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Pain management in cancer patients receiving radiotherapy: GORVAMUR study, a prospective, observational, epidemiological study

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ABSTRACT

Objectives: To assess breakthrough pain management in patients at radiation oncology and its impact on pain control in these patients, as well as the tolerability of the analgesic treatments used and the satisfaction and impact on the quality of life of patients.

Material and methods: An epidemiological, observational, prospective, multicentre study carried out in patients diagnosed with cancer and with cancer pain treated with a 3rd step analgesic therapy who had begun radiotherapy treatment (RT) susceptible to modification by an oncologist, for pain control. Patients were recruited from 15 Radiation Oncology Services centres from the regions of Valencia and Murcia between May 2013 and December 2014. Patient data collected included: demographic data, basal cancer process characterization and baseline pain, and information on basal analgesic treatment and RT employed. Pain level was recorded at 1 and 3 months by assessing: the change in the dimension of Brief Pain Inventory (BPI) pain and the amount of pain caused by episodes of breakthrough pain, the level of satisfaction, the quality of life (EQ-5D), and the tolerability to analgesic treatment.

Results: Patients included in the analysis (n = 49) were mainly males (72.3 %) and the mean age (± Standard Deviation) was 63.7 ± 11.5 years. In 26.5 % of patients the tumours were located in lungs and 28.6 % in head and neck. All but one of the patients reported pain during the baseline visit (20.8 % due to the primary tumour, 54.2 % to metastases, and 22.9 % to RT treatment). The median (Q1-Q3) number of breakthrough crises/day was 3.0 (2-4.5). Overall, 60.4 % were receiving treatment for breakthrough pain and Fentanyl was the most commonly used drug (70.4 %). Pain management strategies were: reinforcement/modification of long-term analgesics (30.4 %), reinforcement/modification of short-term analgesics (21.7 %), reinforcement/modification of long-term and short-term analgesics (21.7 %), and decrease/suppression of any fast- or long-term analgesics (26.1 %). Independently from the strategy, a decrease in the maximum pain and the total amount of pain were observed over time, and an improvement during the follow-up visits was observed in the quality of life, health gain, and overall treatment satisfaction. Only two adverse reactions were reported.

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Conclusions: Breakthrough pain in cancer patients, who underwent radiotherapy treatment, is a symptom of high prevalence. There is no predominant analgesic strategy in the management of these patients, but Fentanyl is the drug most frequently used. Patients are very satisfied with the pharmacologic treatment and the reduction in the breakthrough pain obtained has a favourable effect on the global health status and quality of life of patients.

Key words: Breakthrough cancer pain, radiotherapy, fentanyl.

RESUMEN

Objetivos: Estudiar el manejo del dolor irruptivo en pacientes de oncología radioterápica que lo experimentan, y su impacto en el control analgésico del mismo, la tolerabilidad de los tratamientos analgésicos utilizados, así como la satisfacción y el impacto en la calidad de vida del paciente.

Material y métodos: Estudio epidemiológico, observacional, prospectivo, multicéntrico, en pacientes con diagnóstico de cáncer y dolor de origen oncológico tratado con una pauta analgésica de 3er escalón, que iniciaron un tratamiento con radioterapia (RT) susceptible de que el oncólogo modificara su control analgésico. Los pacientes se reclutaron de 15 servicios de Oncología Radioterápica procedentes de centros de las regiones de Valencia y Murcia entre mayo de 2013 y diciembre de 2014. Basalmente se recogieron: datos sociodemográficos, caracterización del proceso oncológico y del dolor, tratamiento analgésico y tipo, y dosis/intensidad de la RT empleada. Al mes y a los tres meses se caracterizó el dolor mediante la valoración del cambio en la dimensión del dolor del cuestionario breve de dolor (CBD) y de la cantidad de dolor producido por episodios de dolor irruptivo, el nivel de satisfacción, la calidad de vida (EuroQol-5D) y la tolerabilidad al tratamiento analgésico.

Resultados: Los pacientes incluidos en el análisis (n = 49) fueron mayoritariamente hombres (72,3 %) y la edad media (± desviación estándar) 63,7 ± 11,5 años. En el 26,5 % de los pacientes el tumor se encontraba en pulmón y en el 28,6 % en cabeza y cuello. Todos, excepto uno, refirieron dolor en el momento de la visita basal (20,8 % debido al tumor primario, 54,2 % metástasis y en 22,9 % tratamiento con RT). La mediana (Q1-Q3) del número de crisis al día fue 3,0 (2-4,5). El 60,4 % estaban recibiendo tratamiento para el dolor irruptivo, siendo fentanilo el principio activo más frecuentemente utilizado (70,4 %). Las estrategias para manejar el dolor fueron: refuerzo/modificación de analgésicos de larga duración (30,4 %), corta duración (21,7 %), ambos (21,7 %) o disminución/supresión en analgésicos de acción rápida o de larga (26,1 %). Independientemente de la estrategia, se observa una disminución en cuanto al "máximo dolor", y la cantidad total de dolor entre las 3 visitas, y una mejoría en cuanto a la "calidad de vida", "ganancia de salud" y la "satisfacción global del tratamiento". Solo se reportaron dos reacciones adversas.

Conclusiones: El dolor irruptivo en los pacientes oncológicos en tratamiento de radioterapia, constituye un síntoma de elevada prevalencia. No hay una estrategia analgésica predominante para el manejo de estos pacientes, pero el fentanilo es el fármaco más frecuentemente utilizado. Los pacientes están satisfechos con el tratamiento y la reducción del dolor irruptivo repercute favorablemente en el estado general y calidad de vida de los pacientes.

Palabras clave: Dolor irruptivo oncológico, radioterapia, fentanilo.

