

Analysis of the Clinical Management and Quality of Life of Frail Patients with Cancer and Breakthrough Pain in Clinical Practice.

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Abstract

Background

The purpose of this study was to analyse the clinical management and quality of life of frail patients with cancer, chronic pain and breakthrough pain (BTP) and to assess whether treatment was conditioned by their frailty status.

Methods

This was an observational study in adult frail patients with cancer, chronic background pain and BTP. Outcomes of interest collected include clinical and sociodemographic data, Karnofsky Performance Status, quality of life (EuroQoL-5D-5L), chronic pain and BTP characteristics, as well as treatments administered for their control.

Results

A total of 222 patients were included with a mean age of 68 years (range 24-91), 60.5% men, with a mean Karnofsky of 63.2%. The number of daily episodes of BTP was 3.8 (95% CI 3.3-4.3), with a duration of 34.6 minutes (95% CI 28.8-40.3), and 56.8% had a gradual onset. Opioids were administered to 88.3% of patients for the chronic pain, and to 83.8% for BTP. The treatment's daily doses administered for chronic pain and BTP did not differ from those usually recommended. Quality of life was significantly worse in frail patients with cancer than no frail patients and was related to performance status ($p < 0.001$) and to the social-familial status ($p = 0.045$).

Conclusions

BTP in frail patients with cancer presents with more episodes, of a shorter duration and more gradual onset compared to other patients with BTP, and Quality of life was seriously affected. No relevant differences were seen in the doses or method of administration of treatments for chronic pain and BTP in frail patients with cancer as compared to the standard recommendations for non-frail patients.

Trial registration: Not applicable to the study.

Background

Frailty is defined as a physiologic state with increased vulnerability to stress factors, resulting from the decline in physiologic reserve or dysregulation of multiple physiologic systems [1]. It is a particularly important risk factor for patients with cancer because cancer itself and its treatment adds stressors that can reduce the patient's physiologic reserve. The frequency of frailty in elderly patients with cancer is high, and approximately half of them are frail or pre-frail [2], with a greater risk of postoperative complications, chemotherapy intolerance, disease progression, and death [3-7]. Frailty has been associated in different studies with an increased risk of chemotherapy-related toxicity and poorer tolerance to treatment [8-9]. For these reasons, many studies in patients with different types of cancer now recognize the importance of the evaluation of frailty for the stratification of risk for patients in the selection of the cancer therapy and for the decision of pharmacological or non-pharmacological treatment like radiotherapy and brachytherapy [7,10-12]. Furthermore, the relationship between frailty and the prognosis of the tumour process has been widely demonstrated, and is, therefore, a factor that should be considered in these patients [13]. Therefore, the International Society of Geriatric Oncology (SIOG) recommends frailty assessment in all cancer patients over 70 years of age to help the oncologist make decisions about the most appropriate treatment for the patient [10].

Most patients with cancer suffer chronic pain, with a prevalence between 33% and 64%, reaching over 70% in patients in advanced stages of the disease [14]. Furthermore, patients with chronic pain may experience, at some point in their course, the onset of breakthrough pain (BTP), which is defined as a "transient exacerbation of pain occurring spontaneously or related to a specific predictable or unpredictable trigger, despite stable and adequately controlled background pain" [11,16].

The incidence of BTP varies across studies between 35-95% [17]. In cancer patients, the prevalence of BTP increases as the disease progresses and can reach up to 80% [14]. This frequency increases in patients with low performance status and advanced stages of the disease and is an indicator of poor prognosis [18].

Recognition of frailty status in patient with cancer conditions the decision of the type of treatment for the cancer and its dose, and it is related to its prognosis. However, in the group of frail patients with chronic pain and BTP, it is not known whether the choice of analgesic therapy is conditioned by the presence of frailty. In this regard, the objectives of this study were to analyse the clinical management and quality of life of frail patients with chronic pain and BTP and the treatments administered for pain control in standard clinical practice.

Methods

A cross-sectional observational study was conducted involving 29 investigators from sites in 12 Spanish provinces, including 17 medical oncology units, six pain units, three palliative care units, two geriatric departments, and one home hospitalization unit.

Patients were included from 27-June-2018 to 13-May-2019. The study was approved by the Medicinal Product Research Ethics Committee of HM Hospitales de Madrid (2-April-2018; Minutes 132).

Written informed consent was obtained from all patients. The study protocol was in accordance with the ethical standards described in the Declaration of Helsinki.

Patient selection

Patients were consecutively selected from those who attended to the clinics and who met the screening criteria, completing a single visit. No treatment was administered as a requirement of the study.

The study population consisted of frail patients with a history of controlled background chronic pain and a diagnosis of BTP. Patients with cancer were analysed in this report.

The Frail scale was used to identify frail patients. This is a validated scale consisting of five questions corresponding to a domain: Fatigue, Resistance, Ambulation, Illness and Weight Loss. Each domain is scored with one point. Patients were classified as frail when they scored three or more points, over five [19].

