TITLE:

ACTIVE Study. Undetected prevalence and clinical inertia in the treatment of breakthrough cancer pain (BTcP).

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ABSTRACT:

Aims: To prove if there is clinical inertia in the identification and treatment of episodes of breakthrough cancer pain (BTcP), comparing actual results from clinical practice with clinical oncologists' prior perception.

Design: Observational and descriptive study, using information collected by practising medical oncologists, at three moments: a) questionnaire regarding their professional judgement of the handling of patients with BTcP in their practice, b) cross-sectional clinical screening, to detect possible existing cases of BTcP in a representative sample of their patients, c) retrospective self-audit of clinical case histories of patients diagnosed with BTcP to find out about how it has been handled.

Participants and study period: A random sample on a state level of 108 specialists in medical oncology. 540 patients who suffer some type of cancer pain on the designated study date for each specialist (July-December'16).

Results: The global prevalence of BTcP in the study sample covered 91.3% of the patients who were suffering some type of cancer pain. Barely 2% of the doctors surveyed suspected figures around this mark. 40.9% of the cases had not been previously detected as BTcP by their doctors. Although 90% of the patients who had previously been diagnosed with BTcP received a specific analgesic treatment for the symptoms, 42% of those patients with known BTcP were not able to control their episodes of pain.

Conclusions: Clinical inertia is a serious problem in the handling of BTcP in medical oncology services, where it is the subject of a significantly low level of detection and treatment, despite the contrasting perception of specialists.

KEY WORDS:

Breakthrough cancer pain (BTcP), clinical inertia, prevalence of BTcP

Introduction:

Episodes of **breakthrough cancer pain (BTcP)** are one of the painful manifestations of the cancerous disease. Despite its high prevalence and significant impact on the quality of life of cancer patients [1,2], it is an area which could be improved in terms of knowledge, identification and clinical treatment in our field. It involves transient exacerbations of pain which, by definition, occur in patients who are carrying some type of chronic pain which is stabilized and adequately controlled with conventional treatment [3-5].

The crisis may appear incidentally (related to a certain triggering factor, such as walking, coughing, or during the practice of some kind of clinical procedure) or spontaneously and unpredictably. Although the clinical characteristics of BTcP can vary inter- and intra-individually, they are generally episodes which appear rapidly and reach their peak intensity within 3 to 5 minutes, being of moderate to high intensity and variable duration (between 1 minute and 4 hours, with an average of 30 minutes). Its frequency, which typically ranges between 1 to 4 episodes a day, has a crucial impact on the psychological and functional deterioration of the patient and the degree of anxiety arising as a result in caregivers [6-7].

Its diagnosis and evaluation are not complex if specialists have a high level of suspicion of it in the monitoring of their cancer patients and perform a specifically oriented anamnesis towards its identification and perform differential diagnoses from other types of pain, using tools such as Davies' algorithm [8-12]. In addition, the new fast-action opioid formulations administered by transmucosal route have substantially improved the scope for control [13].

However, in our country, it is estimated that up to 77% of episodes of BTcP may not have been detected or treated, or they are handled inappropriately and insufficiently treated (frequently increasing the dose of the opioid used to control baseline pain, or adding a short-action opioid to the previous treatment, such as morphine, hydromorphone or oxycodone, which are inadequate for controlling this problem due to their slow action speed) [14].

As in other chronic diseases, part of this varying and inappropriate clinical practice is due to the recognized problem of **clinical inertia (CI)**, which is understood as the failure during patient follow-up on the part of doctors to study, recommend and prescribe changes in the treatment that are necessary and indicated, leading to detrimental consequences to the health of their patients. CI is considered to exist in situations in which, due to inaction on the part of the doctors, it is not possible to meet the realistic therapeutic goals established in any referential framework of good practice (expert guide). In other words, when there is no change to the medication in order to reach the objectives proposed in the guides, without any adverse effect or any contraindication of the treatment required having been documented previously [15].

Although the most common cause of CI in cancer pain is not increasing the intensity of a treatment the patient insufficiently responds to [16], the widely acknowledged 'therapeutic inertia' also includes cases in which the treatment is not initiated or changed when indicated, despite poorly controlled pain symptoms. There are also cases of the use of incorrectly indicated treatment as a result of lack of evidence which supports its use [14]. In the particular case of BTcP, many other patients do not benefit from receiving appropriate treatment due to 'diagnostic inertia'. This means that an explicit diagnosis is not established despite the existence of particular and characteristic clinical signs of the process.

This current study attempts to estimate the frequency of CI in the habitual handling of BTcP among medical oncology specialists in our country. It also aims to encourage doctors to raise their own awareness and pay attention to this matter, comparing their initial perception on the scope of BTcP among their patients (prevalence and impact), with the actual situation verified through the result of a collective experience (voluntary and confidential) of systemic identification of possible cases of undetected and under-treated BTcP in their consultations.

The study also allows for examination of the variables associated with CI (professional experience, age and clinical profile of the patients, prior incidents in the administration of opiates, familiarity with the available vade mecum and the alternative administration routes, degree of prior training with analgesia, knowledge of the BTcP guidelines, attendance at conferences or scientific meetings on this matter, etc.). All this can offer plenty to reflect on when addressing possible ways of improving the situation.

