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Beyond the pain scale: a pragmatic strategy for managing breakthrough cancer pain in Eastern Morocco

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Abstract

Background: Breakthrough cancer pain (BTcP) represents a significant clinical challenge for oncology patients worldwide. While global data on BTcP prevalence exist, researchers have not systematically documented its specific clinical reality in North Africa, where rapid-onset opioids often remain inaccessible. To address this gap, we conducted the first standardised assessment of BTcP in the region, characterising its clinical and psychosocial impact in Eastern Morocco and proposing a preliminary, resource-adapted management pathway.

Methods: We conducted a cross-sectional study from January to June 2025 at the Regional Oncology Center Hassan II of Oujda. We assessed 312 consecutive adult cancer patients with controlled background pain (Numerical Rating Scale score ≤ 4) using the standardised Davies algorithm. We selected candidate predictor variables - age, sex, cancer site, presence of metastasis and performance status - based on their established clinical relevance in the BTcP literature. We evaluated the multidimensional impact of BTcP using the Hospital Anxiety and Depression Scale and the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30. Researchers previously validated both instruments linguistically and culturally for the Moroccan Arabic-speaking population. We examined associations between BTcP status and psychological and quality-of-life outcomes using the Mann–Whitney *U* test, given the non-normal distributions observed. Based on our findings, we developed a preliminary risk-stratified clinical pathway. We present adjusted odds ratios (aORs) with 95% confidence intervals (CIs) throughout.

Results: We identified a BTcP prevalence of 41.7% (130 out of 312; 95% CI: 36.4%–47.2%). Patients reported a mean of 2.3 episodes daily (SD 1.1), each lasting a mean of 35 minutes (SD 12) with severe intensity (mean Numerical Rating Scale score of 8.1 out of 10, SD 1.4). Multivariable logistic regression analysis revealed that bone metastases (aOR = 2.3; 95% CI: 1.4–3.8; p = 0.001) and poor performance status (ECOG score ≥ 2;

Research

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ecancer 2026, **20**:2194
https://doi.org/10.3332/ecancer.2026.2194

Published: 20/08/2026
Received: 06/03/2026

Publication costs for this article were supported by *ecancer* (UK Charity number 1176307).

aOR = 1.8; 95% CI: 1.1–2.9; p = 0.02) represented the strongest independent predictors. Advanced disease stage (Stage IV) also showed a significant association (aOR = 1.9; 95% CI: 1.2–3.1; p = 0.01).

Conclusion: This study reveals that nearly half of patients surveyed experience severe episodic pain flares despite stable background control. To bridge the gap between international guidelines and local resource constraints, we propose a preliminary clinical pathway - 'The Oujda Protocol' - that prioritises nurse-led triage, safety-checked multimodal analgesia and pre-emptive oral morphine dosing. This protocol requires prospective validation before it can inform standard clinical practice.

Keywords: *breakthrough cancer pain, Morocco, palliative care, oral morphine, global oncology, bone metastases*

Introduction

Cancer-related pain significantly diminishes quality of life and undermines patient dignity. For patients with malignancy, the sudden, intense flares known as breakthrough cancer pain (BTcP) frequently cause severe distress, occurring even when background maintenance therapy appears effective [1, 2]. Current consensus defines BTcP as a transient exacerbation of pain that occurs against a background of otherwise stable baseline pain [3–5].

In high-income settings, clinicians manage these episodes with rapid-onset opioids (ROOs) such as transmucosal fentanyl. ROOs such as oral transmucosal fentanyl citrate provide faster pharmacokinetic alignment with BTcP episodes [6]. However, in Eastern Morocco, as in many low- and middle-income countries, a critical therapeutic gap persists. International guidelines recommend pharmacological agents that remain inaccessible in our setting due to prohibitive costs or regulatory constraints [7, 8]. While the global community debates the relative merits of intranasal versus buccal fentanyl formulations, many African and Middle East and North Africa nations continue to struggle with basic opioid availability [9, 10]. Cultural stigmas and opiophobia further complicate clinical management [11].

This disconnect compels our clinical team to address a fundamental question: How do clinicians effectively manage BTcP when internationally recommended first-line agents remain unavailable? While existing literature from North Africa has documented the general prevalence of cancer pain, data specifically characterising the clinical and multidimensional profile of BTcP flares remains critically sparse [12]. We designed this study to quantify BTcP prevalence and characterise the clinical experience in our region. Based on our data, we propose a preliminary management algorithm - The Oujda Protocol. This protocol represents a theoretical framework that requires prospective clinical validation before broader implementation.