The Davies criteria and algorithm were used to diagnose BTP [16]. This algorithm determines the existence of BTP with: 1) Presence of baseline pain as persistent pain for 12 or more hours per day, in the week prior to the assessment (or that would exist if analgesics were not taken); 2) Adequately controlled background pain: no pain or mild pain (not moderate or severe) for 12 or more hours per day, during the week prior to the assessment; 3) Presence of transient pain exacerbations: severe or unbearable, with a visual analogue scale score for pain intensity greater than seven points over ten points, occurring spontaneously or related to a specific, predictable or unpredictable trigger.

The inclusion criteria were: 1) Adult men and women; 2) Frail patients with ≥ 3 points on the Frail scale [19]; 3) Patients with controlled background pain with a visual analogue scale score for pain intensity ≤ 4 over ten points. 4) Diagnosis of BTP; 5) Patients who have signed the written informed consent to participate in the study.

Evaluation of study objectives

To assess the primary objective, the treatments received by the patient for chronic pain and BTP and their doses and administration route were recorded.

Information was collected on age, sex, race, weight, height, body mass index (BMI) and occupational status.

Social and family status was assessed using the Gijón scale [20,21]. It is a hetero-administered scale consisting of five variables (family situation, economic situation, housing, social relations, and social support), each with five possible categories. The categories are scored from 0 to 4 points, resulting in an overall score ranging from 0 to 20 points. The cut-off point for the detection of social risk is from 16 points on.

Medical history information and the patient's performance status (Karnofsky Performance Status) was recorded. The Karnofsky scale classifies patients into ten categories (0 and 100 points).

The date of cancer diagnosis (date of diagnostic biopsy) and the organ affected by cancer were recorded.

The main characteristics of background pain and BTP were recorded.

Quality of life was assessed using the EuroQoL-5D-5L, a generic questionnaire consisting of five questions and a visual analogue scale with values between 0-100 millimetres (EQ-VAS). Each question has five degrees and evaluates one dimension: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression [22].

Determination of sample size

The most restrictive variable for sample size determination was quality of life. The reference value for EQ-VAS in the Spanish population over 18 years of age is 75.0 points (SD 0.4) [23,24]. A sample of 222 patients would allow for the description of quality of life with a precision of 0.05 points and the power to find differences was 96% with a two-sided alpha error of 0.05 (Sample Power, IBM-SPSS).

Statistical analysis

A descriptive analysis was performed of frequencies and percentages for the qualitative variables, with calculation of the mean, standard deviation, minimum, maximum values, and 95% confidence intervals, for quantitative variables.

Between-group comparisons were made using the Fisher test or the Chi² test if the variables were qualitative, and the Student's t-test or Wilcoxon test was used for quantitative variables.

A multivariate linear regression analysis was performed to explore the relationship between the EQ-VAS score and different patient characteristics: age, sex, Gijón scale score, BMI, Karnofsky Performance Status score, Frail scale score characteristics of BTP, time since diagnosis and location of cancer. Statistical significance was considered at a value of 0.05. The IBM-SPSS version 27.0 statistical package was used throughout. The STROBE guidelines (www.strobe-statement.org) were followed to present the results of cross-sectional studies [2].

Results

A total of 240 patients participated in the study, with 222 patients with cancer selected for this analysis Table 1 shows their anthropometric, sociodemographic, and clinical characteristics. The percentage of patients with a Karnofsky score under 50 was 11.3% (n=25).

A total of 96.8% (n=215) received treatment for some comorbidity. About 79.7% (n=177) of the patients with cancer (n=222) were receiving treatment for cancer. The median time since cancer diagnosis was 14.7 months.

The chronic pain was related to the cancer in 86.5% (n=192). Chronic pain was caused by spinal problems in 5% (n=11), osteoarthritis in 2.3% (n=5), peripheral neuropathy in 1.8% (n=4), trauma in 0.5% (n=1), and other causes in 4.1% (n=9). Chronic pain was mixed in 34.7% of patients (n=77), somatic in 28.8% (n=64), visceral in 23% (n=51), and neuropathic in 13.5% (n=30).

Table 2 describes the main characteristics of the BTP with no differences between patients with or without cancer. The first BTP episode was explored in 60 patients (26%) at the study visit.

Frailty

All patients were frail, with a mean score on the Frail scale of 3.9 points (95% CI 3.8-4). There were no significant differences in the scores per cancer location.

Quality of life

The mean EQ-VAS score was 51.3 mm (95% CI 48.5-54), with a median of 50 mm. Figure 1 shows the distribution of patients in the categories of the five dimensions of the quality-of-life questionnaire. No significant differences were observed in the EQ-VAS score between frail patients or according to the cancer location (Figure 2).

Treatments for pain

For the treatment of background pain, 27 different drugs were administered in 215 patients with a total of 316 administrations. Table 3 details the drugs used and summarizes the mean daily doses administered to patients by compound and route of administration. A total of 65.8% of the active substance administered were opioids (208/316) and they were administered to 196 patients (88.3%).