Material and Technique:

An epidemiological study is carried out on the prevalence of BTcP and the quality of clinical attention offered in oncology consultations in Spain. This is done under the hypothesis that CI exists in dealing with this problem. In other words, there is a certain degree of under-diagnosis and inappropriate treatment. The aim is to establish the real extent of the problem and compare its actual scope with the initial perception of the oncologists themselves.

Study design: An observational and descriptive study is performed, using information collected by a large group of medical oncologists, at three consecutive times:

- Firstly, each specialist conducted an exploratory professional questionnaire about their preliminary impression of the prevalence, handling and clinical results obtained in patients who suffered from BTcP in their consultations. In addition, they gave details of their own degree of knowledge and monitoring in their routine work with regard to the clinical practice standards proposed in a widely distributed recent expert guide on BTcP [14] in our field.
- Secondly, after completing the previous questionnaire, the doctors took part in a descriptive cross-sectional study to perform a clinical screening of BTcP among the patients with any type of cancer pain habitually seen in their consultations. After verifying the eligibility criteria, the Davies diagnostic algorithm [10] was systematically applied to the patients. During this same consultation, descriptive clinical information was collected in each case of an identified BTcP.
- Finally, in the third instance, through a retrospective chart-review study, the information on the recruited patients was completed regarding the detection prior to the study of the cases of BTcP confirmed in the screening and their prior clinical handling. This task required each doctor to review their medical case histories, in the form of a voluntary and confidential self-audit of their clinical practice.

Before its launch, the project went through the compulsory evaluation and authorization by a Research Ethics Committee (in this case the *Comité Autonómico de Ética da Investigación de Galicia. Consellería de Sanidade. Xunta de Galicia (*The Autonomous Research Ethics Committee of the Health Service of Galicia*)*).

Participating doctors and patients:

132 medical oncologists were invited to participate, selected randomly from a register of 1,200 specialists, which is the property of the research sponsor. This study population represented more than 90% of the complete target group of the specialty, according to prior census not available [17]. The sample was stratified by autonomous communities to ensure a wide geographical distribution of doctors and patients representing the whole of the Spanish health service. Although all of them voluntarily accepted to take part in the study. By the end of it, a total of 108 specialists had completed all of the tasks that made up the study. In the case of the 24 who did not complete all the information, the majority [19] cited their unforeseen absence from consultation on the dates of the study, or their inability to collaborate due to heavy workload (5 cases).

The cases which were eligible for the BTcP screening were all patients who, prior to the start of the study, had been treated by the participating doctors as carriers of some type of cancer pain symptoms (regardless of the type, degree of activity and possible treatment received). Patients who had participated in a clinical trial related to their pain or cancer symptoms in the last year were excluded. To avoid bias in the selection of specific cases, oncologists were told to perform the selective screening of possible BTcP on the first five eligible patients who were attended to during a routine clinical working day, randomly pre-scheduled with each doctor. Each researcher therefore provided an identical quota of cases [5] to the total study sample, which brought together complete and valid information on 540 patients. This sample size ensured a maximum error in the central estimate of the study (percentage of patients, previously identified or not as carriers of BTcP) of 4.2%, for a confidence level of 95%, even in the most unfavourable result circumstances of a binomial distribution (p=q=0.5).

Study variables:

The variables for the professional were: basic demographic and professional information of the participating oncologists; professional opinion on the prevalence of BTcP in their consultations and on the possibility and consequences of their being unknown or inappropriately treated cases of BTcP among

their patients; routine clinical habits regarding BTcP (self-declared degree of monitoring on the main recommendations of a recent expert consensus on this matter) [14].

The patient variables were:

- Information collected through a patient interview: basic demographic data, result of the screening after applying Davies' algorithm (presence/absence of BTcP) and characteristics of the episodes (intensity, duration, frequency, time of evolution and impact on the patient's daily life).
- Information collected from their clinical case history: complementary clinical and epidemiological information of interest regarding the patients, prior identification or not of the cases of BTcP by the doctor, recommended treatment prior to the study (if there was any) and therapeutic results obtained.

Instrumentation:

The researchers used two tools to collect the information needed for the study:

- The doctor survey was self-administered through an anonymous electronic questionnaire, accessible from a specific website. The date for completing this survey was pre-arranged and signalled the start of the field work for each specialist.
- The field work (the prospective systematic screening of possible cases of BTcP) was made on a data collection logbook (DCL) in paper format which each doctor used during clinical interviews with their eligible patients according to protocol. After finalizing the recruitment of their patients, the doctors completed the information remaining in the DCLs regarding the patients with BTcP with the data collected from reviewing the case histories. All this data was transferred to the project website by completing a specific questionnaire for each patient.

Time period and plan of study:

The field work was completed by all specialists within eight calendar weeks, between July and December 2016. Each researcher was assigned a random date to start the process described. This was a convenient and viable moment in line with their appointment schedule when it was possible for them to complete the personal questionnaire. The first available day of normal clinical practice (after doing the personal questionnaire) was selected as the day of screening (BTcP day). On this day, it was foreseeable that the specialists would attend to and recruit the expected quota of patients who they were monitoring as a result of a cancer process which would include pain symptoms. If, during the specified date, it was not possible to fill the quota of cases due to the lack of eligible patients, the consecutive recruitment was extended for the next few days as necessary.