INTRODUCTION

In the field of radiation therapy (RT) for cancer, the growing use of aggressive RT regimens means that pain poses a problem in daily clinical practice (1), so it is very important to control this pain to make the treatment more comfortable and to avoid suspending radiation therapy for this reason, with the risk of lost effectiveness it would involve (2). In patients undergoing RT with radical intent, patients may suffer acute pain associated with mucositis and epitheliopathy caused by the treatment. Furthermore, in the medium term, patients who have received radical or complementary radiotherapy may suffer painful syndromes such as brachial or lumbosacral plexopathy, radiation osteoradionecrosis or proctitis or cystitis (3). In addition to these specific situations, we should add that many oncological processes are accompanied by painful symptomatology treatable with baseline analgesic therapy. In these cases, the impact of RT may exacerbate the pain caused by the pathology itself and/or of the appearance of breakthrough pain episodes, spontaneously or associated with dysfunction caused in affected areas. In any event, recovery of analgesic control may require modification to this analgesic regimen.

Breakthrough cancer pain (BCP) is defined as an acute exacerbation of pain with sudden onset, short duration and moderate to high severity, which appears in cancer patients with chronic pain controlled therapeutically with opioid drugs (4,5).

Recommendations for treating BCP have historically included the addition of a short-acting opioid. However, guidelines have more recently stressed the usefulness of fast-acting fentanyl. These agents have a rapid onset and short duration, which coincide with the profile of a typical BCP episode (6-8).

Data from surveys indicates that BCP is far from being optimally treated (9-11) which leads to an increase in perceived pain intensity (12), reduced patient quality of life (11) and a significant economic burden (13).

There do not exist controlled studies to measure the management, intensity and effectiveness of treatment of pain caused by cancer treatment such as RT. With this background, the main objective of this study was to analyze pain management in cancer patients undergoing RT and its impact on their analgesic control, to evaluate the effectiveness and tolerability of the analgesic treatment used, as well as patient satisfaction and its impact on their quality of life.

MATERIAL AND METHODS

Study design

Epidemiological, observational, prospective, multicenter study of patients diagnosed with cancer, of any tumor location and stage, who required step 3 analgesic treatment for their cancer pain and who began RT (not combined with other treatments) subject to analgesic control modification by their radiotherapist. Patients were recruited from 15 Radiation Oncology Services at centers in the regions of Valencia and Murcia from May 2013 and the period of recruitment lasted until December 2014. Each investigator consecutively recruited an average of 10 patients who visited their clinic and who met all the selection criteria.

Inclusion criteria were: ambulatory, above 18 years old, diagnosed with cancer (any location) regardless of stage, who were to begin treatment with radiation therapy (RT). Additionally, they had to have a life expectancy greater than 6 months, step 3 baseline analgesic medication to treat pain that, in the radiotherapist's opinion, could be altered and who authorized their participation in the study by signing their informed consent in writing.

The study excluded patients who, despite beginning treatment with RT, did not have step 3 analgesic treatment initiated and who, in the investigator's opinion, did not have sufficient cognitive capacity, presented sensory or psychiatric disability or linguistic barriers that prevented or obstructed their participation and collaboration in taking part in the study.

A monitoring period of three months was established, with a baseline control that coincided with the first RT session, and two monitoring visits (after one month and at three months after initiating RT).

The investigators at each center collected information in a databook designed for the purpose, which included information from each patient's clinical history and from a direct interview with them. For complete monitoring, a diary was attached for patients to write down any breakthrough pain episode with its respective characteristics, together with the medication taken, over a period of three months.

Variables analyzed

The visit at the beginning of the study collected: patients' sociodemographic data (sex and age), baseline characteristics of the cancer process (tumor location, stage and general state of the cancer patient - ECOG score), pain level (Brief Pain Inventory [BPI], Visual Pain Scale), baseline analgesic treatment (type and dose), and dose of RT used. Throughout monitoring, data on the analgesic treatment collected, regarding both baseline and rescue treatment (type, dose, initiation date and final date of each treatment or dose). Results were collected regarding the different analgesic treatment strategies throughout monitoring, which included: a) patients for whom the baseline analgesic treatment is maintained; b) patients for whom the baseline analgesic treatment is reinforced or modified with an analgesic regimen of longer or more intense duration; c) patients for whom the baseline analgesic regimen is increased with an on-demand, fast-acting analgesic for breakthrough pain episodes, and d) patients for whom the baseline analgesic regimen is increased with a fast-acting analgesic in a programmed way to prevent the occurrence of breakthrough pain episodes associated with dysfunction caused in affected areas.

Data was also collected on the safety of the treatments used (adverse reactions) during the whole monitoring period.

Analgesic control was defined in terms of relative change from baseline to one month/three months' monitoring of maximum pain intensity measured on the Visual Analogue Scale (VAS) of the BPI (Brief Pain Inventory). Minimum clinically significant changes correspond to ±15%. Standardized amount of pain caused by breakthrough pain episodes was also evaluated (minimum significant difference, for a significance level of 95%, corresponds to ±1.96).

Pain was characterized at one month and at three months from initiation of RT by evaluating the change in the dimension of BPI pain and in the amount of pain caused by breakthrough pain episodes throughout the patient monitoring period (time by intensity). Additionally, patient satisfaction level was assessed at one month and when monitoring ended, according to the satisfaction questionnaire (with Likert-type responses) and quality of life using the EuroQol-5D scale.

Statistical analysis

A sample size of 150 patients was assessed, assuming that baseline characteristics explain 15% of variance in the dependent variable (r2 of the baseline with baseline factors = 0.15), and that management strategies explain a minimum of 10%; that the desired significance level was 95%, with a power of 90% (130 patients); and monitoring losses would be around 10%. Quantitative variables were described by: mean, standard deviation, SD 95% (mean confidence interval 95%), median, interquartile range and minimum and maximum value. Qualitative variables were described by frequency and percentage. Comparison of qualitative variables between two or more groups was carried out using the Chi-squared test and/or Fisher's exact test. To determine whether quantitative variables fit a normal distribution, Kolmogorov Smirnoff's test or the Shapiro-Wilk test were used. All statistical tests are considered bilateral and level of significance is taken as $\alpha = 0.05$.