The drugs used for the treatment of BTP, the doses administered, and the administration routes are described in Table 4. A total of 11 different active substances were administered in 196 patients with a total of 219 administrations of which 196 (89.5%) were opioids administered to 83.8% of patients (186/222).

Factors related to Quality of life

In multivariate regression analysis, the higher the Gijón social-familial evaluation scale score (plus social exclusion), the EQ-VAS quality of life score worsened in a statistically significant manner ($p=0.045$), so that one point higher on the Gijón scale represented a reduction in quality of life of 0.9 mm (95% CI 0.02-1.8). It was also seen that the lower the Karnofsky score, the quality-of-life score in EQ-VAS significantly worsened manner ($p<0.001$), so that ten points lower on the Karnofsky scale implied a 4 mm impairment in quality of life (95% CI 0.2-0.5).

Discussion

This observational study provides, for the first time, an overview of the clinical, social-health, and quality of life characteristics of frail patients with cancer, chronic pain and BTP together with their management in real life in Spain. It also evaluated the analgesic treatment received by patients for chronic pain and BTP and whether their choice was conditioned by the patients' own frailty status.

Characteristics of BTP in frail cancer patients have not been described previously. However, Mercadante et al. recently published a large study in 4,016 patients with cancer and BTP [26]. A comparison between our study and the latest encountered interesting results. Frail patients reported significantly greater mean number of BTP episodes per day than those in the reference study, 3.8 (95% CI 3.3-4.3) versus 2.4 (SD 1.4). The duration of BTP episodes reported by frail patients was shorter, 34.6 minutes (95% CI 28.8-40.3) versus 43.3 minutes (SD 36.9). The onset of BTP was sudden (short onset) in 43.2% of our frail patients, while this type of onset was seen in 68.9% of patients in the reference study. Even though the assessment of the BTP intensity was measured differently in both studies, we observed severe or unbearable BTP in 17.1% of our frail patients, and Mercadante et al. reported a mean intensity of 7.5 over 10 points [26]. Furthermore, in another study conducted in 1,000 cancer patients, Davies et al reported severe BTP in 62.4% of patients. Similar results were observed among frail patients (62.6%) in our study [27].

Predictable BTP was found in 35.1% of our frail patients, alike data (30.5%) described by Mercadante et al.³⁰ Difference on BTP mechanism was observed in both populations. Neuropathic pain was more frequently observed among our frail patients (16.7% vs 8.1%), while mixed pain was more common in those cancer patients of the referred study (71.8%, vs 31.1%) [26].

The higher the number of BTP episodes, the shorter the duration and the more gradual onset seen in frail patients. A pathophysiological process related to frailty status might underly these observations since a greater frequency of BTP episodes has been reported in patients with worse performance status [27]. Interestingly, the performance status of patients observed in both studies was similar, 63.2 (95% CI 61-65.4) versus 61.8 (SD 18.73) [26].

Among our frail patients, 79.7% of them were in active treatment for cancer, likewise 78% of patients in the reference study. This situation should be considered, since receiving this type of treatment could condition the administration of other treatments, such as, for example, for background pain and BTP [26].

Drugs for the treatment of chronic pain and BTP administrated to frail patients did not substantially differ on their doses and the frequency of administration (Tables 3 and 4), to the standard treatment for chronic pain. Regarding BTP treatment, in our study, 83.8% of frail patients with cancer received opioid treatment for BTP control, just as patients with cancer included in other studies [26,27]. Transmucosal immediate release fentanyl was administered to 68.5% of frail patients with cancer, the treatment of choice for BTP in cancer patients [14]. The doses of the treatments were within the range recommended in their prescribing information. On the other hand, our attention was caught by the fact that 10 patients used drugs that are not usually indicated for BTP but for basal pain therapy in standard practice, such as dexketoprofen, ibuprofen, metamizole or paracetamol, frequently complementary to the opioids administrated for the background chronic pain. In the Table 4 the number of administrations for such treatments were 28, but only 6 patients received only these drugs.

We observed BTP interference with daily activities in 93.7% of frail patients (Figure 1) while Mercadante et al reported that in 86% of their patients [32]. Furthermore, they found that age, Karnofsky, BTP severity, short onset, and longer duration of BTP significantly interfered with daily activities of cancer patients. In our study, we were able to relate a poorer quality of life score (EQ-VAS) to a worse Karnofsky score in frail patients, already described in different studies [26,28,29]. In addition, our study found a significant association between quality of life and social exclusion in frail patients with cancer but due to the cross-sectional design we cannot know which one was the first event.

The EuroQoL-5D-5L questionnaire conducted in healthy Spanish population revealed that the 65–74-year-old age group reported problems with mobility (29.3%), self-care (10.4%), daily activities (19.1%), pain (43%), and anxiety or depression (20%) [30]. According to our study, frail cancer patients with BTP seem to be more impaired, as 93.2% of frail patients experienced greater mobility problems, 74.2% self-care problems, 93.7% problems with activities of daily living, 98.2% pain, and 81.4% anxiety or depression (Figure 1). Meanwhile, data observed in a review of 32 studies in patients with cancer shows impairment rates for mobility ranging from 2-60%, self-care 2-50%, daily activities 15-100%, pain 12-80%, and anxiety or depression 13-100%, i.e., there is greater deterioration in frail patients in our study in three of the five dimensions [31].