All the information for the study was collected solely by the oncologists which they transferred themselves, anonymously and after safely identifying themselves on the project website. The data was introduced in a single electronic database on a state level. Neither the researchers nor the analysts could identify the particular patients or specialists during its use. This was required to avoid any intentional bias in the information collected by the specialists about their clinical habits and routine treatment.

Statistical analysis:

The version 13.0 of the integrated SPSS-W package was used to do the description of the qualitative variables (through calculation of the relative frequency distribution (%) and appropriate graphical representations) and quantitative (through central tendency, dispersion and measures of position). The central estimates of prevalence which were the subject of study (prevalence of BTcP, under-diagnosis and under-treatment) were accompanied by their corresponding confidence interval at 95%.

Results:

1. Professional and social welfare profile of the oncologists surveyed.

The sample of 108 oncologists, aged between 29 and 68 (average 38.4) was made up mainly of females (66.6%; 72). Their professional experience ranged between 1 and 37 years practice (average 9.5 years). Most of the doctors (95.4%; 103) worked in public health services, although others (10.2%; 11) also practised, either additionally or exclusively, in the private sector. The larger share of participants (59.3%;

64) recruited their patients in an outpatient setting, followed by hospital outpatient care (26.8%; 29), hospitalization (12%; 13) and others (3.7%; 4).

The care load (patients seen to by the oncologist per day) and the frequency of care for patients with BTcP (cases per week), estimated by those surveyed is summarized in table 1.

Table 1. Care load and frequency of care for cases of BTcP*; information offered by the oncologists.*

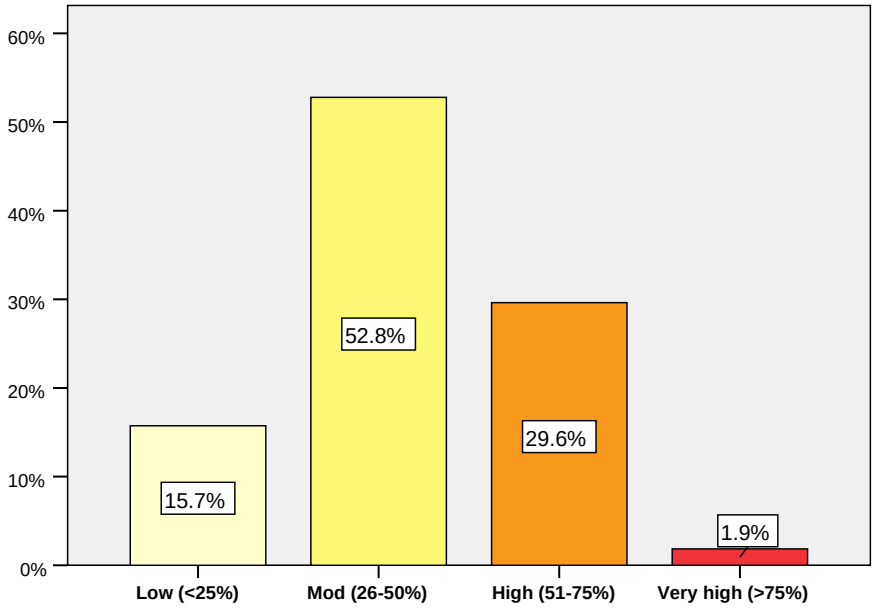
Care load	*Average*	*Medium*	*INF*	*SUP*	*P25*	*P75*
Patients / day	18.5	18	15	20	15	20
Cases of BTcP **/ week**	14.8	10	1	80	5	20

54.6% (59) of the oncologists surveyed stated that they had read the guidelines *Diagnosis and treatment of breakthrough cancer pain: consensus recommendations* [14]. In addition, 60% (65) had recently participated in some type of clinical session at their hospital/clinic on the subject of BTcP. 49% (53) had attended a conference or meeting specifically on BTcP and 41% (44) had recently completed some type of training course on BTcP.

2. Prior impression (opinions) of the oncologists on the prevalence of BTcP in their consultations and the adequacy of its detection and treatment.

The subjective impression on the prevalence of episodes of BTcP among their patients was variable, as shown in figure 1. No significant differences were seen in the perception regarding their normal healthcare environment (consultations, outpatient hospital and inpatients), except for the 2 specialists who stated that they deal with a very high prevalence (>75% of their patients), who worked in outpatient oncology consultations.

Figure 1. *Distribution of those surveyed (n=108) according to their perception of the prevalence of BTcP among their patients (the categories of the variable indicate estimated % of patients who suffer episodes)*



Regarding their habitual methods for actively exploring possible episodes of BTcP among their patients, 34.3% (37) of the specialists stated that they systematically ask their patients about it. Another 46.3% (50) only did it if the patient was undergoing analgesic treatment for cancer pain. 11.1% (12) said they considered the possibility if 'they had the time', and a final 8% (9) only dealt with it if the patient spontaneously referred to symptoms which suggested BTcP.

