an NRS (0–10) was 2 (SD ± 2.8; range 0–10)
 257 (Table 2). Pain was the most commonly reported reason for
 258 disturbed sleep during the observation night (20%), followed
 259 by a need to use the bathroom (15%), disturbances from med-
 260 ical equipment, e.g., intravenous lines (10%) and racing
 261 thoughts (5%). Other symptom intensities are given in Table 2.

262 **Patient-reported sleep**

263 The mean patient-reported total sleep time was 442 min (SD ±
 264 106), mean sleep onset latency was 46 min (SD ± 64), mean
 265 number of awakenings was 2 (SD ± 1), and mean total amount
 266 of time awake during the night was 37 min (SD ± 35). The
 267 mean percent of time in bed being asleep was 83% (SD ± 12)
 268 (Table 3). Frequency of missing PROM responses for the

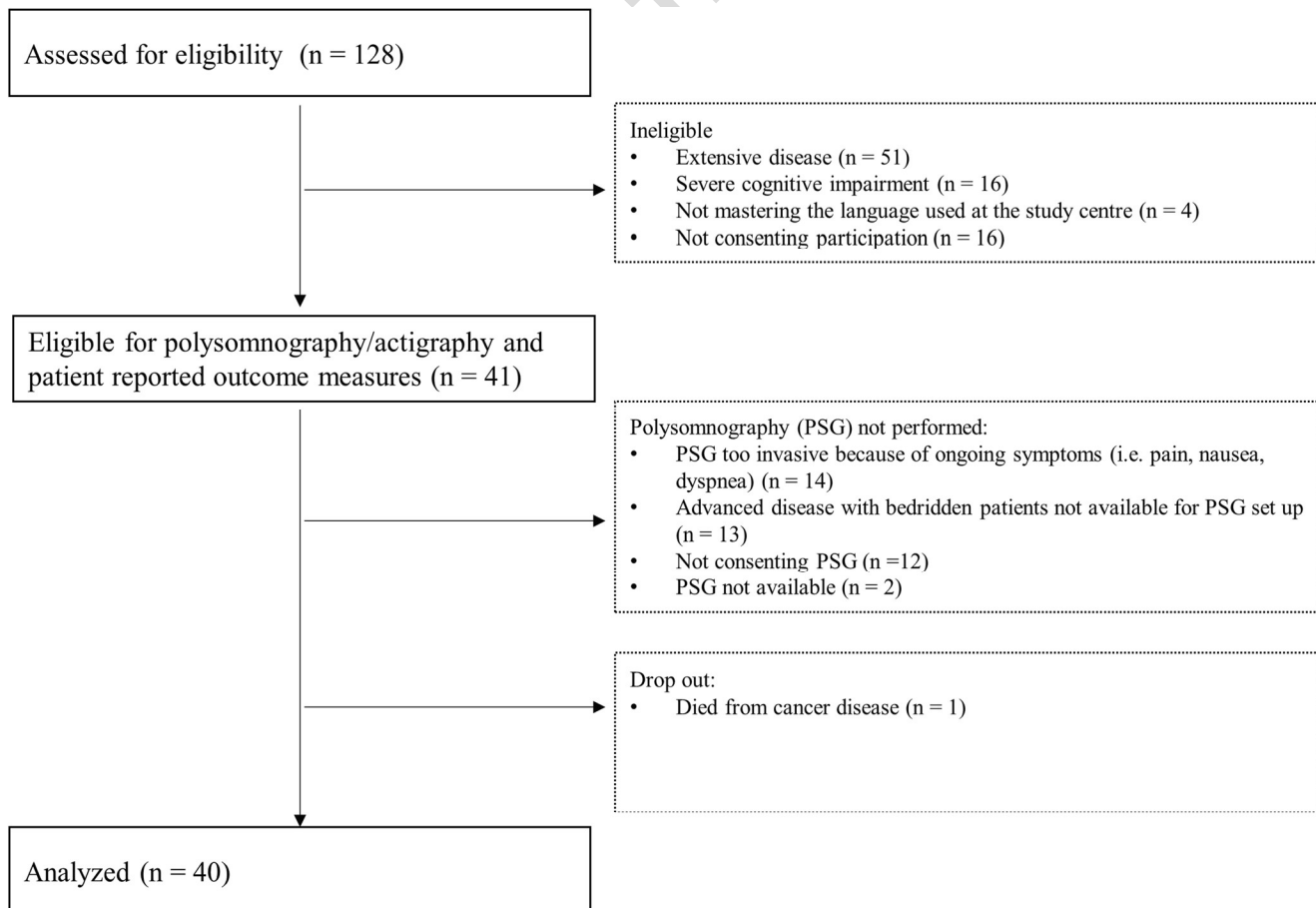


Fig. 1 Flowchart of the patient recruitment and completion of measurement

Table 1 Demographic and clinical characteristics of the cohort at inclusion

Variable	Median (range)	n (%)
Age in years	70 (46–91)	
Karnofsky Performance Status Score ^a	50 (20–90)	
Oral daily morphine equivalent dose (mg)	80 (10–1750)	
Number of days on opioids	54 (7–710)	
Hemoglobin serum concentrations (g/dl)	11.6 (9–16)	
Number of drugs	9 (3–14)	
Time since cancer diagnosis (months)	30 (0–288)	
Gender		
Female		16 (40.0)
Male		24 (60.0)
Primary cancer diagnosis		
Gastro intestinal/liver/pancreas		22 (55.0)
Prostate		8 (20.0)
Pulmonary		2 (5.0)
Skin		2 (5.0)
Urological cancer		2 (5.0)
Breast		1 (2.5)
Female reproductive organs		1 (2.5)
Head and neck		1 (2.5)
Hematological		1 (2.5)
Metastases		40 (100)
Bone		18 (45.0)
Liver		19 (47.5)
Lung		15 (37.5)
CNS		2 (5.0)
Lymph nodes		13 (32.5)
Use of medication that may influence sleep:		
Steroids		25 (62.5)
Antidepressants		7 (17.5)
Sedatives/anxiolytics		8 (20.0)
Hypnotics		12 (30.0)

^aKarnofsky Performance Status using a 0 (dead) to 100 (i.e., normal activity) scale [36]

Table 2 Descriptive statistics of global sleep quality and cancer-related symptoms

Variable	Mean	SD	Min	Max