Ethical considerations

The study protocol was presented for evaluation by the clinical investigation Ethics Committee of the foundation Instituto Valenciano de Oncología, which approved the study on 2 October 2012. Subsequently, this committee was requested to enlarge the number of centers, receiving approval for this measure on 6 May 2013. In addition to this committee, due to the study's prospective nature, it had to be evaluated by committees in the communities of Valencia and of Murcia. In the case of 4 participating centers, re-evaluation by the respective ethics committees was required.

RESULTS

Of the 15 centers envisaged for participation, three did not contribute patients and only one of them contributed the 10 patients planned according to the study protocol. Finally, and after extending the recruitment period four times consecutively, information on a total of 60 patients was collected (response rate 40%), one of which did not meet the selection criteria, so the eligible population numbered 59 patients. All the patients signed their informed consent. However, upon verifying the database, a further 3 patients were detected who did not meet the selection criteria (no treatment with step 3 opioids) and 7 more in whom the date of their baseline visit deviated from protocol conditions as regards radiotherapy initiation date (baseline visits carried out before or after one month from date of initiating RT). Therefore, the final sample consisted of 49 patients (33% of intended size). Figure 1 shows the study flow-chart.

Baseline characteristics

Table I summarizes the characteristics of patients, characterization of the oncological process and pain at baseline visit. 72.3% of this study's patients were men. Mean patient age was 63.7 ± 11.5 years old (range 32-84). 26.5% of patients had a tumor in the lung and 28.6% in the head and neck; and in the rest of patients, location varied greatly (3 colon/rectum and breast, 2 prostate and pancreas and 1 kidney, bladder, uterus, esophagus and skin; in 4 cases location was unknown). 70.8% were stage IV cancers. Median (P25-P75) time elapsed from diagnosis was 4.0 (2.5-13.5) months. According to the ECOG scale (0-4), 17.0% of patients were fully active, 51.1% were limited in carrying out strenuous physical activity, 23.4% were treated as ambulatory and were capable of self-care, 8.5% had limited ability to care for themselves and no patient was wholly incapable.

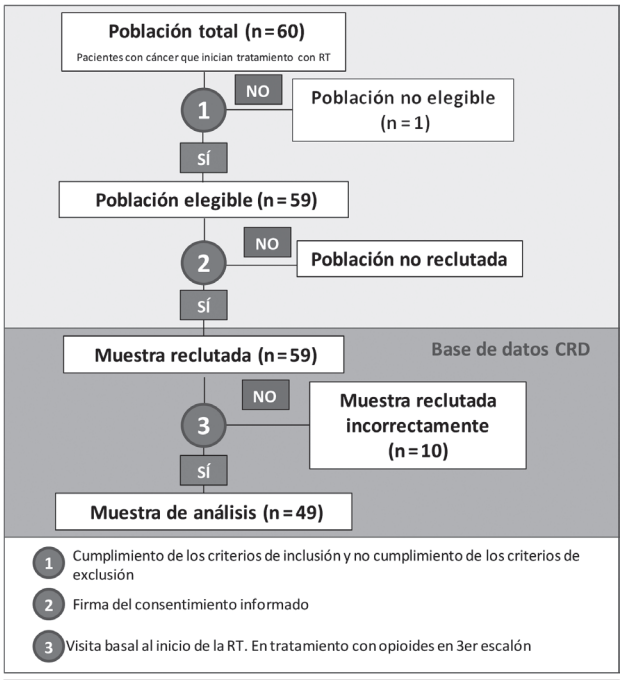

Fig. 1. Study flow-chart.

All except one of the patients reported pain at the time of the baseline visit. Primary tumor was the cause of pain in 20.8%, metasteses in 54.2% and RT in 22.9%. The median (P25-P75) number of episodes in the previous month was 56.2 (14.8-90) and the median number of crises per day was 3.0 (2-4.5). Of the 48 patients with pain, 60.4% were receiving treatment for breakthrough pain. Fentanyl was the most frequently used active agent (70.4%), followed by morphine or hydromorphone (14.8%), oxycodone (7,4%), tramadol (3,7%) and NSAIDs or dipyrone (3.7%). According to the results of BPI questionnaire (Table I), pain severity at baseline on a 0-40 scale, obtained as the sum of worst pain, slightest, average and current pain, was 18.9 ±7. Maximum pain experienced in the previous 24 hours on a 0-10 scale was 7.8 ±2.1, and the impact of pain on daily activities on a 0-10 scale, calculated as the average of the 7 articles that evaluate this dimension, was 4.9 ±2.6.

As regards characterization of baseline RT, all patients began external RT. The most frequent locations were: neck (28.6%), thorax (22.4%), spine (20.4%), pelvis (16.3%) and skull (12.2%). A dose of 300 cGy was used in 20.8% and 400 cGy in 6.3%; the rest (72.9%) received other doses, with a median (P25-P75) of 500 (200-6,000). In the visit at 1 month, 38.7% received RT at that visit. Doses of 300 cGy were used in 8.3%, and in the remaining 91.7% other doses were used, with a median (P25-P75) of 212 (200-350).