The perception of the specialists on the possibility that cases of BTcP go unnoticed and can remain undetected in their consultations varies significantly, as shown in table 2. Among the causes attributed to the patient which could lead to such a situation, the doctors suggested patients hiding the symptoms due to fear of receiving more opiate treatment (43%); the lack of consultation by the patient as a result of being unaware of BTcP and the possibility of receiving effective treatment (41%); and cases of patients omitting the matter in consultations as they were able to tolerate the short duration of the episodes (40%). In addition, the specialists identified other possible causes which were their own responsibility. These included forgetting to specifically ask about the possibility of BTcP (31%) and the diagnostic doubts about whether the patient's symptoms corresponded to a BTcP (20%). None of those surveyed doubted the current diagnostic criteria for BTcP.

Table 2 also contains the variable perception of the specialists on the possibility that some of their patients with BTcP do not receive a specific analgesic treatment (fast-acting opiates) in addition to their baseline treatment. Although 47% of those surveyed attributed this to the patients and/or family members, who may prefer not to treat these episodes with more opioids, there are also other factors which are strictly down to the specialists. These include attempts to mitigate the BTcP adjusting the baseline analgesic guidelines (18%); doubts on which is the best treatment option for certain patients (11%); being unsure about choice as a result of excessive analgesic formulations for BTcP (6%); fear of side effects deriving from indicating free use of fast-acting opiates (5%); and lack of personal up-to-date scientific knowledge on the therapeutic handling of BTcP (1%).

Table 2. Subjective impression of the specialists (n=108) on the possibility that patients with BTcP go unnoticed in their consultations, or that those cases detected do not receive a specific analgesic treatment

	Very unlikely	**Unlikely**	**Quite likely**	**Very likely**
Possibility of under-detection in cases of BTcP in their consultation	11.1%	62%	25%	1.9%
Possibility of inappropriate treatment in cases of BTcP	15.7%	67.6%	15.7%	0.9%

3. Description by the oncologists (self-declaration) of their routine clinical practice in the management of breakthrough cancer pain.

The Davies algorithm has a wide dissemination and acceptance among experts as a clinical tool for detecting possible episodes of BTcP: 78% of oncologists stated they used it 'almost always' or 'frequently', opposed to the rest who claimed they did not use it more than 'occasionally' or 'hardly ever'.

Table 3 offers the description that the specialists surveyed made on their habitual clinical practice before a suspected case of BTcP. Table 4 shows the stated therapeutic procedures after detecting cases of BTcP. In both cases, the specialist declares the degree of monitoring (according to their personal impression) of the good practice recommendations laid out in the clinical guide on BTcP which was used as a reference for this study [14].

Table 3. Declaration of the specialists (n=108) on their routine diagnostic habits before a suspected case of BTcP.

Before the suspicion of BTcP and after prescribing treatment.	*Almost always*	*Usually*	*Occasionally*	*Hardly ever*
• *Asking about the number of episodes*	79.4%	27.8%	0.9%	0.9%
• *Asking about the physiopathology characteristics*	46.3%	42.6%	10.2%	0.9%
• *Asking about the characteristics of the pain*	62%	33.3%	3.7%	0.9%
• *Asking about triggers*	57.4%	31.5%	10.2%	0.9%
• *Asking about relieving factors*	42.6%	38.9%	18.5%	-
• *Asking about the medication used up to that time*	81.5%	18.5%	-	-

Table 4. Declaration of the specialists (n=108) on their routine therapeutic habits after diagnosing a BTcP.

After diagnosing BTcP.	*Almost always*	*Usually*	*Occasionally*	*Hardly ever*
If the patient has no baseline treatment with opioids, I schedule this treatment to try to control the symptoms.	59.3%	28.7%	9.3%	2.8%
If the patient already has an effective baseline treatment schedule with opioids, I increase that treatment to also try to control the BTcP.	17.7%	25%	25.9%	32.4%
If the patient already has an effective baseline treatment with opioids, I immediately prescribe a specific treatment (fast-acting opioids), as a <u>complement</u> to the baseline treatment.	66.7%	28.7%	4.6%	-
I prescribe co-analgesic therapeutic measures (anti-seizure drugs and/or antidepressants) to help control the pain and reduce the dose of opioids.	16.7%	43.5%	36.1%	6.7%
From the start of the specific treatment, I add treatment to prevent or minimize the side effects (nausea, vomiting, constipation).	47.2%	40.7%	10.2%	1.9%
For the specific control of the episodes of BTcP, I choose a form of fentanyl, independent to the baseline analgesia.	53.7%	40.7%	4.6%	0.9%
Depending on the clinical situation and my patients' wishes, I usually use the following routes of fentanyl administration.	*Almost always*	*Usually*	*Occasionally*	*Hardly ever*
• *Oral*	13%	21.3%	35.2%	30.6%
• *Sublingual*	43.5%	48.1%	6.5%	1.9%
• *Intranasal*	7.4%	20.4%	38%	34.3%
If I prescribe a fast-acting opioid for the BTcP.	*Almost always*	*Usually*	*Occasionally*	*Hardly ever*
• *I advise to start with the lowest available dose and increase the dose at time intervals, until the minimum effective dose is found.*	51.9%	41.7%	5.6%	0.9%
• *I recommend recording the dose, interval and maximum number of daily doses of the drug administered.*	61.1%	26.9%	7.4%	4.6%
• *I recommend a follow-up appointment for the patient within the first 72 hours, to evaluate the effectiveness and tolerability, to then adjust the dose.*	12%	30.6%	34.3%	23.1%
• *I explain to the patient and/or their family the importance of administering the treatment early during each episode.*	70.4%	26.9%	2.8%	-