PSQI global score ^a	6.5	3.4	2	13
Subjective sleep quality	1.1	1.0	0	3
Sleep latency	0.9	1.1	0	3
Sleep duration	0.3	0.6	0	3
Habitual sleep efficiency	1.2	0.4	0	3
Sleep disturbances	1.0	0.4	0	3
Use of sleep medication	1.0	1.3	0	3
Daytime dysfunction	0.9	0.9		
Karolinska Sleepiness Scale ^b				
Evening	6.4	1.8	3	9
Morning	4.8	2.1	1	8
Pain ^c				
Average pain, evening	2.2	2.5	0	10
Average pain, morning	2.0	2.8	0	10
Nausea ^c	0.9	2.3	0	10
Shortness of breath ^c	2.1	2.8	0	10
Depression ^c	0.7	1.5	0	5
Anxiety ^c	0.7	1.6	0	6
Feeling of well-being ^c	3.4	2.8	0	10
Tiredness ^c	3.9	2.7	0	10
Drowsiness ^c	4.1	2.9	0	10
Overall QoL ^d	51.8	25.4	0	83.3
Pain last week ^e	66.1	29.4	16	100

^aSleep quality last month assessed by the Pittsburgh Sleep Quality Index (PSQI) [29]

^bKarolinska Sleepiness Scale (1–9) [28]

^cAssessed by the EAPC basic dataset, numerical rating scale 0–10 [27]

^dQoL assessed by the European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ-C15-PAL) [36] for the last week (0–100), where a high score on overall QoL scale means a good quality of life

^ePain last week assessed on the EORTC QLQ C15-PAL symptom scale (0–100), where a high score on symptom scales denotes higher symptom burden

selected sleep parameters were TST 27%, SOL 27%, NWAK 25%, WASO 50%, and SE 27%.

The mean PSQI global score was 6.5 (0–21) (SD ± 3.4). The PSQI revealed that 46% of the patients were categorized as poor sleepers defined by the PSQI global score > 5. Twenty-one percent of the patients had a PSQI global score > 8. Twelve patients were not able to complete the PSQI. The mean value of total sleep quality assessed in the morning on an NRS (0–10) was 3 (SD ± 2.5; range 0–8).

Sleep assessed by actigraphy

Actigraphy revealed that the mean total sleep time was 418 min (SD ± 138), mean sleep onset latency was 35 min

(SD ± 61), mean number of awakenings was 24 (SD ± 15), and mean total amount of time awake during the night was 40 min (SD ± 21). The mean percent of time in bed spent asleep was 78% (SD ± 23) (Table 3).