Tables II and III summarize baseline analgesic treatment. The most frequently prescribed rescue treatment was fentanyl (77.6% of patients) with a dose of 200 (100-400),

TABLE I
BASELINE CHARACTERISTICS OF PATIENTS AND PAIN

Sociodemographic and clinical characteristics	
Age (mean ± SD)	63,7 ± 11,5
> 60 (%)	67,3 %
Sex (men)	72,3 %
Time since diagnosis. Median (interquartile range)*	4,0 (2,5-13,5)
Location of primary tumor:	
Lung	26,5 %
Head and neck	28,6 %
Other locations	44,9 %
Cancer classification: stage (TNM scale):	
0	0 %
I	4,2 %
IIA	2,1 %
IIB	2,1 %
IIIA	10,4 %
IIIB	8,3 %
IIIC	2,1 %
IV	70,8 %
ECOG:	
Fully active	17,0 %
Restricted in strenuous physical activity	5,1 %
Ambulatory, capable of self-care	23,4 %
Capable of only limited self-care	8,5 %
Incapable of self-care	0,0 %
Currently reports pain	98 %
Type of pain:	
Somatic	60,4 %
Visceral	25 %
Neuropathic	31,3 %
Pain due to:	
Primary tumor	20,8 %
Metastasis	54,2 %
RT treatment	22,9 %
Receiving analgesic treatment for breakthrough pain	60,4 %
Treatament (including tr. received for breakthrough pain):	
Fentanyl	70,4 %
Morphine / hydromorphone	14,8 %
Oxicodone	7,4 %
Tramadol	3,7 %
NSAID/dipyrone	3,7 %
Duration of breakthrough pain crisis:	
1-2 min.	6,5 %
3-5 min.	19,6 %
6-10 min.	17,4 %
11-15 min.	4,3 %
> 15 min.	52,2 %
Brief pain inventory:	
Baseline pain intensity (0-40)[1]. Mean ± SD	18,9 ± 7,0
Impact of pain on daily activities (0-10)[2]	4,9 ± 2,6
Maximum pain last 24 h (0-10)	7,8 ± 2,1
Breakthrough pain	
Initial/final pain intensity (VAS). Median (P25-P75)	8 [5-9]/3,3 [2,6-8]
Number of episodes in the last month. Median (P25-P75)	56,2 (14,8-90,0)
Number of crises per day. Median (P25-P75))	3 [2-4,5]

*The low number of observations makes it advisable to use the median and the interquartile range to describe these variables. 1: calculated as the sum of worst pain, slightest and average in the last 24 hours and current pain. 2: calculated as the average of 7 items assessing the impact of pain on daily activities.
SD: standard deviation. VAS: visual analogue scale. RT: radiotherapy.

and the most common route of administration was sublingual (57.9%; at dose 200 [100-400]), followed by inhaled (15.8%; at dose 400 [162,5-850]); in 23.7% the route of administration was not specified. As a second rescue drug prescribed, transdermal fentanyl was administered in 2 patients and metamizole in one. 16,3% of patients had no rescue treatment prescribed.

Main objective

Table IV summarizes the characteristics of pain in visits at month 1 and month 3, in addition to treatment and different treatment strategies. In the visit at month 1, no rescue treatment was prescribed in 23.3% of patients. In those who did receive rescue medication, mean use since previous visit was 24.8 ±20.0 times. Change of treatment or dose occurred in 74.2% of patients who attended the visit after the first month. In 82.6% of cases, fentanyl was the drug used after the change, and sublingual was the most common route of administration (31.6% of cases where fentanyl was used). As regards treatment in the month 3 visit, rescue medication was prescribed to 60% of patients and mean use since the previous visit was 38.6 ±29.9 times. Change of treatment or dose took place in 20.0% of patients who attended the month 3 visit and in 66.6% of cases fentanyl was the drug used after the change. Sublingual (50%) and inhaled (50%) were the only routes of administration used.

Figures 2 and 3 show the mean and median values of the relative change in maximum pain and amount of pain between visits. The outcomes show a decrease in maximum pain and in amount of pain in the visit at one month and at three months with respect to the baseline visit. Between the visit at 1 month and the visit at 3 months, the relative change is smaller.

Table V describes the relative change in maximum pain and in amount of pain among the 3 visits of the study according to pain management strategy. None of the 3 comparisons found an association between the relative change in maximum pain and the analgesic strategy, so the option to carry out a multivariate analysis was discarded. In analyzing the relative change in amount of pain according to analgesic strategy, an association was found between relative change in maximum pain and analgesic strategy ($p = 0.036$) between baseline visit and month 3.

TABLE II
BASELINE ANALGESIC TREATMENT (N = 49). DRUGS USED AND DOSE/DAY

	n	%	*Dose/day*					
			n	*median*	*P25*	*P75*	*Min.*	*Max.*
Step one								
Paracetamol (mg/day)	13	26,5	9	2.330,0	1.500,0	3.000,0	1,0	3,0
NSAIDs and derivatives (mg/day)	6	32,7	8	1.800,0	750,0	1.800,0	600,0	1.800,0
Dipyrone (metamizole) (mg/day)	8	16,3	5	1.650,0	887,5	4.000,0	575,0	6.000,0
No step one treatment received	4	8,2						
Step two (mild opioids)								
Codeine (mg/day)	2	4,1	1	30,0	na	na	na	na
Tramadol (mg/day)	4	8,2	3	300,0	100,0	na	100,0	1.800,0
No step two treatment received	43	89,9						
Step three (strong opioids)								
Morphine (mg/day)	7	14,3	6	37,5	21,8	77,5	12,0	130,0
Hydromorphone (mg/day)	1	2,0	1	5,0	na	na	na	na
Methadone	0	0,0	0	na	na	na	na	na
Fentanyl (µg/day)	34	69,4	31	600,0	300,0	1.200,0	150,0	4.800,0
Diamorphine	0	0,0	0	na	na	na	na	na
Oxicodone (mg/day)	8	16,3	8	35,0	20,0	80,0	20,0	160,0
Others: tapentadol (mg/day)	4	8,2	4	175,0	75,0	200,0	50,0	200,0

Min.: minimum. Max.: maximum. P25: percentile 25. P75: percentile 75. na: not applicable.