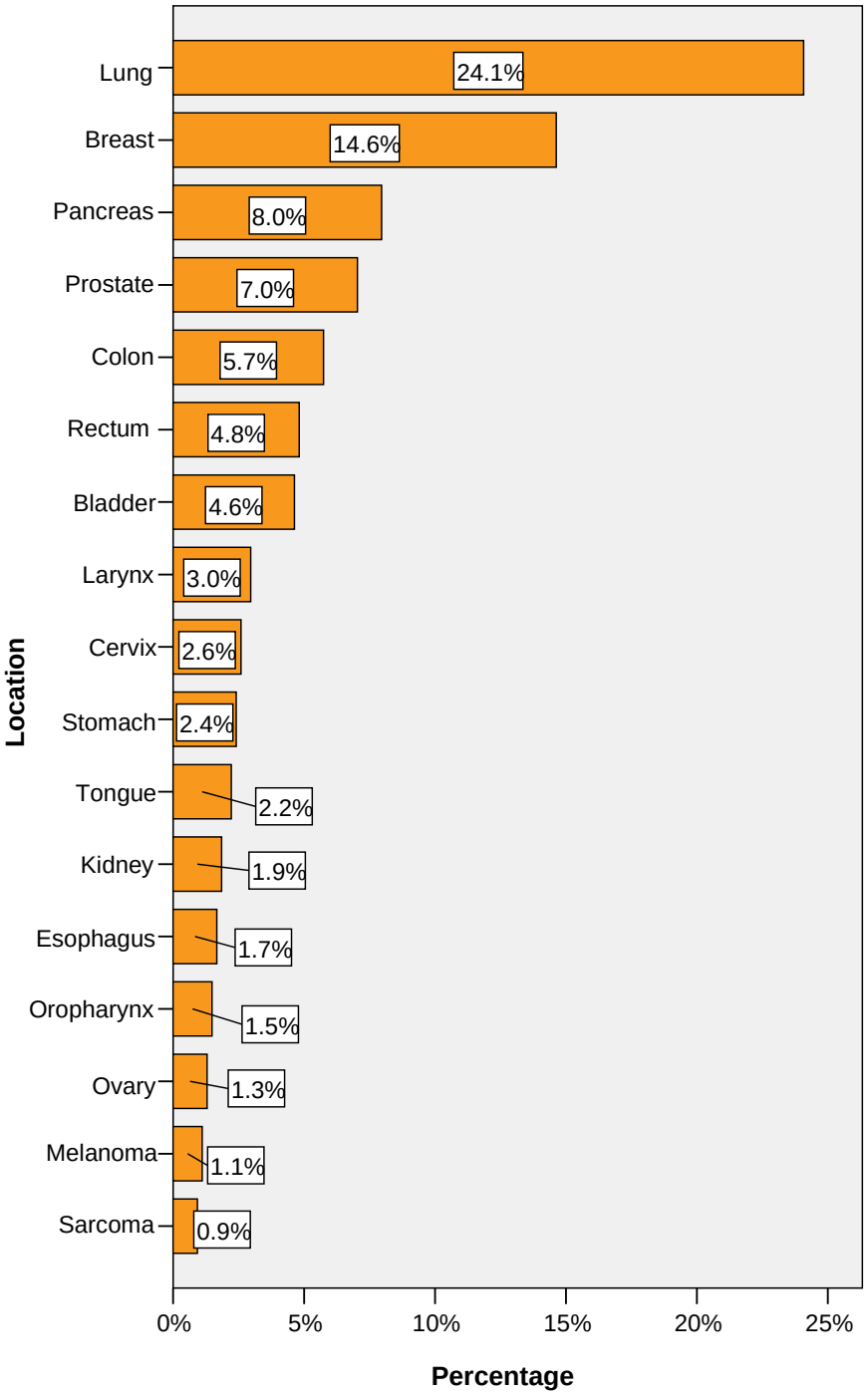
4. Demographic and clinical profile of the patients in the study (n=540)

It involves 540 cancer patients who had been previously identified as suffering from some sort of cancer pain being monitored by clinical oncologists. The sample had a wide range of ages (5 to 88) with the average age of 61.7 ($CI_{95\%}$ = 60.7-62.7) and median of 63. 40% (214) were female. The ages of the males were significantly greater than those of the females, with an average of 63.2 compared with 59.6 (t Student= 3.263 $p<0.001$).