There was no significant difference in sleep quality between patients with a lower functional status score (KPS of ≤ 50) and patients with a higher functional status score (KPS > 50) (Supplementary Table 1).

Agreement between PROMs and actigraphy

We observed differences between PROMs and actigraphy in some individuals. Further analyses showed moderate correlations (Spearman’s correlations) between PROMs and

Table 3 Sleep quality (mean ± SD) and comparison of sleep parameters estimated by actigraphy and patients reported outcome measures (PROMs)

Sleep parameters	Actigraphy (A) (mean ± SD)	PROMs (B) (mean ± SD)	Difference (A – B) (mean ± SD)	Spearman's rank correlation (rho)
TST (min)	418 ± 138	442 ± 106	– 23.8 (128.1)	0.61*
SOL (min)	35 ± 61	46 ± 64	– 11.4 (72.0)	0.26
NWAK	24 ± 15	2 ± 1	22 (14.4)	0.30
WASO (min)	40 ± 21	37 ± 35	3.6 (35.4)	0.21
SE (%)	78 ± 23	83 ± 12	– 5.3 (22.8)	0.48*

TST, total sleep time; SOL, sleep onset latency; NWAK, number of awakenings; WASO, wake after sleep onset; SE, sleep efficiency

* $p < 0.005$

actigraphy for total sleep time and sleep efficiency ($r_s = 0.61$ and 0.48) while sleep onset latency, number of awakenings, and wake after sleep onset all showed correlations below 0.40 (Table 3). Number of awakenings was statistically significantly higher based on actigraphy than PROMs with a mean difference of 22 (SD ± 14.8 , $p < 0.005$). Compared with PROMs, the actigraphy measured lower total sleep time (23.8 min, SD ± 128.1), lower sleep onset latency (11.4 min, SD ± 70.7), lower sleep efficiency (5.3% , SD ± 22.8), and higher wake after sleep onset (3.6 min, SD ± 35.4). None of these differences were statistically significant, although an examination with the Bland-Altman plots demonstrated large variability in individual assessments (Supplementary Fig. 4). There were no differences in the discrepancy between actigraphy and PROMs in patients with $KPS \leq 50$ ($N = 15$) compared with those with $KPS > 50$ ($N = 14$) (Supplementary Table 2).

Association between PROMs and actigraphy with total sleep quality and sleepiness

Finally, we also explored the associations between PROMs and actigraphy on total sleep quality. Total subjective sleep quality, assessed in the morning on an NRS ($0-10$), was associated with patient-reported sleep onset latency (Spearman's rank correlations (r_s) = 0.349), number of awakenings ($r_s = 0.347$), and wake after sleep onset ($r_s = 0.457$). Longer wake after sleep onset, as measured with actigraphy, was significantly associated with worsening of total subjective sleep quality ($r_s = 0.45$).

Discussion

The present study examined sleep quality in hospitalized patients with advanced cancer near end of life, who received strong opioids for cancer pain. Sleep quality was examined using a combination of PROMs and actigraphy. Both PROMs and actigraphy revealed poor sleep quality in one third of the patients.

To our knowledge, this is the first study examining sleep quality with the combination of PROMs and actigraphy in hospitalized patients with advanced cancer and short-expected survival time. Previous studies have usually included patients with early-stage cancer [12–15], higher performance status [9, 11, 16–19], or outpatients [10, 20]. Such studies may not be representative for hospitalized patients with advanced cancer at end of life. In these patients, sleep may be more affected than at earlier stages of the disease, and poor sleep might aggravate other symptoms or reduce quality of life. Thus, it is important to examine sleep quality in patients receiving palliative care, in order to improve future diagnostic and treatment of sleep disturbances, and as such make a novel contribution to the literature in this area.

Short sleep latency, few awakenings, and short wake after sleep onset are indicators of good sleep quality [39]. In this study, both PROMs and actigraphy revealed longer sleep onset latency compared with results from other studies in palliative care [11, 20]. However, the mean number of minutes it took to fall asleep as measured by actigraphy is shorter than in a study that examined the relationship between pain, sleep disturbance, and circadian rhythms in patients with cancer pain (35 vs. 41 min) [40]. Moreover, both PROMs and actigraphy showed that patients were awake more than 30 min on average during the night (37 and 40 min, respectively). These results agree with previous findings in outpatients with advanced cancer [10, 11, 20].