The mean EQ-VAS score, as a measure of patient-perceived quality of life, was 51.3 mm (95% CI 48.5-54) in frail patients with BTP in our study, values well below those seen in the general Spanish population of the same age group, 69 mm (Figure 2) [23]. In addition, this value is much more affected than in cancer patients, analysed in a review of 32 studies, who presented a value of 68.6 mm [31].

It is known that the occurrence of BTP has a significant impact on patient quality of life [32]. In the case of patients in our study, the low quality of life levels observed could be due to both BTP and frailty status, or to the interaction of both factors.

In Spain, the prevalence of frailty has been studied in six cohort studies, ranging from 2.4% to 27.3% in patients over 65 years of age [24]. However, in the setting of our study, conducted mainly in medical oncology units and in some pain and geriatric units, the prevalence of frailty is much higher [7,10,13], so the results of this study are relevant to standard clinical practice in these units.

This study has several limitations inherent to the cross-sectional observational design, which prevents causal relationships from being established. Patients were classified as frail using the Frail scale [19], following national recommendations [24], so frail patients could be classified differently from other classification scales not based on the Fried criteria [1]. As this is a cross-sectional study, patients were included at different follow-up times after the onset of BTP. For this reason, we could not analyse which were the first treatments for BTP in frail patients or their doses, which could differ at the start, and then be adjusted. Other treatments for patients with cancer such radiotherapy and brachytherapy play an important role in this setting of patients for the treatment of pain with many advantages in elderly and frail patients, but not collected in our study that was focused on pharmacological treatment [11,12]

Conclusions

This study concluded that some characteristics of BTP in frail patients with cancer differ from those reported in other studies. In addition, it has been seen that the treatments used for both chronic pain and BTP in frail patients are like those commonly prescribed in non-frail patients. Quality of life in frail patients has also been found to be severely impaired as compared to the population of patients with cancer and was related to a poorer performance status of the patient and poorer social-familial status. This relationship between frailty and impaired quality of life highlights the importance of the frailty assessment in all patients with BTP.

Abbreviations

BMI: Body mass index

BTP: Breakthrough pain

CI: Confidence Interval

EQ-VAS: Visual analogue scale of the EuroQoL-5D-5L Quality of life questionnaire

QoL: Quality of life

SD: Standard deviation

SIOG: International Society of Geriatric Oncology

Declarations

Ethics approval and consent to participate

The study was approved by the Medicinal Product Research Ethics Committee of HM Hospitales de Madrid (2-April-2018; Minutes 132).

Written informed consent was obtained from all patients. The study protocol was in accordance with the ethical standards described in the Declaration of Helsinki, and all participants' privacy rights were respected.

Consent for publication

Not applicable.

Availability of data and material

The study data is available upon reasonable request to the corresponding author.

Competing interest

GSG, JPC and SFS received payment from Kyowa Kirin Farmacéutica, S.L. for their participation in the design and coordination of the study. AJJL, ACA and IHG are employees at Kyowa Kirin Farmacéutica, S.L. BSL was contracted by Kyowa Kirin Farmacéutica, S.L. for project management. The rest of the authors declare that they have no conflicts of interest with the study results.

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Author's contributions

GSG, JPC, SFS, contributed to the study concepts, the study design, data acquisition and manuscript review. AJJL, ACA and IHG contributed to the study concepts and design and the manuscript review. BSL contributed to the study design, quality control of data, statistical analysis, and manuscript preparation.

All authors have read and approved the manuscript.

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References

1. Fried LP, Ferrucci L, Darer J, Williamson JD, Anderson G. Untangling the concepts of disability, frailty, and comorbidity: implications for improved targeting and care. *J Gerontol A Biol Sci Med Sci* 2004; 59(3):255–63. <https://doi.org/10.1093/gerona/59.3.m255>.