The location of the primary tumours, headed by the lung, is shown in figure 2. The patients presented a wide variety of evolutionary stages. In this regard, it is worth highlighting a greater number of cases with primary involvement T3-T4 (72.4%) and of cases N1-N2 (87.8%) in terms of lymph node involvement. 80% of cases studied were at a metastatic stage of the illness at the time of the study.

Although all the patients recruited (n=540) were previously identified by their doctors as carriers of some type of pain associated to their cancer, only 428 patients (79.3%) referred to having these pain symptoms on the day of the consultation. Among the latter, the origin of the pain was of the somatic type (38%), neuropathic (24.9%), visceral (24.2%), incidental (6.7%) or undefined (6.2%). Its intensity varied between mild (5.1%), moderate (49.9%) and severe (45%). The baseline analgesic treatment prescribed to the 540 subjects of the global sample (categories were non-exclusive) prior to the study were: non-opioid analgesics (37.6%), 'weak' opioids (12.6%) or strong opioids (79.7%). In addition, 42% of the patients were taking some type of co-adjuvant drugs.

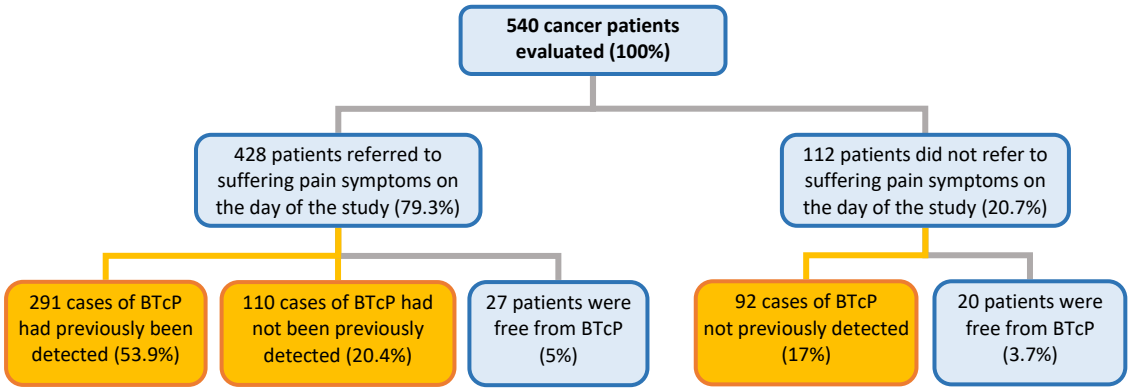
Figure 2. Distribution of the primary tumour locations of the patients in the study (n=540)



5. Prevalence of BTcP and low detection of cases among the patients participating in the study.

The results of the 540 patients recruited being submitted to the screening for BTcP using the Davies algorithm are summarized in figure 3.

Fig. 3. Overall outcome of the screening process for BTcP by applying the Davies algorithm to the 540 patients involved in the study.



Of the 540 cancer patients evaluated in this study using the Davies algorithm, 493 of them were diagnosed as carriers of BTcP, either previously detected (291), or detected in the prospective screening process made for this study (202).

Regarding the proportion of patients who had been identified by their doctors as carriers of BTcP before the study, the prevalence of the problem detected was 53.9% (291/540; CI95% = [51.9-55.9]). Adding this figure to the hidden cases detected during the screening, the true prevalence of BTcP among patients who are carriers of some previous cancer pain is increased to 91.3% (493/540; CI95% = [88.9-93.7]).

Among the total number of patients who are carriers of BTcP episodes in our study, the 202 subjects who were previously not identified by their doctors as such, represent a low diagnosis of 40.9% of the existing cases (202/493; CI95% = [36.6-45.2]). It is therefore clear that from the total number of patients being clinically monitored for some type of cancer pain which had previously been established, 37.4% (202/540; CI95% = [33.3-41.5]) suffer episodes of BTcP which are unknown (and not treated) by their doctors.

6. Clinical profile of the cases of BTcP (n=493).

The most common aetiology of the BTcP is tumoural (91.2%) as opposed to non-tumour cases. 45.5% of the time, the pain was of a mixed physio-pathological type, while in 36.6% of cases, it was of nociceptive type and 17.9% neuropathic. 60% of the patients referred to the presence of an incidental type trigger, while 37% an idiopathic type. The remaining 3% of the cases were interpreted as an 'end-of-dose' phenomenon. The intensity of the pain of these episodes was very variable, between unbearable (13.4%), high (56.6%), moderate (28.4%) or low (1.5%). The patients referred to between 1 and 15 episodes of BTcP a day, with an average of 3.6 episodes (CI95% 3.5-3.8) and median of 3 episodes.

7. Therapeutic approach and results obtained in the patients with BTcP (n=493), in accordance with the information obtained from the audit of their clinical case history.