Using the suggested cutoff by Buysse et al. [29] for the PSQI (scores > 5), nearly half of the patients (46%) reported poor sleep quality on the PSQI questionnaire, which corresponds with high prevalence of self-reported poor sleep quality in advanced cancer patients observed in other studies [40–42]. Carpenter et al. suggested to use a PSQI score > 8 as the cutoff in cancer patients. This suggestion was based on the mean PSQI score in patients with sleep problems in their study [30]. A cutoff of > 8 have reduced the number of patients reporting poor sleep in our study. The argument for using a higher PSQI cutoff in cancer patients is to avoid influence of cancer-related symptoms on the sleep variable.

366 We observed that almost one third of the patients could not
367 report PROMs on sleep quality because of complex symptom
368 burden and advanced disease. Therefore, to rely solely on
369 PROMs in this group of patients will result in a lack of im-
370 portant information on sleep quality in many patients. In situ-
371 ations where patient perception about sleep is impossible,
372 actigraphy provides useful feedback to health care providers
373 about the overall sleep pattern [43].

374 Consistent with findings in the general population and in pa-
375 tients undergoing oncological treatment [11, 33, 44], we found
376 discrepancies between PROMs and actigraphy. These differ-
377 ences between actigraphy and PROMs on sleep quality were
378 larger in our study than in healthy individuals of similar age as
379 in our sample, where the mean number and standard deviation of
380 the difference between actigraphy and sleep diary for total sleep
381 time was 13 and 62 respectively, compared with 23 and 128 in
382 our study [45]. It has not been established to what extent the
383 discrepancies between actigraphy and PROMs result from inac-
384 curate measurements by the actigraphy or whether it is related to
385 imprecise perceptions of sleep in the subjective patient reports or
386 both [5]. In our study, the discrepancy could be affected by both
387 erroneous interpretation of inactivity as sleep by the actigraphy
388 and the patients' inability to report sleep. This issue could have
389 been clarified using PSG. However, as illustrated in supplement-
390 ary Fig. 1, PSG has a complicated setup that precluded installa-
391 tion of PSG in our cohort. Our lack of successful use of PSG
392 illustrates the challenges in applying PSG for seriously ill patients
393 with advanced cancer and should be carefully considered for
394 future studies. PSG may be applicable in the palliative setting
395 depending on the logistics of the study setting and the stage of
396 disease, as shown by Good et al. who investigated sleep apnea in
397 patients with advanced cancer [9]. However, in that study, time to
398 death was not reported and patients may have survived longer
399 than the median 38 days in our study.

400 Sleep quality is a complex construct to evaluate, and the
401 discrepancy between subjective and objective measures of
402 sleep may also be explained by PROMs and actigraphy mea-
403 suring different dimensions of sleep quality [6]. It is previously
404 reported that for older adults, perceived sleep quality is different
405 from objective sleep quality [46]. Thus, in the assessment of
406 sleep quality, patients' experience of sleep may be more impor-
407 tant than some of the objective sleep parameters, such as total
408 sleep time. Interestingly, patients' total sleep quality in our
409 study was related to PROMs of sleep onset latency, number
410 of awakenings, and wake after sleep onset, but not to total sleep
411 time. This is similar to findings by Palesh et al. where subjective
412 complaints of sleep disturbances were not associated with total
413 sleep time duration in patients with metastatic colorectal cancer
414 [11]. Also, for our participants, it seems that total subjective
415 sleep quality was more influenced by perceived sleep distur-
416 bances than actual total sleep time. However, the low number of
417 patients included precludes the analysis of other factors (i.e.,
418 anxiety, pain) that could influence sleep quality.

Strengths and limitations

419

420 An important strength of this study is the examination of
421 sleep quality combining PROMs and actigraphy in hospi-
422 talized patients with advanced cancer near end of life. It is
423 noteworthy that there are few, if any, comparable studies
424 in similar populations. However, for reasons described
425 above, PSG was not feasible in this cohort, which resulted
426 in a lack of the gold standard of sleep evaluation [5].
427 Another limitation is that our study only had a duration
428 of one night. However, this was decided to reduce the
429 patient burden, and there is always a balance between
430 the need to get optimal data and the consideration of the
431 participating patients. Finally, the observation night was
432 not standardized with respect to time since admission.
433 Some patients were recruited upon admission, others
434 shortly before discharge. Hence, one may speculate that
435 improved symptom control during hospitalization might
436 have been achieved after a few days and might have im-
437 proved sleep quality. However, the sample size did not
438 permit specific subgroup analyses nor was this not a spe-
439 cific study aim. Understanding sleep experiences of hos-
440 pitalized patients with cancer at the end of life is impor-
441 tant. Therefore, larger studies with a longitudinal design
442 that combine objective and subjective sleep assessments
443 are needed.