Materials and methods

Study design and setting

We conducted a descriptive and analytical cross-sectional study at the Centre Régional d'Oncologie Hassan II (Mohammed VI University Hospital, Oujda) between January and June 2025. This centre serves as the primary oncology referral hub for the entire Eastern region of Morocco.

Participants and eligibility

During the 6-month study period, we initially evaluated 345 consecutive adult outpatients with histologically confirmed cancer. To ensure the accurate diagnosis of true breakthrough pain (distinguishing it from uncontrolled background pain), we applied strict inclusion criteria:

1. Age ≥ 18 years.
2. Presence of cancer pain treated with opioids (WHO Step 2 or 3).

3. Adequately controlled background pain, defined as a Numerical Rating Scale (NRS) score of ≤ 4/10, maintained for at least one week before inclusion [3].

We excluded 33 patients from the initial pool: 14 did not achieve stable background pain control, 11 declined participation and 8 presented with significant cognitive impairment or communication barriers that precluded accurate pain assessment. Consequently, we enrolled a final cohort of 312 patients (Figure 1).

Sample size rationale

We calculated the required sample size using the single population proportion formula. Assuming an estimated BTcP prevalence of 40% based on African regional data, a 95% confidence level (CI) (Z = 1.96), a 5% margin of error and anticipating a 10% non-response rate, we determined a minimum target sample of 302 patients. Our final recruited sample of 312 patients adequately powered the study.

Data collection and instruments

We adopted a patient-centred approach using three validated international instruments. We linguistically and culturally validated all instruments used in this study for Moroccan and Arabic-speaking populations:

1. The Davies Algorithm: We utilised this standard diagnostic tool to confirm BTcP. It verifies stable background pain and identifies transient flares, strictly filtering out end-of-dose failure [3].
2. Hospital Anxiety and Depression Scale (HADS): We assessed psychological distress using the linguistically validated Arabic version. We applied the validated threshold of ≥ 8 to define clinically significant anxiety or depression [13, 14].
3. European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30): We measured health-related quality of life using the culturally validated Arabic version [15]. We calculated scores according to EORTC guidelines and considered a difference of > 10 points as the minimal important difference regarding clinical significance [16, 17].