TABLE III
BASELINE RESCUE TREATMENT (N = 49). DRUGS USED AND DOSE/DAY

	n	*%*	*Dose/day*					
			n	*median*	*P25*	*P75*	*Min.*	*Max.*
Rescue treatment prescribed								
Fentanyl (µg/day)	38	77,6	36	200,0	100,0	400,0	50,0	1.600,0
Sublingual	22	57,9	21	200,0	100,0	400,0	100,0	800,0
Inhaled	6	15,8	6	400,0	162,5	850,0	50,0	1.600,0
Oral	1	2,6	1	600,0	na	na	na	na
Unspecified	9	23,7	8	150,0	100,0	525,0	100,0	1.600,0
Morphine (mg/day)	2	4,0	1	40,0	na	na	na	na
Oxicodone (mg/day)	1	2,0	1	40,0	na	na	na	na
Others (second rescue drug)								
Transdermal fentanyl (µg/day)	2	4,1	2	2.700,0	600,0	na	600,0	4.800,0
Metamizole (mg/day)	1	2,0	1	2.300,0	na	na	na	na
No rescue treatment prescribed	8	16,3						

Min.: minimum. Max.: maximum. P25: percentile 25. P75: percentile 75. na: not applicable. Dose/day does not follow normal distribution or they show a small number of observations, making it advisable to use the median and interquartile range to describe them.

TABLE IV
CHARACTERIZATION OF PAIN AND TREATMENT IN THE VISIT AT ONE MONTH AND AT THREE MONTHS

	VISIT 1 month (n = 31)	*VISIT 3 months (n = 16)*
The patient currently reports pain	16 (51, 6 %)	6 (37, 5 %)
Current VAS pain intensity	6 [5-7]	5 [3,5- 8]*
Current BPI pain intensity(0-40)[1]. Mean ± SD	12,6 ± 9,4	7,5 [1-13]*
Impact of pain on daily activities (0-10)[2]	3,2 ± 2,6	1,1 [0-6,9]*
Maximum pain last 24 h (0-10)	5,1 ± 3,2	4 [0-7]*
Cause of pain Mucositis Radiodermatitis Esophagitis Other (metastasis, primary tumor, etc.)	 4 (25 %) 3 (18,8 %) 1 (6,3 %) 13 (81,3 %)	 0 (16,1 %) 0 (16,1 %) 0 (0 %) 5 (83,3 %)
The patient has had a breakthrough pain episode since the last visit (n = 31)	21 (67,7 %)	8 (50,0 %)
Number of episodes. Mean ± SD	22,8 ± 22,9	56,3 ± 34
Time until initiation of relief > 15 min.	10 (47,6 %)	4 (50,0 %)
Mean crisis duration > 15 min.	11 (52,4 %)	6 (61,2 %)
Intensity of VAS pain last crisis: VAS initiation / VAS end. Mean ± SD	7 [5-8]/4 [2,5-5]*	5 [3-7,8]/4 [1,5-5,4]
Since previous visit, prescribed rescue medication has been used	23 (76,7 %)	9 (60,0 %)
No. of times medication was used. Mean (SD)	24,8 ± 20,0	38,6 ± 29,9
Patients whose treatment was changed	23 (74,2 %)	3 (20,0 %)

(Continue in the next page)

TABLA IV (CONT.)
CARACTERIZACIÓN DEL DOLOR Y TRATAMIENTO EN LA VISITA AL MES Y A LOS TRES MESES

	VISIT 1 month (n = 31)	*VISIT 3 months (n = 16)*
Treatment strategy and change in máximum pain intensity with respect to baseline		
No change in treatment	0 (0 %)	0 (0 %)
Reinforcement or modification of long-acting analgesics without changes to fast-acting analgesics	7 (30,4 %)	1 (50,0 %)
Reinforcement or modification of long-acting analgesics and in fast-acting analgesics	5 (21,7 %)	5 (0 %)
Reinforcement or modification of fast-acting analgesics without changes to long-term analgesics	5 (21,7 %)	5 (0 %)
Reduction/supression of fast-acting or long-acting analgesics without changing others	6 (26,1 %)	1 (50,0 %)
Drugs		
Fentanyl	19 (82,6 %)	2 (66,6 %)
Sublingual	6 (31,6 %)	1 (50 %)
Inhaled	3 (15,8 %)	1 (50 %)
Transdermal	4 (21,1 %)	0 (0 %)
Unspecified	6 (31,6 %)	0 (0 %)
Morphine	1 (4,3 %)	0 (0 %)
Oxicodone	3 (13 %)	1 (33,3 %)

* The small number of observations makes it advisable to use the median and the interquartile range to describe these variables. 1: calculated as the sum of worst, slightest and average pain in the last 24 hours and pain experienced right now. 2: calculated as the average of 7 items that assess the impact of pain on daily activities. SD: standard deviation. VAS: visual analogue scale.

Patient satisfaction

Figure 4 shows overall satisfaction with treatment, with high mean and medium values and very close to each other in both visits, though slightly higher at the 3-month visit. Results of the satisfaction test show a moderate to high satisfaction level with episode control, route of administration, tolerability, effectiveness, effect speed and overall satisfaction, with an improvement at the 3-month visit with respect to the 1-month visit (Table VI). No association was found between patient satisfaction and treatment strategy.

Quality of life and health gain

Figures 5 and 6 show the relative change in quality of life and health gain among the three visits. Positive changes show greater quality of life between visit 1 and baseline and visit 3 and baseline in both parameters. As regards treatment strategies, no association was found between relative change in patient quality of life or health gain (Table V). Table VII shows the results of the EuroQoL-5D test in the three visits studied, finding an improvement in the two visits compared with baseline and a significant drop in the percentage of patients with a high perception of pain or pain-associated discomfort.