Conclusion

444

445 The present study showed that both PROMs and
446 actigraphy documented poor sleep in hospitalized patients
447 with advanced cancer. In individual patients, actigraphy
448 and PROMs of sleep quality differed, reflecting a poten-
449 tial uncertainty related to these methods. Moreover, one
450 third of the patients could not complete PROMs of sleep
451 quality, and objective measures are needed to assess sleep.
452 Our findings illustrate the importance of improving as-
453 sessment of sleep quality and treatment of sleep distur-
454 bance in hospitalized patients with advanced cancer near
455 end of life.

456 **Acknowledgments** We would like to thank all participating patients. In
457 addition, we would like to thank the Department of Palliative Medicine,
458 Cancer Clinic, St. Olav's hospital, Trondheim University Hospital,
459 Trondheim, Norway, for important contribution to patient recruitment
460 and completion of the study. We thank Ragnhild Green Helgås for lan-
461 guage editing.

462 **Funding information** This work was funded by grants from the Central
463 Norway Regional Health Authority awarded by the Liaison Committee
464 for Central Norway (Project number 46083200, year 2015). The funder
465 had no role in the trial design, collection, analysis and interpretation of
466 data, or writing.
467

468 **Compliance with ethical standards**

469 **Conflict of interest** Gunnhild Jakobsen, Morten Engstrøm, Morten
470 Thronæs, Erik Torbjørn Løhre, Peter Fayers, Marianne Jensen
471 Hjermstad, and Pål Klepstad have nothing to disclose. Stein Kaasa is
472 one of the shareholders in Eir Solution A/S and has research funding from
473 Nutricia for other studies. He declares no income, dividend, or financial
474 benefits from the work presented here.

475 **Ethical standards** The study was conducted in accordance with ethical
476 principles in the Declaration of Helsinki and was consistent with ICH/
477 Good Clinical Practice and applicable regulatory requirements. The
478 Regional Committee for Medical and Health Research Ethics, Rec
479 North, approved the study (approval number 2015/1631).

480 **Informed consent** Informed consent was obtained from all individual
481 participants included in the study.

482 **References**

483 1. Jakobsen G, Engstrom M, Fayers P, Hjermstad MJ, Kaasa S, Kloke
484 M, Sabatowski R, Klepstad P (2018) Sleep quality with WHO step
485 III opioid use for cancer pain BMJ supportive & palliative care.
486 Published Online First: 17 July 2018. [https://doi.org/10.1136/](https://doi.org/10.1136/bmjspcare-2017-001399)
487 [bmjspcare-2017-001399](https://doi.org/10.1136/bmjspcare-2017-001399)
488 2. Mercadante S, Adile C, Ferrera P, Masedu F, Valenti M, Aielli F
489 (2017) Sleep disturbances in advanced cancer patients admitted to a
490 supportive/palliative care unit. *Support Care Cancer* 25:1301–1306
491 3. Davidson JR, MacLean AW, Brundage MD, Schulze K (2002)
492 Sleep disturbance in cancer patients. *Soc Sci Med* 54:1309–1321
493 4. Otte JL, Carpenter JS, Manchanda S, Rand KL, Skaar TC, Weaver
494 M, Chernyak Y, Zhong X, Igega C, Landis C (2015) Systematic
495 review of sleep disorders in cancer patients: can the prevalence of
496 sleep disorders be ascertained? *Cancer medicine* 4:183–200
497 5. Chen D, Yin Z, Fang B (2018) Measurements and status of sleep
498 quality in patients with cancers. *Support Care Cancer* 26:405–414
499 6. Madsen MT, Huang C, Gogenur I (2015) Actigraphy for measure-
500 ments of sleep in relation to oncological treatment of patients with
501 cancer: a systematic review. *Sleep Med Rev*. 20:73–83
502 7. Berger AM, Wielgus KK, Young-McCaughan S, Fischer P, Farr L,
503 Lee KA (2008) Methodological challenges when using actigraphy
504 in research. *J Pain Symptom Manage* 36:191–199
505 8. Carney CE, Buysse DJ, Ancoli-Israel S, Edinger JD, Krystal AD,
506 Lichstein KL, Morin CM (2012) The consensus sleep diary: stan-
507 dardizing prospective sleep self-monitoring. *Sleep* 35:287–302
508 9. Good P, Pinkerton R, Bowler S, Craig J, Hardy J (2018) Impact of
509 Opioid Therapy on sleep and respiratory patterns in adults with
510 advanced cancer receiving palliative care. *J Pain Symptom*
511 *Manage* 55:962–967
512 10. Bernatchez MS, Savard J, Savard MH, Aubin M, Ivers H (2017)
513 Sleep-wake difficulties in community-dwelling cancer patients re-
514 ceiving palliative care: subjective and objective assessment. *Palliat*
515 *Support Care* 16:756–766
516 11. Palesh O, Haitz K, Levi F, Bjarnason GA, Deguzman C, Alizeh I,
517 Ulusakarya A, Packer MM, Innominato PF (2017) Relationship
518 between subjective and actigraphy-measured sleep in 237 patients
519 with metastatic colorectal cancer. *Qual Life Res* 26:2783–2791
520 12. Ancoli-Israel S, Liu L, Rissling M, Natarajan L, Neikrug AB,
521 Palmer BW, Mills PJ, Parker BA, Sadler GR, Maglione J (2014)
522 Sleep, fatigue, depression, and circadian activity rhythms in women
523 with breast cancer before and after treatment: a 1-year longitudinal
524 study. *Support Care Cancer* 22:2535–2545