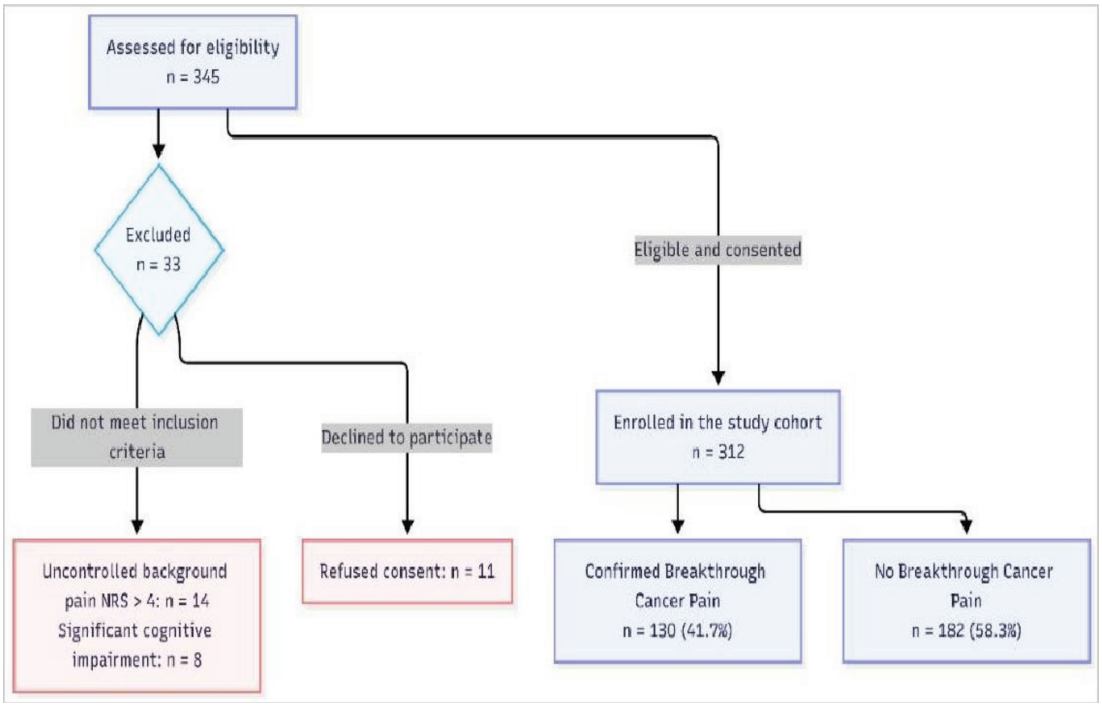

Figure 1. Flow diagram of the study population and screening process (*n* = 345 initially evaluated).

Statistical analysis

We performed statistical analyses using SPSS v25.0. We described continuous variables as means (±SD) and categorical variables as frequencies. To identify independent predictors ('red flags') of BTcP, we conducted a multivariable logistic regression analysis. We selected candidate covariates a priori based on clinical plausibility and prior literature: age, sex, cancer site, presence of metastasis and performance status. All variables with a univariate p-value < 0.20 entered the multivariable model. We report adjusted odds ratios (aORs) with 95% CIs. We addressed missing data by excluding incomplete records (complete-case analysis). We encountered no missing data for any variable included in the primary analysis. We compared HADS and EORTC QLQ-C30 scores between groups using the Mann–Whitney U test, setting the final significance level at $p < 0.05$.

Ethics

The Ethics Committee of the Faculty of Medicine and Pharmacy of Oujda (Ref: 05/2024) approved the study. We conducted all procedures in accordance with the Declaration of Helsinki.

Results

The prevalence and profile of pain

Of the 312 patients assessed, 130 presented with BTcP, yielding a prevalence of 41.7% (95% CI: 36.4–47.2%). This figure indicates that despite adequate background analgesia, two out of five patients experience severe pain spikes. Patients reported severe peak intensity (mean NRS 8.1 ± 1.4). Multivariable analysis identified bone metastases (aOR = 2.3; 95% CI: 1.4–3.8; $p = 0.001$), Stage IV disease (aOR = 1.9; 95% CI: 1.2–3.1; $p = 0.01$) and ECOG ≥ 2 (aOR = 1.8; 95% CI: 1.1–2.9; $p = 0.02$) as independent predictors. Although included in the model, opioid therapy (strong opioids) did not reach statistical significance as an independent predictor (aOR = 1.4; 95% CI: 0.8–2.5; $p = 0.21$) (Appendix Table 1).

The clinical profile of these episodes revealed high severity (Appendix Table 2):

- Intensity: Patients reported a mean peak intensity of 8.1/10 (SD ± 1.4).
- Duration: Episodes lasted an average of 35 minutes (SD ± 12).
- Frequency: Patients endured a mean of 2.3 episodes per day.
- Nature: While 56.2% of episodes occurred spontaneously, 43.8% were 'incident pain', triggered specifically by movement, cough or medical care.

Predictors of risk

Multivariable analysis isolated specific risk factors (Appendix Table 3). The risk of developing BTcP significantly increased in the presence of:

1. Bone metastases (aOR = 2.3; $p = 0.001$).
2. Advanced disease (Stage IV) (aOR = 1.9; $p = 0.01$).
3. Poor performance status (ECOG ≥2) (aOR = 1.8; $p = 0.02$).

The psychological and functional toll

Our data uncovered a strong association between episodic pain and psychological distress. Patients with BTcP reported significantly higher anxiety levels (mean HADS-A: 10.2 versus 7.1; $p < 0.001$) and depression scores (mean HADS-D: 9.4 versus 7.5; $p < 0.01$) compared to those without BTcP (Appendix Table 4).

Consequently, quality of life deteriorated markedly. The Global Health Status (EORTC QLQ-C30) averaged 52.6 in the BTcP group versus 68.3 in the control group ($p < 0.001$). This 15-point gap exceeds the threshold for clinical relevance, highlighting a profound impact on daily functioning.