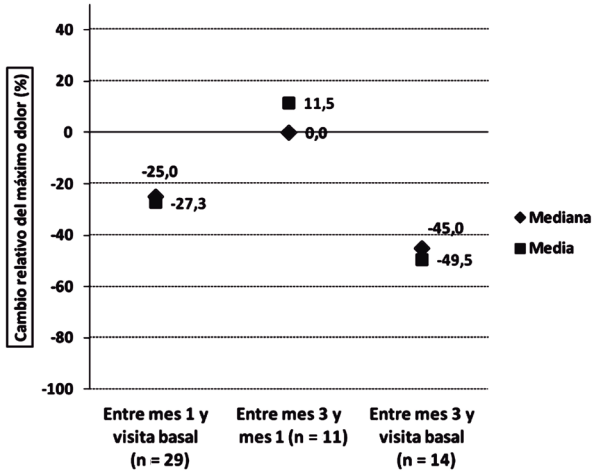

Fig. 2. Relative change in maximum pain between visits.

Tolerability

Only 2 patients suffered an adverse reaction during the study. The first consisted of "drowsiness" of slight intensity, related with increased drug dose (transdermal fentanyl); no action was taken as a result of the AR. The second adverse reaction consisted of "disorientation" of moderate

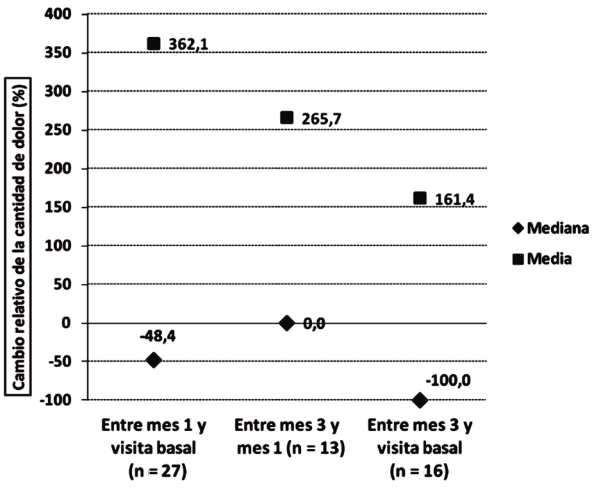

Fig. 3. Relative change in amount of pain between visits.

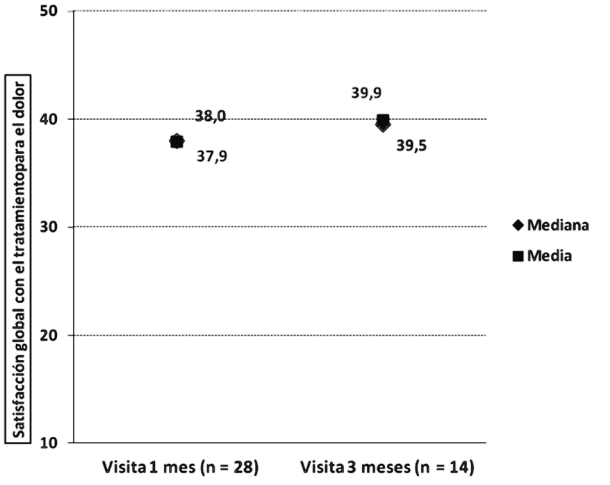

Fig. 4. Overall satisfaction with treatment for pain.

intensity, related with oxicodone administration. It had a duration of 19 days until the drug was suspended. The outcome of both was improvement.

DISCUSSION

Breakthrough pain in cancer patients who are undergoing RT, according to this study's findings, shows a greater prevalence than as observed in cancer patients in our area not subjected to radiation therapy (14), with major repercussions on patients' general state and quality of life, as well as on the daily clinical practice of Radiation Therapy Services, as regards its management and possible alteration to the proper administration of radiotherapy. Accordingly, it is important to know these patients' specific profile, to characterize their pain and to evaluate the different treatment strategies available to guarantee effective treatment and optimal quality of life. This is the first observational study to focus on pain management in the field of Radiation Oncology care. The profile of patients affected by this pain selected for RT is mostly men, above 60 years old, who suffer from stage 4 cancer diagnosed during the previous year, frequently located in the lung, head and neck. Tumor locations coincide with the findings of other international studies regarding the type of tumor location with the greatest prevalence in breakthrough cancer pain (15). The number of initial daily breakthrough pain crises is higher than as mentioned in other cancer studies of patients not subjected to RT, but with a similar level of initial intensity (VAS scores of 7-8) which returned to moderate pain levels after more than 15 minutes of crisis in most cases (14). Considering the sum of baseline pain and pain caused by breakthrough crisis, patients reported daily activities to be affected at levels mid-way between zero impact and maximum possible (16) and moderate levels of anxiety or depression that, added to the high prevalence of pain, reflected quality of life levels well below those of the general Spanish population (51.8 compared with 77.53 in the general population) (17). In subsequent reviews, after establishing different analgesic strategies to control pain based fundamentally on fentanyl, the percentage of patients reporting pain was reduced, the severity of this pain was reduced, the pain intensity's effect on daily activities decreased progressively and a greater percentage of patients reported that anxiety/depression symptoms had disappeared and that quality of life had improved. These results coincide with data recently published regarding patients with BCP treated with fentanyl, where the dimensions of physical activity, anxiety and depression improved significantly after treatment (18).

