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ORIGINAL RESEARCH

Multidisciplinary approach, continuous care and opioid management in cancer pain: case series and review of the literature

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Abstract

Underlying cancer pain has heterogenous aetiologies and mechanisms. It requires detailed and comprehensive pain assessment, combined with personalized treatment. A multidisciplinary team is essential to providing the best management of cancer pain at every disease stage, improving the quality of life and outcomes in patients with cancer. This narrative literature review emphasizes the value of providing all patients with multidisciplinary pain management in their preferred care setting. Real-life experiences are also reported to witness the efforts of physicians to properly manage cancer pain.

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Introduction

A systematic review and meta-analysis by van den Beuken-van et al.[1] in 2016 found that pain affected 50.7% of patients at all cancer stages and 70–90% of patients with advanced disease. Cancer pain is therefore a common symptom that has a notable impact on both health-related quality of life (QoL) and adherence to antitumoural treatment.[2–5]

A modern, multidisciplinary approach to cancer-related pain would ensure better health outcomes and an improved QoL for patients with cancer.[6–9]

Methods

With the aim of highlighting the importance of a multidisciplinary approach to cancer pain management, we performed a literature search in the databases PubMed, Scopus, ISI-Web of Science and Google Scholar for article titles containing the keywords "cancer pain", "opioids" and "multidisciplinary". The search was restricted to human, adult, English language and published in the period 2012–2022. Additional studies were manually included from the reference lists of identified articles. Four clinical cases were then described, with a focus on emphasizing the value of multidisciplinary teams in the management of complex cases of cancer pain. In accordance with the World Medical Association Declaration of Helsinki, all patient data were anonymized, excluding any details that would enable patient reidentification.

Review

Cancer-related pain may be due to the disease itself or to treatments such as surgery, radiotherapy,

chemotherapy, and hormonal, biological and immune therapies.[10] In approximately 10% of cases, pain is due to other sources, unrelated to cancer.[11] Due to the diverse aetiologies and underlying mechanisms, cancer pain may be acute or chronic, nociceptive, neuropathic or visceral. Patients may experience mixed types of pain simultaneously, and pain might fluctuate over a given day or specific time period.[11]

Individualized, detailed and comprehensive pain assessment is essential to providing the best management approach for patients with cancer. Pain assessment must be repeated regularly to guide treatment strategies at each stage of illness.[10,12–16] The description of the quality of pain, location, daily pattern and extent of relief after receiving medication are all fundamental attributes when investigating pain; however, pain intensity (mild, moderate, severe) is recognized as the most relevant clinical dimension of pain experience.[17]

Amongst standardized unidimensional pain intensity scales,[13,18] the visual analogue scale, verbal rating scale and numeric rating scale (NRS) are the most widely used worldwide.[19] Specialized scales are also available for sub-populations (e.g. older adults with comorbidities and polypharmacy,[16,20] non-verbal patients,[21,22] and patients with substance use disorders[23–25]). Clinicians should identify the most suitable scale for an individual patient, using that same scale at each subsequent assessment to track changes in pain intensity over time.[25] Long-term historical pain must also be evaluated through verbal history or pain diaries, which can promote patient empowerment and involvement in pain management. The average pain score from the past months or weeks, the highest and lowest pain scores, any precipitating factors, and response to analgesic regimen are key factors to be defined as a part of pain history.[25] This information allows for better differentiation between background pain, defined as the underlying persistent pain usually controlled by long-term analgesic treatment and episodes of breakthrough cancer pain (BTcP).

As defined in 2009 by the task group of the Science Committee of the Association for Palliative Medicine of Great Britain and Ireland,[26] BTcP is an acute, transient exacerbation of severe pain occurring spontaneously or due to a specific trigger (walking, changes in position, coughing),[26–30] in a patient whose background pain is stable and controlled for a greater part of the time.[26–30] BTcP is associated with greater distress and poorer QoL[27,28,31,32]; therefore, its assessment should be included in routine cancer pain evaluation.[33–35]

Decisions regarding cancer pain treatments are based on compliance with guideline recommendations as well as on patient perspectives and expectations. Tailored treatment is required, whilst increasing the patient's capacity for self-management.[10,36] Alongside empowering patients to communicate their pain effectively with physicians, pain diaries are tools that proactively involve both parties in pain management.[37–39] Additionally, ongoing research seeks to support whether patient-reported outcome measures affect pain assessment, decision-making, therapeutic relationships and treatment evaluation.[40–43]

In accordance with the World Health Organization (WHO) three-step analgesic ladder and guidelines for chronic cancer-related pain management,[10,16,44] non-opioid analgesics (e.g. paracetamol and non-steroidal anti-inflammatory drugs) are first-line agents for the treatment of mild pain, whilst opioids are indicated for the treatment of persistent, moderate-to-severe cancer pain. Where background pain is controlled by strong opioids, BTcP should be treated with transmucosal immediate-release fentanyl (TIRF), following proper titration.[16,45–50]

Currently, the benefits of modern drug formulation technologies,[51,52] drug delivery systems,[53–55] and digital care options facilitate the management of cancer pain.[56–62] Furthermore, current evidence suggests that the most severe BTcP phenotypes are correlated with specific cancer characteristics or background pain types.[63,64] In these instances, more severe phenotypes could be monitored using telemedicine programmes.[65–68]