525 13. Liu L, Fiorentino L, Rissling M, Natarajan L, Parker BA, Dimsdale
526 JE, Mills PJ, Sadler GR, Ancoli-Israel S (2013) Decreased health-
527 related quality of life in women with breast cancer is associated with
528 poor sleep. *Behav Sleep Med* 11:189–206
529 14. Dhruva A, Paul SM, Cooper BA, Lee K, West C, Aouizerat BE,
530 Dunn LB, Swift PS, Wara W, Miaskowski C (2012) A longitudinal
531 study of measures of objective and subjective sleep disturbance in
532 patients with breast cancer before, during, and after radiation ther-
533 apy. *J Pain Symptom Manage* 44:215–228
534 15. Beck SL, Berger AM, Barsevick AM, Wong B, Stewart KA,
535 Dudley WN (2010) Sleep quality after initial chemotherapy for
536 breast cancer. *Support Care Cancer* 18:679–689
537 16. Aldridge-Gerry A, Zeitzer JM, Palesh OG, Jo B, Nouriani B, Neri
538 E, Spiegel D (2013) Psychosocial correlates of sleep quality and
539 architecture in women with metastatic breast cancer. *Sleep Med* 14:
540 1178–1186
541 17. Parker KP, Bliwise DL, Ribeiro M, Jain SR, Vena CI, Kohles-Baker
542 MK, Rogatko A, Xu Z, Harris WB (2008) Sleep/wake patterns of
543 individuals with advanced cancer measured by ambulatory
544 polysomnography. *J Clin Oncol* 26:2464–2472
545 18. Palesh O, Aldridge-Gerry A, Zeitzer JM, Koopman C, Neri E,
546 Giese-Davis J, Jo B, Kraemer H, Nouriani B, Spiegel D (2014)
547 Actigraphy-measured sleep disruption as a predictor of survival
548 among women with advanced breast cancer. *Sleep* 37:837–842
549 19. Grutsch JE, Wood PA, Du-Quito J, Reynolds JL, Lis CG, Levin RD,
550 Ann Daehler M, Gupta D, Quito DF, Hrushesky WJ (2011) Validation
551 of actigraphy to assess circadian organization and sleep quality in pa-
552 tients with advanced lung cancer. *J Circadian Rhythms* 9:4
553 20. Yennurajalingam S, Tayjasanant S, Balachandran D, Padhye NS,
554 Williams JL, Liu DD, Frisbee-Hume S, Bruera E (2016)
555 Association between daytime activity, fatigue, sleep, anxiety, de-
556 pression, and symptom burden in advanced cancer patients: a pre-
557 liminary report. *J Palliat Med* 19:849–856
558 21. Teunissen SC, Wesker W, Kruitwagen C, de Haes HC, Voest EE, de
559 Graeff A (2007) Symptom prevalence in patients with incurable
560 cancer: a systematic review. *J Pain Symptom Manage* 34:94–104
561 22. Bausewein C, Simon ST, Benalia H, Downing J, Mwangi-Powell
562 FN, Daveson BA, Harding R, Higginson IJ (2011) Implementing
563 patient reported outcome measures (PROMs) in palliative care—
564 users’ cry for help. *Health Qual Life Outcomes* 9:27
565 23. Kotlinska-Lemieszek A, Paulsen O, Kaasa S, Klepstad P (2014)
566 Polypharmacy in patients with advanced cancer and pain: a
567 European cross-sectional study of 2282 patients. *J Pain Symptom*
568 *Manage* 48:1145–1159
569 24. Kurita GP, Lunderoff L, Pimenta CA, Sjogren P (2009) The cog-
570 nitive effects of opioids in cancer: a systematic review. *Support Care*
571 *Cancer* 17:11–21
572 25. Caraceni A, Hanks G, Kaasa S, Bennett MI, Brunelli C, Cherny N,
573 Dale O, De Conno F, Fallon M, Hanna M, Haugen DF, Juhl G, King
574 S, Klepstad P, Laugsand EA, Maltoni M, Mercadante S, Nabal M,
575 Pigni A, Radbruch L, Reid C, Sjogren P, Stone PC, Tassinari D,
576 Zeppetella G (2012) Use of opioid analgesics in the treatment of
577 cancer pain: evidence-based recommendations from the EAPC.
578 *Lancet Oncol* 13:e58–e68
579 26. Buysse DJ, Ancoli-Israel S, Edinger JD, Lichstein KL, Morin CM
580 (2006) Recommendations for a standard research assessment of
581 insomnia. *Sleep* 29:1155–1173
582 27. Sigurdardottir KR, Kaasa S, Rosland JH, Bausewein C, Radbruch
583 L, Haugen DF, on behalf of P (2014) The European Association for
584 Palliative Care basic dataset to describe a palliative care cancer
585 population: results from an international Delphi process. *Palliat*
586 *Med* 28:463–473
587 28. Akerstedt T, Gillberg M (1990) Subjective and objective sleepiness
588 in the active individual. *Int J Neurosci* 52:29–37