As regards RT's possible impact on patients' critical state, more than a third of cases reported pain attributable to the effects of RT, 25% associated with radiation mucositis and 18% to radiodermatitis (19,20). However, there is not sufficient data to make an evaluation regarding the effect of RT on changes in pain assessment, whether a possible increase in pain due to side effects of the radiation therapy or a possible beneficial antialgic effect of the radiation (pain originating from the tumor).

We should make special mention of levels of patient satisfaction with the treatment received to control pain episodes based on different routes of fentanyl administration, predominantly sublingual, with high-to-very-high satisfaction levels regarding its simple, convenient route of administration, very good tolerance, effective, fast relief that coincides with the findings of other studies on managing BCP with different fentanyl preparations (21,22). The

TABLE V

RELATIVE CHANGE IN PAIN INTENSITY, MAXIMUM PAIN, QUALITY OF LIFE AND HEALTH GAIN ACCORDING TO TYPE OF STRATEGY

	MAX. PAIN INTENSITY			*AMOUNT OF PAIN*		
	B-V1	B-V3	V1-V3	B-V1	B-V3	V1-V3
Overall mean ± SD	-25+ [-78, -11]	-45+ [-100, -16]	0+ [-17, 0]	-48+ [-100, 0] *	-100+ [-100, -3]*	0+ [-68, 45] *
No change in treatment	-64 ± 34	-77 ± 33	20 ± 109	-58 ± 128	-83 ± 37	318 ± 1.090
Reinforcement or modification of long-acting analgesics without changes to fast-acting analgesics	-27 ± 33	-16 ± 5	---	-29 ± 38	38 ± 70	16 ± 16
Reinforcement or modification of long-acting analgesics and fast-acting analgesics	6,9 ± 39	33 ± nd	---	15 ± 111	0	-
Reinforcement or modification of fast-acting analgesics without changes to long-acting analgesics	-24 ± 50	-16 ± 16	---	2.119 ± 4.853	1.761 ± 2.600	-
Reduction/supression of fast-acting or long-acting analgesics without changing others	-15 ± 133	-54 ± 37	-57 ± 57	-59 ± 47	-108 ± 16	-69 ± nd
p	ns	ns	ns	ns	0,036	ns
	CALIDAD DE VIDA			*GANANCIA SALUD*		
	B-V1	B-V3	V1-V3	B-V1	B-V3	V1-V3
Overall mean ± SD	17+ [-12, 60]	30+ [7, 45]	4,3+ [0, 34]	0,013 ± 0,023	0,066 ± 0,073	0,008 ± 0,029
No change in treatment	37 ± 29	37 ± 29	37 ± 29	0,02 ± 0,02	0,11 ± 0,06	0,02 ± 0,03
Reinforcement or modification of long-acting analgesics without changes to fast-acting analgesics	37 ± 29	37 ± 29	37 ± 29	0,02 ± 0,02	0,08 ± 0,01	-0,03 ± 0,002
Reinforcement or modification of long-acting analgesics and fast-acting analgesics	37 ± 29	37 ± 29	37 ± 29	-0,004 ± 0,02	0,03 ± nd	-0,02 ± nd
Reinforcement or modification of fast-acting analgesics without changes to long-acting analgesics	37 ± 29	37 ± 29	37 ± 29	-0,002 ± 0,02	0,00 ± 0,06	0,008 ± 0,001
Reduction/supression of fast-acting or long-acting analgesics without changing others	37 ± 29	37 ± 29	37 ± 29	0,025 ± 0,025	0,04 ± 0,07	0,03 ± 0,03
p	ns	ns	ns	ns	ns	ns

na: not available. +Median and interquartile range. ns: not significant. B: baseline. V1: visit at month 1. V3: visit at third month. SD: standard deviation. *$p < 0.05$.

TABLE VI
PATIENT SATISFACTION WITH TREATMENT IN VISITS AT ONE MONTH AND AT THREE MONTHS

	V1 (%)	*V3 (%)*
Overall satisfaction (scale 10-50)	37,9 ± 5,6	39,5 [37-43]*
In general terms, with regard to the treatment you have received to control the pain episodes you have experienced most recently, you are:		
Not at all satisfied	0,0	0,0
Rather dissatisfied	6,9	0,0
Normal	20,7	7,1
Satisfied	51,7	71,4
Very satisfied	20,7	21,4
The night following your last pain episode and after receiving treatment for it, you slept with:		
Total difficulty	0,0	0,0
Great difficulty	10,3	7,1
Some difficulty	24,1	21,4
Little difficulty	44,8	42,9
No difficulty	20,7	28,6
Are you satisfied with the route of administration for the treatment your doctor has prescribed you for pain (oral, intranasal, intravenous, etc.)?:		
Not at all satisfied	0,0	0,0
Rather dissatisfied	0,0	0,0
Normal	20,7	21,4
Satisfied	58,6	50,0
Very satisfied	20,7	28,6
At the moment the drug was administered you experienced:		
Total discomfort	0,0	0,0
Great discomfort	3,4	0,0
Some discomfort	13,8	7,1
Little discomfort	41,4	57,1
No discomfort	41,4	35,7
You found the instructions/indications for administering the drug:		
Very difficult to understand	0,0	0,0
Quite difficult to understand	0,0	0,0
A bit difficult to understand	6,9	7,1
Not very difficult to understand	55,2	57,1
Not at all difficult to understand	37,9	35,7
In general terms, you consider the treatment's tolerability to be:		
Very poor	0,0	0,0
Quite poor	0,0	0,0
Normal	58,6	28,6
Very good	24,1	50,0
Excellent	17,2	21,4
In general terms, you consider the treatment's effectiveness to be:		
Very poor	0,0	0,0
Quite poor	6,9	0,0
Normal	48,3	35,7
Very good	37,9	50,0
Excellent	6,9	14,3

(Continue in the next page)