68% (340/493; CI95% = [63.9-72.1]) of the patients with BTcP were receiving fast-acting opioid treatment on the day of the study. As only 291 of the patients with BTcP had been previously diagnosed by their doctors, a certain number of undetected cases of BTcP were also receiving treatment with drugs which were adequate (fast-acting opioids) for the disorder. Analysing this in more detail, it can be seen that 264 of the 291 patients (90.7%; CI95% = [87.4-94.0]) diagnosed prior to the study as carriers of BTcP and 76 of the 202 patients (37.6%; CI95% = [30.9-44.3]) not specifically detected as carriers of BTcP prior to the study were being treated with fast-acting opioids at the time they were evaluated. Of all these treatments, the most common administration route prescribed was sublingual, in 61% of cases. This was followed by the oral route in 22.6% of cases. According to the clinical judgement of the oncologists themselves, 41.6% (121/291; CI95% = [35.9-47.3]) of the patients identified as carriers of BTcP prior to the study were not able to suitably control their pain episodes.

With regard to the tolerability of the treatment with opioids specifically for the BTcP, 68% of the patients treated with these drugs (231/340; CI95% = [63.1-72.9]) had been prescribed some type of preventative drug for the foreseeable side effects at the start of treatment for BTcP. Despite this, on the whole, 17.9% of the patients who were administered fast-acting opioids (61/340) presented undesirable effects. Most notably, in decreasing order, constipation (57%), nausea or vomiting (25%) and sedation (18%).

With regard to any deviation from the quality criteria recommended by the guide for monitoring patients with a specific treatment for BTcP, the oncologists detected in their own clinical case histories that 14.1% (41/291) of the patients had not been advised titration dose up to the minimum effective at the time of prescribing the treatment with fast-acting opioids. In 12.7% of the cases (37/291), it had not been considered worthwhile to make adjustments to the dose in previous consultations despite the persistence of episodes of BTcP. Also, in 8.3% (24/291) of the cases, before considering changes, the compliance of the patient was not previously verified, or whether they were applying it as an early treatment as soon as the episodes of BTcP began.

Discussion:

This current study presents data showing a prevalence of BTcP in a broad group of patients (n=540) who are prior carriers of some type of cancer pain and analyses the clinical results obtained in their treatment. This was carried out via a self-audit conducted by the doctors (108 specialists in medical oncology on a state level, of varied profile, with a significant level of attention and clinical practice, generally in the outpatient setting).

Several precautions were taken to increase the accuracy and confidence level of the estimates made based on the findings of the study. The size and wide geographical dispersion of the sample of participating physicians and patients, stratified by autonomous communities, incorporates any possible professional and clinical or epidemiological variations between the different participating health services. The random assignment of a recruitment day for each doctor and the systematic recruitment of patients as of that date, increases the external validity of the findings of the prevalence of BTcP with regard to the state-level target group of cancer patients who are carriers of some type of cancer pain symptoms. Moreover, the voluntary nature and anonymous character of the information referred by specialists and patients minimize the risk of intentional bias when providing the information. This could have been motivated by the desire to project a favourable professional image, leading to falsification of the results provided.

The study confirms, as was raised in the starting hypothesis, that there is a significant prevalence of BTcP and a notable diagnostic inertia (low detection of clinically manifested cases) and therapeutic inertia (not starting treatment in patients who have been diagnosed, or not modifying unsuitable or ineffective treatment regimes) in its handling in the oncology health services. These deficits do not appear to depend, essentially, on the bias of the selection of the group of participating specialists or patients, who were chosen as an attempt to be representative of both groups.

BTcP does not seem to be a topic of much interest among the physicians who were surveyed: almost half of them declared that they had not recently received any type of specific training on BTcP (via sessions, conferences or specific programmes) and had not read the guide of consensus recommendations for the diagnosis and treatment of BTcP, which has been widely distributed and is accessible to all. This material

has been used as a reference for good practice in this study. This data can determine the deviation of the personal impressions of the doctors regarding the current situation of BTcP in Spain.

In this sense, the perception and opinion of the oncologists, which were offered prior to the self-audit on their clinical practice, were generally optimistic in the face of the real situation, both on the prevalence of BTcP among cancer patients and the professional habits in the active search for cases of BTcP in their consultations and the suitability and results of the treatment of identified cases.

The figure of prevalence of BTcP obtained after the screening of patients in consultation (91%) was much higher than what the oncologists predicted beforehand (their opinions) and the evidence in the audit of the clinical records prior to the study (54%). The prevalence of BTcP among patients being monitored in oncology services exceeds the figures of previous studies in the same field. It actually comes close to the number of patients attended to in palliative care units or pain units [18-21]. In the light of this data, the patients with some type of previous cancer pain symptoms should be considered as a population at a very high risk of presenting episodes of BTcP. However, this does not seem to be the general opinion a priori among oncologists, the majority of whom underestimated this factor among their patients. Less than 2% of specialists had a previous realistic perception of the situation and considered that the frequency of the problem could be 'greater than 75% of their patients', getting closer to the actual figures gleaned from the study sample.

These opinions are logically compatible with a notable under-detection of BTcP by oncologists, verified after performing a systematic screening of potential cases. Although the noticed prevalence (cases known about by the specialists prior to the study) represented slightly more than half of the cancer patients evaluated, a striking additional hidden prevalence was detected (cases unknown to the doctors which surfaced during the screening), which reached up to more than another third (37.4%) of the patients being monitored for some type of cancer pain. On the whole, the under-diagnosis of BTcP exceeds 40% in all cases of actual BTcP present in the study sample. From this data, the potential consequences on the deterioration in the quality of life of these patients who were undetected and did not receive appropriate treatment for their episodes of BTcP can be inferred.