Discussion

Interpreting the burden in context

Our observed BTcP prevalence of 41.7% falls within the range of global estimates (40%–70%) documented in systematic reviews [18]. While researchers have reported the burden of general cancer pain in West African settings, data specific to BTcP remain critically limited across the African continent [19]. This concordance suggests a shared continental burden of episodic cancer pain. However, our study extends beyond prevalence estimates to systematically evaluate the multidimensional impact of BTcP. Unlike previous regional reports, we correlated episodic pain flares with validated psychological and quality-of-life instruments, demonstrating that the clinical burden of BTcP manifests not only as heightened pain intensity but also as severe emotional distress and functional impairment.

The pharmacokinetic challenge

We must consider the clinical implications of these findings against the pharmacological constraints of our setting. An average BTcP episode in our cohort lasted 35 minutes. Immediate-release oral morphine - the primary rescue analgesic available to us [20, 21] - requires 30–45 minutes to achieve peak plasma concentration (T_{max}) [22]. This temporal mismatch creates a situation in which patients frequently achieve meaningful analgesia only after the spontaneous episode has begun to resolve. This pharmacological constraint may necessitate aggressive titration strategies and can lead to a cycle of delayed relief followed by post-episode sedation [21].

Mechanisms: the role of bone metastases

The strong association between bone metastases and BTcP (aOR = 2.3) supports the hypothesis that mechanical instability contributes substantially to episodic pain in this population. Tumour-induced bone remodelling generates a state of peripheral sensitisation, in which even minor mechanical stimuli trigger intense pain signalling via prostaglandin-mediated inflammatory pathways [23, 24]. This mechanistic link connects local bone pathology to the systemic inflammatory milieu frequently observed in advanced cancer pain [25].

Barriers to care: the access abyss

Structural barriers across North Africa - including restrictive formularies and inconsistent pharmaceutical supply chains - impede effective BTcP management. The Lancet Commission on Palliative Care and Pain Relief characterised this global disparity as an access abyss [26]. In Morocco specifically, opioid prescribing constraints persist [11]. Furthermore, reliance on family members for medication administration introduces additional complexity when caregivers harbour fears of causing overdose. Addressing these barriers requires coordinated advocacy from the global oncology community to support local initiatives [27, 28].

Moving from analysis to action: the Oujda protocol

The Oujda protocol: Given the continued unavailability of ROOs in our setting, clinicians must adapt existing tools to improve BTcP management [29, 30]. Based on our epidemiological findings, we propose a preliminary clinical model - The Oujda Protocol [7, 8, 20, 21]. We strongly emphasise that this pathway represents a theoretical, pragmatic proposal requiring rigorous prospective validation. It is not currently a validated intervention or a definitive standard of care. The proposed model rests on three conceptual pillars (Figure 2):