2. Mohile SG, Xian Y, Dale W, Fisher SG, Rodin M, Morrow GR, et al. Association of a cancer diagnosis with vulnerability and frailty in older Medicare beneficiaries. *J Natl Cancer Inst* 2009;101: 1206-15. <https://doi.org/10.1093/jnci/djp239>.
3. Clough-Gorr KM, Stuck AE, Thwin SS, Silliman RA. Older breast cancer survivors: geriatric assessment domains are associated with poor tolerance of treatment adverse effects and predict mortality over 7 years of follow-up. *J Clin Oncol* 2010;28:380-6. <https://doi.org/10.1200/JCO.2009.23.5440>.
4. Clough-Gorr KM, Thwin SS, Stuck AE, Silliman RA. Examining five- and ten-year survival in older women with breast cancer using cancer-specific geriatric assessment. *Eur J Cancer* 2012;48:805-12. <https://doi.org/10.1016/j.ejca.2011.06.016>.
5. Makary MA, Segev DL, Pronovost PJ, Syin D, Bandee-Roche K, Patel P, et al. Frailty as a predictor of surgical outcomes in older patients. *J Am Coll Surg* 2010;210:901-8. <https://doi.org/10.1016/j.jamcollsurg.2010.01.028>.
6. Tan KY, Kawamura YJ, Tokomitsu A, Tang T. Assessment for frailty is useful for predicting morbidity in elderly patients undergoing colorectal cancer resection whose comorbidities are already optimized. *Am J Surg* 2012;204:139-43. <https://doi.org/10.1016/j.amjsurg.2011.08.012>.
7. Handforth C, Clegg A, Young C, Simpkins S, Seymour MT, Selby PJ et al. The prevalence and outcomes of frailty in older cancer patients: a systematic review. *Ann Oncol* 2015;26:1091-1101. <https://doi.org/10.1093/annonc/mdu540>.
8. Hurria A, Togawa K, Mohile SG, Owusu C, Klepin HD, Gross CP, et al. Predicting chemotherapy toxicity in older adults with cancer: a prospective multicenter study. *J Clin Oncol* 2011;29:3457-65. <https://doi.org/10.1200/JCO.2011.34.7625>.
9. Hamaker ME, Seynaeve C, Wymenga AN, van Tinteren H, Nortier JWR, Maartense E, et al. Baseline comprehensive geriatric assessment is associated with toxicity and survival in elderly metastatic breast cancer patients receiving single-agent chemotherapy: results from the OMEGA study of the Dutch Breast Cancer Trialists' Group. *Breast* 2014;23:81-7. <https://doi.org/10.1016/j.breast.2013.11.004>.
10. Wildiers H, Heeren P, Puts M, Topinkova E, Janssen-Heijnen MLG, Extermann M et al. International Society of Geriatric Oncology consensus on geriatric assessment in older patients with cancer. *J Clin Oncol* 2014; 32:2595-2603. <https://doi.org/10.1200/JCO.2013.54.8347>.
11. Lancellota V, Kovács G, Tagliaferri L, Perrucci E, Colloca G, Valentini V, Aristei C. Age is not a limiting factor in interventional radiotherapy (brachytherapy) for patients with localized cancer. *Biomed Research international*;Vol 2018. Article ID 2178469. <https://doi.org/10.1155/2018/2178469>
12. Lancellota V, Kovács G, Tagliaferri L, Perrucci E, Reimbielak A, Stingeni L et al. The role of personalized interventional radiotherapy (brachytherapy) in the management of older patients with nono-melanoma skin cancer. *J Geriatr Oncol* 2019;10(3):514-7. <https://doi.org/10.1012/j.jgo.2018.09.009>
13. Ethun CG, Bilan MA, Jani AB, Maithel SK, Ogan K, Master VA. Frailty and Cancer: Implications for Oncology Surgery, Medical Oncology, and Radiation Oncology. *CA Cancer J Clin* 2017;67:362–77. <https://doi.org/10.3322/caac.21406>.
14. Fallon M, Giusti R, Aielli F, Hoskin P, Rolke R, Sharma M, et al. Management of cancer pain in adult patients: ESMO Clinical Practice Guidelines. *Ann Oncol* 2018; 29 (supplement_4): iv166-iv191. <https://doi.org/10.1093/annonc/mdy152>.
15. Portenoy RK, Hagen NA. Breakthrough pain: definition, prevalence and characteristics. *Pain* 1990;41:273-81. [https://doi.org/10.1016/0304-3959\(90\)90004-w](https://doi.org/10.1016/0304-3959(90)90004-w).
16. Davies AN, Dickman A, Reid C, Stevens AM, Zeppetella G, Science Committee of the Association for Palliative Medicine of Great Britain and Ireland. The management of cancer-related breakthrough pain: recommendations of a task group of the Science Committee of the Association for Palliative Medicine of Great Britain and Ireland. *Eur J Pain* 2009; 13(4): 331-8. <https://doi.org/10.1016/j.ejpain.2008.06.014>.
17. Gómez-Batiste X, Madrid F, Moreno F, Gracia A, Trelis J, Nabal M, et al. Breakthrough cancer pain: prevalence and characteristics in patients in Catalonia, Spain. *J Pain Symptom Manage* 2002;24:45-52. [https://doi.org/10.1016/s0885-3924\(02\)00421-9](https://doi.org/10.1016/s0885-3924(02)00421-9).
18. Nikolaichuck CL, Fainsinger RL, Lawlor PG. A validation study of a pain classification system for advanced cancer patients using content experts: the Edmonton Classification System for Cancer Pain. *Palliat Med* 2005;19:466-76. <https://doi.org/10.1191/0269216305pm1055oa>.
19. Morley JE, Malmstrom TK, Miller DK. A simple frailty questionnaire (FRAIL) predicts outcomes in middle aged African Americans. *J Nutr Health Aging* 2012; 16(7):601–8. <https://doi.org/10.1007/s12603-012-0084-2>.
20. Diaz ME, Domínguez O, Toyos G. Resultados de la aplicación de una escala de valoración sociofamiliar en atención primaria. *Rev Esp Geriatr Gerontol* 1994;29:239-245.
21. Alarcón MT, González JI. La escala sociofamiliar de Gijón, instrumento útil en el hospital general. *Rev Esp Geriatr Gerontol* 1998;33:178-9.
22. Herdman M, Gudex C, Lloyd A, Janssen MF, Kind P, Parkin D et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res* 2011 Dec;20(10):1727-36. <https://doi.org/10.1007/s11136-011-9903-x>.
23. Szende A, Janssen B, Cabases J Editors, 2014. Self-reported population health: An international perspective based on EQ-5D. https://doi.org/10.1007/978-94-007-7596-1_1.
24. Ministerio de Sanidad, Servicios Sociales e Igualdad. Documento de consenso sobre prevención de fragilidad y caídas en la persona mayor. Estrategia de Promoción de la Salud y Prevención en el SNS, 2014. https://www.mscbs.gob.es/profesionales/saludPublica/prevPromocion/Estrategia/docs/FragilidadyCaidas_personamayor.pdf. [accessed 12 February 2021].
25. The Plos Medicine Editors. Observational studies: Getting clear about transparency. *PloS Med* 2014;11(8):e1001711. <https://doi.org/10.1371/journal.pmed.1001711>.