589 29. Buysse DJ, Reynolds CF 3rd, Monk TH, Berman SR, Kupfer DJ
590 (1989) The Pittsburgh Sleep Quality Index: a new instrument for
591 psychiatric practice and research. *Psychiatry Res* 28:193–213
592 30. Carpenter JS, Andrykowski MA (1998) Psychometric evaluation of
593 the Pittsburgh Sleep Quality Index. *J Psychosom Res* 45:5–13
594 31. SOMNOmedics (2019) [https://sommomedics.eu/solutions/sleep_](https://sommomedics.eu/solutions/sleep_diagnostics/stationary_sleep_lab_psg/somnoscreen-plus/)
595 [diagnostics/stationary_sleep_lab_psg/somnoscreen-plus/](https://sommomedics.eu/solutions/sleep_diagnostics/stationary_sleep_lab_psg/somnoscreen-plus/) Accessed
596 02 July 2019
597 32. Boyne K, Sherry DD, Gallagher PR, Olsen M, Brooks LJ (2013)
598 Accuracy of computer algorithms and the human eye in scoring
599 actigraphy. *Sleep Breath* 17:411–417
600 33. Sadeh A (2011) The role and validity of actigraphy in sleep medi-
601 cine: an update. *Sleep Med Rev.* 15:259–267
602 34. Ancoli-Israel S, Cole R, Alessi C, Chambers M, Moorcroft W,
603 Pollak CP (2003) The role of actigraphy in the study of sleep and
604 circadian rhythms. *Sleep* 26:342–392
605 35. Gronli J, Melinder A, Ousdal OT, Pallesen S, Endestad T, Milde
606 AM (2017) Life Threat and sleep disturbances in adolescents: a
607 two-year follow-up of survivors from the 2011 Utoya, Norway,
608 Terror Attack. *J Trauma Stress* 30:219–228
609 36. Groenvold M, Petersen MA, Aaronson NK, Arraras JI, Blazeby
610 JM, Bottomley A, Fayers PM, de Graeff A, Hammerlid E, Kaasa
611 S, Sprangers MA, Bjorner JB (2006) The development of the
612 EORTC QLQ-C15-PAL: a shortened questionnaire for cancer pa-
613 tients in palliative care. *Eur J Cancer* 42:55–64
614 37. Karnofsky DA, Abelmann WH, Craver LF, Burchenal JH (1948)
615 The use of nitrogen mustards in the palliative treatment of carcino-
616 ma. *Cancer* 1:23
617 38. Bland JM, Altman DG (1986) Statistical methods for assessing
618 agreement between two methods of clinical measurement. *Lancet*
619 1:307–310
620 39. Ohayon M, Wickwire EM, Hirshkowitz M, Albert SM, Avidan A,
621 Daly FJ, Dauvilliers Y, Ferri R, Fung C, Gozal D, Hazen N, Krystal
651 A, Lichstein K, Mallampalli M, Plazzi G, Rawding R, Scheer FA,
622 Somers V, Vitiello MV (2017) National Sleep Foundation's sleep
623 quality recommendations: first report. *Sleep health* 3:6–19
624 40. Ma CL, Chang WP, Lin CC (2014) Rest/activity rhythm is related to
625 the coexistence of pain and sleep disturbance among advanced can-
626 cer patients with pain. *Support Care Cancer* 22:87–94
627 41. Delgado-Guay M, Yennurajalingam S, Parsons H, Palmer JL,
628 Bruera E (2011) Association between self-reported sleep distur-
629 bance and other symptoms in patients with advanced cancer. *J*
630 *Pain Symptom Manage* 41:819–827
631 42. Akman T, Yavuzsen T, Sevgen Z, Ellidokuz H, Yilmaz AU (2015)
632 Evaluation of sleep disorders in cancer patients based on Pittsburgh
633 Sleep Quality Index. *Eur J Cancer Care (Engl)* 24:553–559
634 43. Marino M, Li Y, Rueschman MN, Winkelman JW, Ellenbogen JM,
635 Solet JM, Dulin H, Berkman LF, Buxton OM (2013) Measuring
636 sleep: accuracy, sensitivity, and specificity of wrist actigraphy com-
637 pared to polysomnography. *Sleep* 36:1747–1755
638 44. Redeker NS, Pigeon WR, Boudreau EA (2015) Incorporating mea-
639 sures of sleep quality into cancer studies. *Support Care Cancer* 23:
640 1145–1155
641 45. Van Den Berg JF, Van Rooij FJ, Vos H, Tulen JH, Hofman A,
642 Miedema HM, Neven AK, Tiemeier H (2008) Disagreement be-
643 tween subjective and actigraphic measures of sleep duration in a
644 population-based study of elderly persons. *J Sleep Res* 17:295–302
645 46. Landry GJ, Best JR, Liu-Ambrose T (2015) Measuring sleep qual-
646 ity in older adults: a comparison using subjective and objective
647 methods *Front Aging. Neurosci* 7:166
648