TABLE VI (CONT.)
PATIENT SATISFACTION WITH TREATMENT IN VISITS AT ONE MONTH AND AT THREE MONTHS

	V1 (%)	*V3 (%)*
The effect caused by the treatment was:		
Very slow	0,0	0,0
Slow	17,2	0,0
Normal	41,4	57,1
Fast	37,9	35,7
Very fast	3,4	7,1
The treatment gave you:		
No relief from the pain episode	0,0	0,0
Little relief from the pain episode	13,8	0,0
Normal relief from the pain episode	31,0	14,3
A lot of relief from the pain episode	41,4	71,4
Total relief from the pain episode	13,8	14,3
If you experience a new breakthrough pain episode, you would agree to receive the same treatment:		
Strongly disagree	0,0	0,0
Slightly agree	7,1	0,0
Agree	28,6	14,3
Strongly agree	50,0	71,4
Totally agree	14,3	14,3

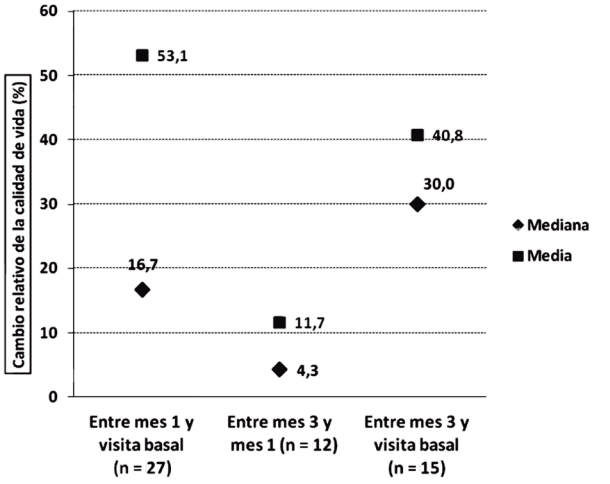

Fig. 5. Relative change in quality of life according to the EuroQoL-5D scale.

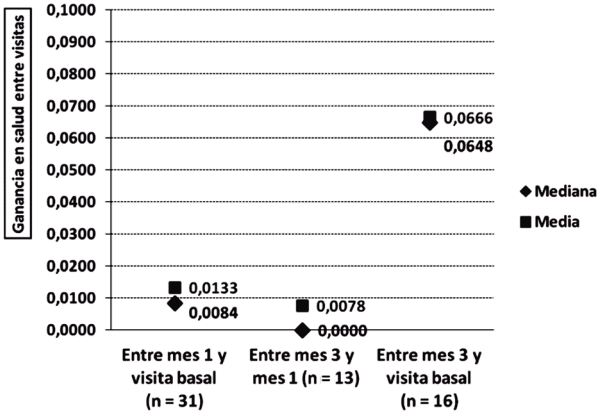

Fig. 6. Health gain between visits.

analgesic regimen was managed dynamically, adapted to patients, with changes and adjustments distributed between reinforcing and decreasing baseline analgesia, or rescue analgesia or reinforcing the combined strategy of both. However, in personalizing management strategies, the dispersion of cases into different strategies together with the drop in the number of patients available for monitoring does not allow assessment of their different impact, and we may only assert that considerable variability exists in analgesic management, that reinforcement regimens reduce pain, and that in cases where reinforcement is necessary, fentanyl is the medication most used, both to reinforce the baseline analgesia and to treat breakthrough pain

One of this study's main limitations has been the small sample size, not just in the number of patients, which was reduced to 49 patients (a third of what was proposed), but also in the loss of observations in visits by patients who made up the sample. With this number of observations, the power to find univariate association between the variables derived from the study and treatment strategy is very lim-

TABLE VII
QUALITY OF LIFE ACCORDING TO EURoQoL-5D

	BASELINE	*VISIT 1*	*VISIT 2*
EuroQoL-5D "thermometer" (scale 0-100)	51,8 ± 18,6	57,7 ± 15,5	68,1 ± 19,2
EuroQoL-5D (temporal scale 0-1)	0,467 ± 0,236	0,642 ± 0,267	0,709 ± 0,308
Quality of life according to EuroQoL-5D	*(%)*	*(%)*	*(%)*
Mobility			
I have no problems in walking about	57,1	64,5	81,3
I have some problems in walking about	38,8	29,0	12,5
I have to stay in bed	4,1	6,5	6,3
Self-care			
I have no problems with self-care	59,2	77,4	75,0
I have some problems with washing or dressing myself	34,7	19,4	18,8
I am unable to wash or dress myself	6,1	3,2	6,3
Usual activities			
I have no problems doing my usual activities	30,6	45,2	56,3
I have some problems doing my usual activities	49,0	41,9	31,3
I am unable to do my usual activities	20,4	12,9	12,5
Pain / discomfort			
I have no pain or discomfort	0,0	32,3	50,0
I have moderate pain or discomfort	55,1	54,8	37,5
I have extreme pain or discomfort	44,9	12,9	12,5
Anxiety/depression			
I am not anxious or depressed	30,6	51,6	50,0
I am moderately anxious or depressed	59,2	41,9	37,5
I am extremely anxious or depressed	10,2	6,5	12,5

ited. Another limitation is heterogeneous data collection regarding dose of RT used, so the data must be interpreted with caution. We should also consider the limitation arising from the derived variable "Relative change in amount of pain" based on "Intensity of pain in last breakthrough pain crisis".

CONCLUSIONS

Breakthrough pain in cancer patients undergoing radiation therapy constitutes a highly prevalent symptom. There is no predominant analgesic strategy for managing these patients, but fentanyl is the drug most frequently prescribed. Analgesic treatment based on this drug to treat breakthrough pain favorably affects patients' general state and quality of life, tolerability of treatment is excellent and patients report a high level of satisfaction.

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CONFLICT OF INTERESTS

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