26. Mercadante S, Marchetti P, Cuomo A, Caraceni A, Mediati RD, Velluci R et al. Factors influencing the clinical presentation of breakthrough pain in cancer patients. *Cancers (Basel)* 2018;10:175; <https://doi.org/10.3390/cancers10060175>.
27. Davies A, Buchanan A, Zeppetella G, Porta-Sales J, Likar R, Weismayr W, et al. Breakthrough cancer pain: An observational study of 1000 European oncology patients. *J of Pain Symptom Manage* 2013;46 (5):619-28. <http://dx.doi.org/10.1016/j.jpainsymman.2012.12.009>.
28. Baier P, Ihorst G, Wolff-Vorbeck G, Hull M, Hopt U, Deschler B. Independence and health related quality of life in 200 onco-geriatric surgical patients within 6 months of follow-up: Who is at risk to lose?. *Eur J Surg Oncol* 2016; 42(12):1890–7. <https://doi.org/10.1016/j.ejso.2016.07.013>.
29. Faller H, Brähler E, Härter M, Keller M, Schulz H, Wegscheider K, et al. Performance status and depressive symptoms as predictors of quality of life in cancer patients. A structural equation modelling analysis. *Psychooncology* 2015; 24(11):1456–62. <https://doi.org/10.1002/pon.3811>.
30. Ministerio de Sanidad, Servicios Sociales e Igualdad. Encuesta Nacional de Salud. España 2011/12. Calidad de vida relacionada con la salud en adultos: EQ-5D-5L. Serie Informes monográficos nº 3. Madrid: Ministerio de Sanidad, Servicios Sociales e Igualdad, 2014. http://www.mscbs.gob.es/estadEstudios/estadisticas/encuestaNacional/encuestaNac2011/informesMonograficos/CVRS_adultos_EQ_5D_5L.pdf. [accessed 12 February 2021].
31. Pickard AS, Wilke C, Lin Hsiang-Wen, Lloyd A. Impact of cancer on Health Related Quality of Life: Evidence using the EQ-5D. Barcelona 2006 EuroQol Proceedings, 26-08-2006. <https://euroqol.org/search-for-eq-5d-publications/> [accessed 12 February 2021].
32. Fortner BV, Okon TA, Portenoy RK. A survey of pain-related hospitalizations, emergency department visits, and physician office visits reported by cancer patients with and without history of breakthrough pain. *J Pain* 2002; 3: 38-44. <https://doi.org/10.1054/jpai.2002.27136>.

Tables

Table 1. Sociodemographic and clinical data of frail patients with cancer and breakthrough pain.

Sociodemographic or clinical variable (n=222)		% (n) or mean (95% CI)
Age		68.2 (66.6-69.8)
Gender	Male	135 (60.8)
	Female	39.2 (87)
Race	Caucasian	80.2 (178)
	Hispanic	19.4 (43)
	Black	0.4 (1)
Employment status	Employee	2.3 (5)
	Temporary work disability	12.6 (28)
	Permanent work disability	15.8 (35)
	Retirees	69.3 (154)
Gijón Scale	Overall score (0-20)	4.9 (4.5-5.3)
	No social-familial risk (<16)	99.6 (221)
	With social-familial risk (≥16)	0.4 (1)
Body Mass Index (kg/m²)		25.1 (24.2-25.7)
Classification according to body mass index (BMI) (n=229)	Cachexic (BMI <20 kg/m ²)	14.9 (33)
	Normal (BMI ≥20 and <25 kg/m ²)	37.4 (83)
	Overweight (BMI ≥25 and <30 kg/m ²)	31.1 (69)
	Obese (BMI ≥30 kg/m ²)	16.6 (37)
Karnofsky performance status		63.2 (61-65.4)
Time since cancer diagnosis (months)		33.9 (27.3-40.5)
Primary cancer location	Lung	33 (73)
	Gastrointestinal	23.5 (52)
	Breast	7.2 (16)
	Prostate	5 (11)
	Other	31.5 (70)

Table 2. Characteristics of breakthrough pain in frail patients with cancer.