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations. 649 650

652 **Affiliations**

653 **Gunnhild Jakobsen**^{1,2} • **Morten Engstrøm**^{3,4} • **Morten Thronæs**^{1,2} • **Erik Torbjørn Løhre**^{1,2} • **Stein Kaasa**^{1,5} •
654 **Peter Fayers**⁷ • **Marianne Jensen Hjermsstad**^{5,6} • **Pål Klepstad**^{1,8,9}

655 ¹ European Palliative Care Research Centre (PRC), Department of
656 Clinical and Molecular Medicine, Faculty of Medicine and Health
657 Sciences, NTNU - Norwegian University of Science and
658 Technology, Postbox 8905, NO-7491 Trondheim, Norway
659 ² Cancer Clinic, St. Olav's Hospital, Trondheim University Hospital,
660 Trondheim, Norway
661 ³ Department of Neuromedicine and Movement Science, Norwegian
662 University of Science and Technology, Trondheim, Norway
663 ⁴ Department of Neurology and Clinical Neurophysiology, St. Olav's
664 Hospital, Trondheim University Hospital, Trondheim, Norway
665 ⁵ European Palliative Care Research Centre, Department of Oncology,
666 Oslo University Hospital and Institute of Clinical Medicine,
667 University of Oslo, Oslo, Norway
⁶ Regional Advisory Unit of Palliative Care, Department of Oncology,
668 Oslo University Hospital, Oslo, Norway
⁷ Division of Applied Health Sciences, University of Aberdeen,
669 Aberdeen, UK
⁸ Department of Anaesthesiology and Intensive Care Medicine, St.
670 Olav's Hospital, Trondheim University Hospital,
671 Trondheim, Norway
⁹ Department of Circulation and Medical Imaging, Faculty of
672 Medicine and Health Sciences, Norwegian University of Science and
673 Technology NTNU, Trondheim, Norway
674
675
676
677