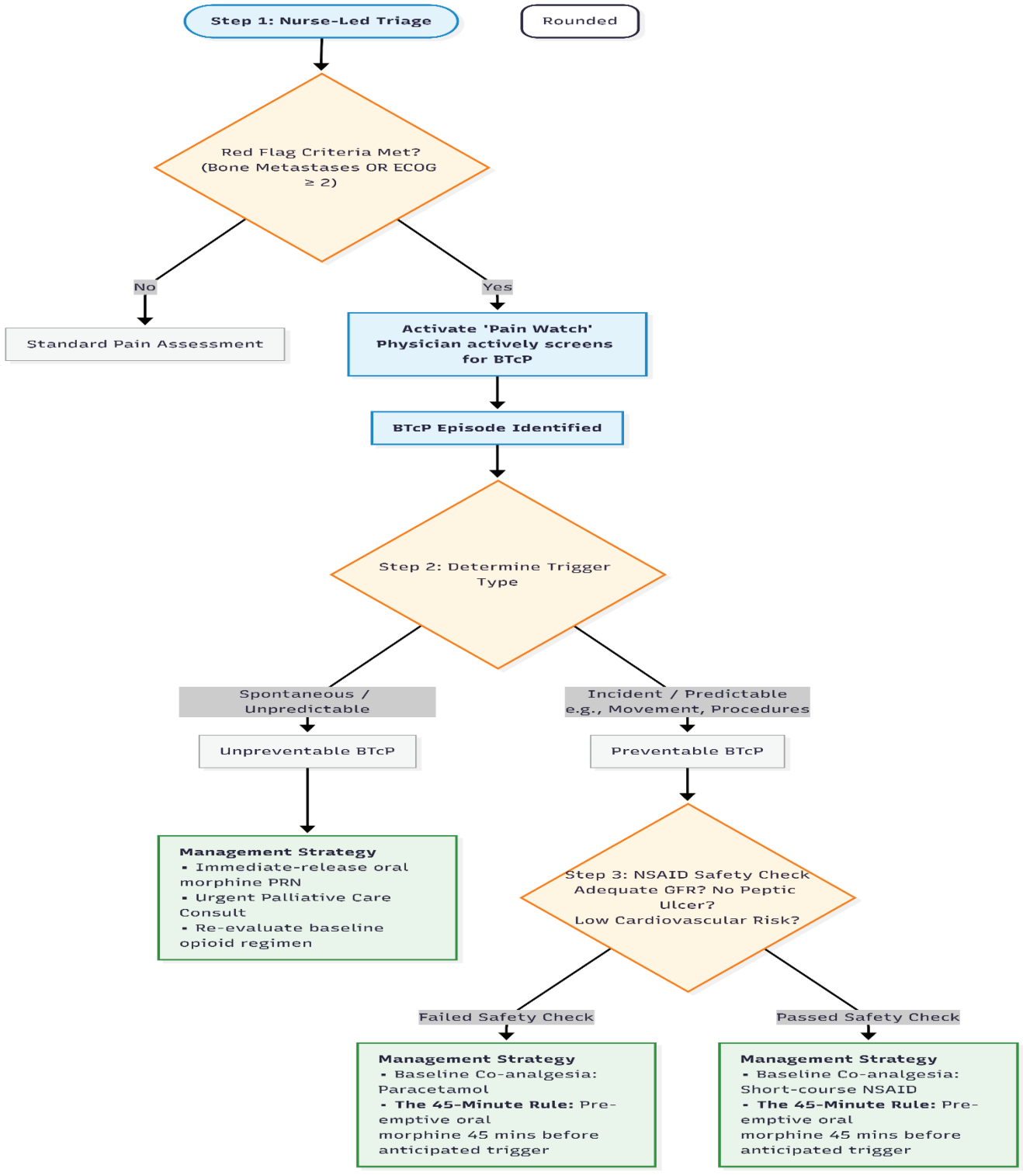

Figure 2. The Oujda protocol algorithm for BTcP management.

1. **The Red Flag triage (nurse-led screening)**

Oncologists frequently lack sufficient time to conduct systematic BTcP screening. We propose a task-shifting model in which triage nurses identify high-risk individuals using two clinical indicators: the presence of bone metastases or an ECOG performance status ≥ 2. When a patient meets either criterion, the nurse activates a Pain Watch alert, prompting the oncologist to proactively assess for episodic pain. This approach aligns with global assessment protocols and framework developments in similar resource-constrained environments [7, 8, 31].

2. **Bone-targeted co-analgesia (safety-first approach)**

In strict alignment with international protocols for cancer pain management [7, 8], clinicians might consider substituting the default co-analgesic (paracetamol) with an non-steroidal anti-inflammatory drugs (NSAIDs) (e.g., ibuprofen or diclofenac) for the specific subgroup of patients experiencing BTcP driven by bone metastases [32]. This model incorporates strict safety parameters as follows:

- Scientific rationale: NSAIDs inhibit cyclooxygenase-mediated prostaglandin synthesis at sites of bone destruction, potentially reducing opioid requirements [33].
- Mandatory safety screening: Before initiating NSAID therapy, prescribers should carefully verify adequate renal function, confirm the absence of active peptic ulcer disease and assess cardiovascular risk factors, as NSAIDs can increase the risk of adverse cardiovascular events [33].
- Duration limits: Because cancer patients often have multiple comorbidities that preclude prolonged use, the guiding principle is to strictly limit NSAID therapy to the lowest effective dose for the shortest necessary duration [33].

3. **The 45-minute rule for predictable incident pain**

Given the delayed onset kinetics of immediate-release oral morphine, a shift from reactive to pre-emptive dosing appears pharmacologically rational for predictable episodes [22]. In carefully selected patients with predictable incident pain, clinicians may consider educating patients to self-administer their prescribed rescue dose approximately 45 minutes before anticipated pain triggers (such as daily prayer movements, dressing changes or patient transport). This strategy aligns the anticipated peak plasma concentration of morphine (T_{max}) with the timing of the triggering physical event.