Characteristics of breakthrough pain (n= 222)		% (n) or mean (95% CI)
Number of daily episodes		3.8 (3.3-4.3)
Duration of episodes (minutes)		34.6 (28.8-40.3)
Location	Lumbar	30.2 (67)
	Abdomen	22.5 (50)
	Chest	21.2 (47)
	Head	11.7 (26)
	Other	14.4 (32)
Onset	Gradual	56.8 (126)
	Sudden	43.2 (96)
Intensity	Mild	3.2 (7)
	Moderate	34.2 (76)
	Severe	45.5 (101)
	Unbearable	17.1 (38)
Incidental	No	52.5 (116)
	Yes	47.5 (105)
Predictable	No	64.9 (144)
	Yes	35.1 (78)
Time of day when it appears	At night	12.6 (28)
	During the day	36.9 (82)
	Unrelated	50.5 (112)
Type of pain	Somatic	27.5 (61)
	Visceral	24.8 (55)
	Neuropathic	16.7 (37)
	Mixed	31.1 (69)

Table 3. Drugs administered to frail patients with cancer and breakthrough pain for the treatment of chronic pain.

Active ingredient for chronic pain	Administration route	Daily frequency	Daily dose	
			N ^a	Mean
Aceclofenac	Oral	Every 12 h	1	200 mg
Amitriptyline	Oral	Every 24 h	1	10 mg
Baclofen	Oral	Every 24 h	1	10 mg
Butylscopolamine	Parenteral	Every 6 h	1	40 mg
Buprenorphine	Topical/Transdermal	Every 72 h	2	36.8 µg
Clonazepam	Oral	Every 8 h	1	1.5 mg
Dexketoprofen	Oral	Every 12 h	1	50 mg
		Every 8 h	3	75 mg
	Parenteral	Every 8 h	1	75 mg
Dexamethasone	Oral	Every 24 h	11	3.4 mg
		Every 12 h	1	8 mg
		Every 8 h	1	12 mg
	Parenteral	Every 24 h	1	12 mg
		Every 8 h	2	12 mg
Duloxetine	Oral	Every 24 h	2	45 mg
Eslicarbazepine	Oral	Every 24 h	1	800 mg
Etoricoxib	Oral	Every 24 h	2	90 mg
Fentanyl	Respiratory/inhaled	Every 8 h	1	300 µg
		Every 3 h	1	500 µg
	Topical/Transdermal	Every 24 h	37	65.5 µg
		On demand	10	56.3 µg
		Every 48 h	1	50 µg
		Every 72 h	64	14.6 µg
Gabapentin	Oral	Every 24 h	1	600 mg
		Every 8 h	7	1200 mg
Ibuprofen	Oral	Every 8 h	1	1800 mg
Lacosamide	Oral	Every 12 h	1	200 mg
Methadone	Oral	Every 8 h	1	15 mg
Metamizole	Oral	Every 12 h	1	0.8 mg
		Every 8 h	18	1826 mg
	Parenteral	Every 8 h	3	6 mg
Morphine	Oral	Every 24 h	2	65 mg
		Every 12 h	31	85.5 mg
		Every 8 h	5	486 mg
	Parenteral	Every 24 h	6	108.5 mg
		On demand	2	55 mg
Naproxen	Oral	Every 12 h	2	700 mg
Oxycodone	Oral	Every 12 h	5	68 mg
		Every 8 h	2	22.5 mg
		Every 6 h	1	20 mg

Oxycodone/Naloxone	Oral	Every 24 h	2	6.3 mg
		Every 12 h	12	42.5 mg
		Every 8 h	1	90 mg
Paracetamol	Oral	Every 8 h	20	2797 mg
		Every 3 h	1	5000 mg
	Parenteral	Every 8 h	5	2400 mg
Paracetamol/codeine	Oral	Every 8 h	1	3000 mg
Prednisone	Oral	Every 24 h	1	5 mg
Pregabalin	Oral	Every 24 h	4	43.8 mg
		Every 12 h	10	160 mg
		Every 8 h	1	75 mg
Tapentadol	Oral	Every 24 h	2	150 mg
		Every 12 h	10	155 mg
Tramadol	Oral	Every 12 h	1	150 mg
		Every 8 h	6	156 mg
		Every 6 h	1	400 mg
	Parenteral	Every 12 h	1	200 mg
Tramadol/paracetamol	Oral	Every 8 h	1	225 mg

a. N: number of patients with the treatment, patients received one or more treatments.

Table 4. Drugs administered to frail patients with cancer for the treatment of breakthrough pain.