Although the majority of oncologists (>80%) refer to questioning their patients about the possibility of BTcP, only 34% of them do it systematically on all the cancer patients they treat, whether they are carriers or not of some type of pain symptoms associated to cancer. The poor diagnostic results obtained from the study are also in contrast to the prior general perception of the majority of the specialists (almost three-quarters of the doctors surveyed) that it is 'unlikely' that patients with BTcP go unnoticed in their consultations. The specialists should reflect on the apparent disparity between their perceptions and their actual clinical practice, and on the chance to actually include in their anamnesis some type of clinical tool of proven performance, such as Davies' algorithm.

Regarding the treatments offered and the therapeutic results obtained in patients with BTcP, the study also identifies significant room for improvement. Most of the cases of BTcP unknown to specialists (hidden prevalence) logically did not receive a specific treatment for controlling their symptoms (although a third of them were being treated with fast-acting opioids at the time they were evaluated, without expressly being diagnosed with BTcP). Almost 10% of the patients who had already been diagnosed with BTcP before the study were not receiving any appropriate drugs for treating their breakthrough episodes despite them being indicated. In addition to this therapeutic inertia, the most characteristic factor of therapeutic inertia could be seen in slightly less than 13% of clinical case histories evaluated. This refers to inaction on the part of the doctor (not adjusting the dose) despite awareness of the ineffectiveness or partial effectiveness in controlling the episodes. What is more, when this treatment with fast-acting opioids was prescribed, a large share of the patients who received them (41.6%) were still not able to adequately control their pain episodes, according to the oncologists themselves.

On a positive note, in general, it is worth highlighting that the use of specific opioid treatment for BTcP seems to be safe and convenient, as it usually comes with recommended treatment for the prevention of possible side effects and it has a low incidence of undesirable effects. Similarly, there is a general alignment between the high rates of acceptance and theoretical interest in the recommendations of the guidelines for monitoring patients with specific opioid treatment for BTcP and the good practices identified in the audit of most of the clinical case histories. These refer to the dose titration up to achieving the minimum effective dose, the necessary adjustments to dose in cases of crises which are not effectively controlled, and checking in consultations on the compliance and early use of fast-acting opioids by the patient, before considering modifying the schedule.

The possible reasons behind this approach to improving cancer pain and the apparent neglect by oncologists of the problem compared to other clinical priorities are varied and of different responsibility. On the part of the specialists themselves, without a doubt, they as a group should ensure that they are sufficiently updated on BTcP and the current recommendations for identifying and handling it, to reduce diagnostic and therapeutic uncertainty related to the unfamiliarity in handling this problem.
However, other circumstances appear in the care context and related to the patients themselves, which are also barriers to early detection of BTcP and can lead to the therapeutic inertia referred to above. Medical oncology as a specialty is subject to in-depth review of its boundaries (immunology, genetics, and so forth), in the search for specially tailored high-precision treatments. All this requires a determined effort by the specialists to update their professional know-how in the new paradigm of health care, which offers both benefits and risks. The complexity and hyper-technification of oncology today can occupy the attention and interest of many oncologists and specialists, drawing their focus away from the comprehensive understanding of the effects of the illness on the patient and quality of life. It threatens to perpetuate the current unsatisfactory situation, in which cancer pain remains damaging and poorly dealt with.
Organizational aspects of the health care system also have an impact, such as high pressure on consultations, little time available to dedicate to each patient, and the lack of cooperation among interdisciplinary healthcare teams. These all make it difficult to devote sufficient time and effort to controlling pain as an objective in consultations for improving the quality of life of patients (along with the indisputable objectives of controlling the illness or monitoring the treatment to increase the survival of the patient).
Other factors can depend on the cancer patients themselves: lack of information about the existence of BTcP and the treatment available may lead to them neglecting to mention this matter in their appointments with the specialist. On other occasions, the patients or their families are opposed to or reluctant to treatment with opioids in addition to the baseline analgesic treatment, or they cannot guarantee reliable cooperation in assuming autonomy in the titration, adequate use of the drugs in the crises, and evaluation of possible side effects. All of these present additional barriers, external to the specialist, for early identification and achieving control of episodes of BTcP in patients.

Action to improve this situation can be geared in several ways: promote efficient continuous medical education programmes, use reminders for the diagnosis and control in electronic medical records, develop simple protocols which include recommendations specifically aimed at overcoming clinical inertia, involve nursing staff and the patients themselves, who need to be suitably informed, in the detection of new cases and in the request for medical aid in its control. These are some of the measures which may help achieve the desired results [16]. However, there is no doubt that an urgent reflection on the part of the medical practitioners is required to address the situation detected in the present study and to raise personal awareness, beyond what are personal beliefs and opinions on the problem, as there is extensive room for improvement in current oncology practice in dealing with episodes of BTcP. Only in this way can each oncologist be involved in rectifying the part of responsibility which corresponds to them in the serious problem of under-detection and under-treatment of BTcP in oncology services.

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