Importantly, for disruptive, unpreventable spontaneous episodes, our model suggests maintaining a standing order for immediate-release oral morphine as an as-needed rescue medication, paired with an urgent palliative care consultation to re-evaluate and optimise the baseline opioid regimen [4, 7, 20, 21].

Patient education and psychological support

The success of pre-emptive dosing depends on overcoming opiophobia. Structured caregiver education may improve adherence and safe opioid administration in resource-limited settings. Finally, the observed association between BTcP and psychological distress necessitates a dual therapeutic approach [34, 35]. Our results show a quality-of-life deficit comparable to that reported in other African oncology cohorts, including a Ugandan study that documented similarly impaired global health status among cancer patients [36]. Integrating psychosocial support into cancer pain management is as essential as ensuring pharmacological availability [26, 27].

Strengths and limitations

Our study has several important strengths. To our knowledge, we conducted the first standardised multidimensional assessment of BTcP in the North African region. By combining validated international instruments - including the Davies algorithm, the HADS and the EORTC QLQ-C30 - we achieved a comprehensive evaluation encompassing pain characterisation, psychological burden and quality of life. Importantly, we implemented our study in a real-world resource-limited oncology setting, which enhances the clinical relevance and translational value of our findings for similar healthcare contexts. To improve inclusiveness and reduce communication barriers among patients with limited literacy, we also incorporated adapted visual support materials during patient assessment.

Nevertheless, we must acknowledge several limitations. The cross-sectional design precludes causal inference between identified predictors and BTcP. In addition, the single-centre nature of the study may limit the external generalisability of our findings to other healthcare systems

or populations. Our reliance on patient self-reporting for pain intensity and episode duration may introduce recall bias. Furthermore, we performed assessments at a single time point without longitudinal follow-up, limiting our evaluation of temporal fluctuations in BTcP patterns. Finally, although the proposed 'Oujda Protocol' represents a pragmatic and clinically oriented approach for resource-constrained settings, future multicentre studies must validate its prospective clinical effectiveness.

Conclusion

This study provides the first standardised quantitative and psychosocial profile of BTcP in Morocco. We report that BTcP is frequent, severe and meaningfully associated with anxiety, depression and functional decline.

While we endorse the global call for equitable access to ROOs, we maintain that clinicians must not remain passive in the face of current resource constraints. The Oujda Protocol - a preliminary, theoretically grounded proposal - suggests that nurse-led screening, safety-checked multimodal analgesia for bone pain and systematic pre-emptive oral morphine dosing may represent a rational approach to improving BTcP management with currently available medications. This framework transforms the concept of 'low-resource' care into one of 'high-value' optimisation, aiming to reduce patient suffering with pharmacological tools already at hand. We emphasise, however, that this protocol constitutes an untested hypothesis requiring rigorous prospective validation before adoption into routine clinical practice.

Conflicts of interest

The authors declare no conflicts of interest.

Funding

This research received no specific grant.

Declaration of generative AI and AI-assisted technologies in the writing process

The authors used generative AI tools exclusively to assist with translation from French to English and for grammatical editing. The authors did not use AI tools for data generation, analysis or scientific interpretation. All authors reviewed and approved the final manuscript and take full responsibility for its content.

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Appendixes

Table 1. Sociodemographic and clinical characteristics of the study population (*N* = 312).

Variable	Category	*n* (%) or Mean (SD)
Age (years)	Mean (SD)	54.8 (11.6)
Sex	Female	191 (61.2)
	Male	121 (38.8)
Cancer site	Breast	101 (32.4)
	Colorectal	58 (18.6)
	Lung	49 (15.7)
	Other	104 (33.3)
Cancer Stage	I–III	165 (52.9)
	IV disease	147 (47.1)
Residence	Urban	174 (55.8)
	Rural	138 (44.2)
Socioeconomic status	Low	246 (78.8)
	High	66 (21.2)
Education level	Low	192 (61.5)
	Higher	120 (38.5)

*__Abbreviations:__ SD: Standard Deviation

Table 2. Clinical characteristics of BTcP episodes (*n* = 130).

Episode characteristic	Value
Episodes per day, Mean (SD)	2.3 (1.1)
Intensity (NRS 0-10), Mean (SD)	8.1 (1.4)
Duration (minutes), Mean (SD)	35 (12)
Trigger type, n (%)	
Spontaneous (Unpredictable)	73 (56.2)
Incident (Triggered)	57 (43.8)

* **Abbreviations:** NRS: Numerical Rating Scale; SD: Standard Deviation

Table 3. Prevalence of BTcP according to clinical predictors.