Active ingredient for breakthrough pain	Route	Unit dose			Unit dose in the Mercadante study[26]
		N ^a	Mean	(95% CI)	Mean dose (SD)
Dexketoprofen	Oral	2	25 mg	-	-
Duloxetine	Oral	1	30 mg	-	-
Fentanyl	Oral	8	190 µg	(71.1-309)	234.6 (183.1) µg
	Sublingual	81	161.7 µg	(139-184)	231.4 (171.1) µg
	Nasal with pectin	59	155.9 µg	(130-182)	167.7 (125.7) µg
	Nasal without pectin	1	100 µg	-	100 (50.7) µg
	Transdermal	3	29 µg	(-19-77)	-
Ibuprofen	Oral	1	400 mg	-	-
Metamizole	Oral	5	231.2 mg	(-159-621)	-
	Parenteral	4	2 mg	(2-2)	-
Metamizole/ Scopolamine	Parenteral	1	2500/20 mg	-	-
Morphine	Oral	12	11.7 mg	(8-15)	11.8 (8.2) mg
	Parenteral	17	10.7 mg	(7-14)	8.2 (6.1) mg
Oxycodone	Oral	6	9.2 mg	(-2-20)	-
Oxycodone/Naloxone	Oral	1	10 mg	-	-
Paracetamol	Oral	6	683.3 mg	(288-1078)	-
	Parenteral	3	1000 mg	(1000-1000)	-
Tramadol	Oral	6	54.2 mg	(44-65)	-

a. N: number of patients with the treatment.

Figures

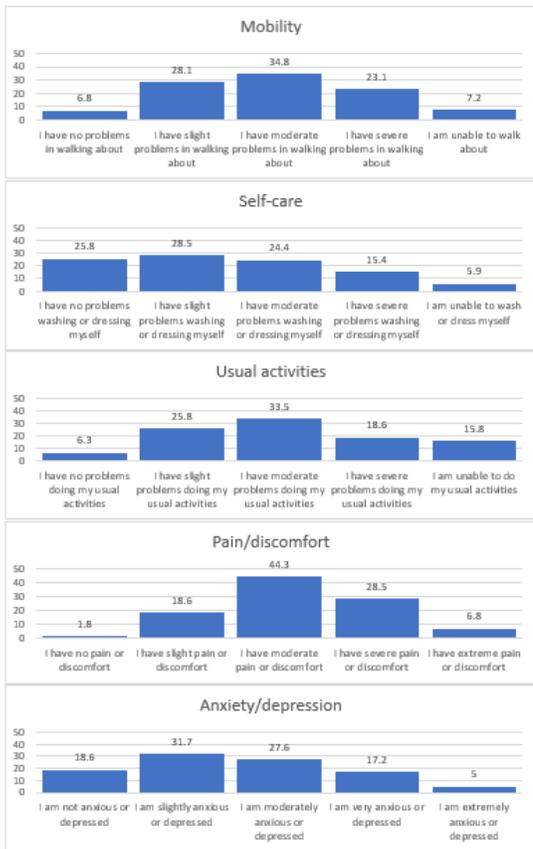


Figure 1
 Distribution of patients in the categories of the five dimensions of the EuroQoL-5D-5L health-related quality of life questionnaire in frail patients with cancer and breakthrough pain.

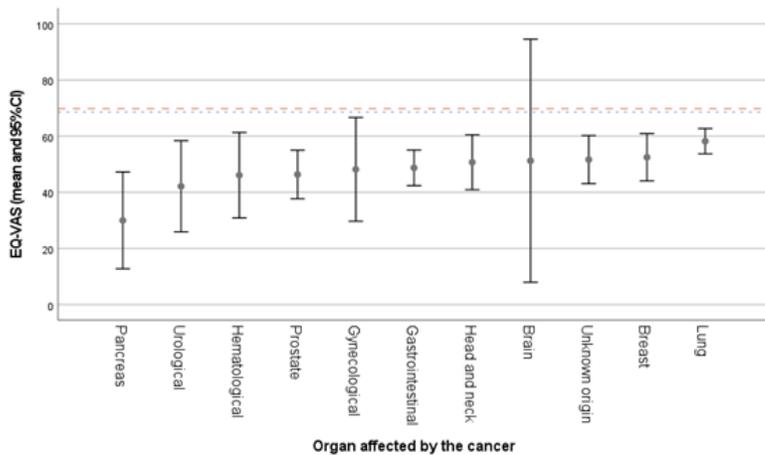


Figure 2
 Mean score of the quality-of-life EQ-VAS in frail patients with cancer and breakthrough pain. Comparison by cancer location and with the general healthy population for the same age group. — — — Mean EQ-VAS score in the general healthy population of the 65-74 years-old age group [30]. - - - - - Mean EQ-VAS score for patients with cancer [31]. EQ-VAS: EuroQoL-5D-5L health-related quality of life questionnaire visual analogue scale; Value 0 means worst quality of life and value 100 means the best quality of life