Factor	Category	Total (*n*)	BTcP present *n* (%)	aOR (95% CI)	*p*-value
Cancer stage	I–III	165	55 (33.3)	1.00 (Ref.)	—
	IV	147	76 (51.7)	1.9 (1.2–3.1)	0.01
Bone metastases	Absent	201	67 (33.3)	1.00 (Ref.)	—
	Present	111	66 (59.5)	2.3 (1.4–3.8)	0.001
ECOG status	< 2	189	65 (34.4)	1.00 (Ref.)	—
	≥ 2	123	65 (52.8)	1.8 (1.1–2.9)	0.02
Opioid therapy	No / Weak	175	59 (33.7)	1.00 (Ref.)	—
	Strong	137	72 (52.6)	1.4 (0.8–2.5)	0.21

* **Abbreviations:** BTcP: Breakthrough Cancer Pain; CI: Confidence Interval; ECOG: Eastern Cooperative Oncology Group; Ref.: Reference category

* **Note:** The multivariable logistic regression model included candidate covariates selected a priori (age, sex, cancer site, presence of metastasis and performance status) that demonstrated a univariate *p*-value < 0.20

Table 4. Psychological distress and quality-of-life scores by BTcP status.

Measure	BTcP (*n* = 130) mean score	No BTcP (*n* = 182) mean score	*p*-value
HADS - Anxiety	10.2	7.1	< 0.001
HADS - Depression	9.4	7.5	< 0.01
EORTC QLQ-C30 Global QoL	52.6	68.3	< 0.001

* **Abbreviations:** BTcP: Breakthrough Cancer Pain; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; HADS: Hospital Anxiety and Depression Scale; QoL: Quality of Life

* **Note:** *p*-values derived from the Mann–Whitney *U* test

The approval of the Ethics Committee for Biomedical Research of Oujda (CERBO):

CERBO
Comité d'Ethique pour la Recherche Biomédicale d'Oujda

Comité d'Ethique pour la Recherche Biomédicale d'Oujda
Faculté de Médecine et de Pharmacie
Université Mohammed Premier Oujda

AVIS DU COMITE D'ETHIQUE POUR LA RECHERCHE BIOMEDICALE D'OUJDA (CERBO)

Oujda le 04/06/2024

Titre et références du projet de recherche

- Reference : **05/2024**
- Intitulé : **« Douleurs cancéreuses : Etude clinique et thérapeutique au niveau du Centre Régional d'Oncologie Hassan II d'Oujda ».**
- Investigateur(rice) principal(e) : **Pr. Ahmed Amine El OUMRI**
- Promoteur : **Laboratoire d'Immunohématologie et Thérapie Cellulaire Faculté de Médecine et de Pharmacie d'Oujda**
- Début de l'étude : **05/06/2024** Durée de l'étude : **Trois (3) ans**

Avis final du CERBO

Après examen et évaluation, le Comité d'Ethique (CERBO) a adopté à l'unanimité la délibération suivante :

Avis favorable

à la réalisation du projet de recherche sus-intitulé et cet avis ne sera valable que pour ce projet.

L'investigateur(rice) principal(e) est prié(e) d'informer le CERBO :

- De tous les incidents ou accidents éventuels survenus pendant l'exécution des activités de recherche de ce projet ;
- De la clôture de l'étude avec un rapport succinct sur son déroulement.

Références du travail du comité

Le comité se base pour ses délibérations sur :

- La loi 28-13 du 17 septembre 2015 relative à la protection des personnes participantaux recherches biomédicales ;
- La décision du ministre de la santé N° 02/DRC/00 du 03 décembre 2012, relative auxrecherches biomédicales.

Pour le Comité d'éthique CERBO
Pr Abdelkader Hakkou

Le Président du Comité d'Ethique pour la Recherche Biomédicale d'Oujda
Signé : Pr. Abdelkader HAKKOU

Secrétariat : CERBO, Faculté de Médecine et de Pharmacie d'Oujda, Hay al Hikma, BP, 4867, Oujda, 60049, Maroc. Tel : 0536531414 ; Fax : 0536531919, E-mail : cerbo2015oujda@gmail.com; Site Web : http://fmpo.ump.ma/fr/recherche/comite-dethique

Research