As an essential component of the multidisciplinary cancer team, responsibilities of the oncology pharmacist include optimizing the benefits of drug therapies, minimizing their toxicity, and working with patients and carers on supportive care issues. Several studies have shown that incorporation of pharmacists into the cancer pain team leads to observable reductions in drug-related issues, with a statistically significant reduction in pain intensity and adverse analgesic reactions.[69,70]

The optimal route of drug administration (oral, parenteral, transdermal, transmucosal), the patient's preferred formulation (tablet, capsules, liquids) and the type of release (immediate or controlled) should be carefully determined according to the pain assessment and may be modified over time. Interventional strategies, such as neurolytic blocks, intrathecal drug delivery systems, vertebral augmentation and neuromodulation for neuropathic pain provide options for managing cancer pain that is refractory to pharmacological therapy.[71–73] Furthermore, rehabilitative medicine (including preventative, restorative, supportive

and palliative rehabilitation) can be combined with other analgesic strategies used to control cancer-related pain,[74–78] whilst a range of adjuvant drugs (coanalgesics) can be combined with analgesic therapies to enhance their effects.[79]

Distress, anxiety and depression are prevalent in patients with cancer and can exacerbate pain expression, requiring appropriate and tailored healthcare interventions.[80–82] A multidimensional approach, combining drugs with psychological and cognitive behavioural treatments, can reduce pain severity and interference with function.[83–85]

The management of adverse effects induced by drugs used for cancer pain requires meticulous understanding of side-effect profiles linked to specific medications; consequently, it is essential to assess the patient's characteristics and comorbidities and to anticipate potential drug–drug interactions.[86–90]

A cancer pain management plan should be reviewed regularly to assess outcomes, rescheduling treatments and gradually discontinuing drugs when no longer required.[10] The active care of patients can be provided by a variety of healthcare professionals simultaneously (e.g. oncologists, surgeons, pharmacists, primary care physicians, nurses, psychologists, physiotherapists and occupational therapists). It is therefore essential to set up a dedicated multidisciplinary team with the knowledge, commitment, communication skills and capacities to manage cancer pain. Cancer care services require adequate resources to provide education to patients, caregivers and staff, whilst pathways for reviewing and improving the quality of pain care must be continually implemented.[91]

Finally, inpatients and outpatients with advanced cancer should receive dedicated and early palliative care services to improve QoL, similarly managed by a multidisciplinary team, with equal consideration of the factors outlined in this discussion.[92–94]

Case reports

We report four real-world clinical cases of managing complex cancer-related pain using a multidisciplinary and comprehensive approach.

All the data referring to the patients were published anonymously without any details allowing re-identification of the patient and in accordance with the World Medical Association Declaration of Helsinki.

Case report #1

A 75-year-old male with a functional status compatible with an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 and no relevant comorbidities underwent routine endoscopy and was diagnosed with a circumferential lesion of the stomach pylorus. The biopsy was compatible with adenocarcinoma stage cT3N0M0. The multidisciplinary tumour board proposed perioperative chemotherapy with 5-fluorouracil (5-FU), leucovorin, oxaliplatin and docetaxel. Four cycles pre-surgery and post-surgery were scheduled and primary neutropenic prophylaxis with filgrastim for 4 days was also prescribed. The first cycle was performed at 50% 5-FU, pending the detection of genetic variants of dihydropyrimidine dehydrogenase (DPYD). The second and third cycles were performed on 100% 5-FU.

Ten days after the third cycle, the patient was admitted at outpatients and complained of abdominal cramping (NRS 4–5) lasting 3–5 days. He reported oropharyngeal pain, nausea and anorexia that limited oral intake and diarrhoea grade 2 on CTCAE (Common Terminology Criteria for Adverse Events V 5.0)[95] with liquid stool,[96] seven times a day and then twice or three times daily. No blood, mucus or purulent appearance were observed.

On clinical examination, the patient was dehydrated and debilitated with an ECOG PS scale of 1. Oropharyngeal candidiasis was observed, and the abdomen was plain and smooth with diffuse tender to deep palpation but no irritable signs. Blood tests revealed decreased albumin and elevated C-reactive protein levels with no other significant alterations. Gastroenteritis was suspected and the patient was started on hydration and intravenous bolus morphine. After 4–6 h with no pain exacerbation, the patient was discharged with ciprofloxacin (500 mg, twice daily), tapentadol (50 mg, twice daily), fluconazole (100 mg, once daily) and a suitable diet.

At the next clinical evaluation, scheduled 2 days later, the patient complained of excruciating irruptive abdominal cramps, was unable to ingest due to oropharyngeal pain exacerbation and had no stool passage in the last 48 h. The patient had lost 3 kg since the beginning of treatment and appeared dehydrated, with evidence of oropharyngeal candidiasis. An abdominal X-ray and ultrasound showed small bowel distension. The patient was admitted for supportive measures with hydration and intravenous morphine for pain control. He was discharged a few hours later with hypercaloric and hyperproteic enteral supplements, TIRF (25 µg/h) and rescue sublingual fentanyl (133 µg up to four times, daily). The fourth cycle was postponed for 1 week to facilitate recovery.

The evaluation before treatment showed CTCAE V 5.0 Grade 2 asthenia, recovered appetite, abdominal discomfort without pain or need for rescue medication in the last 48 h, regular intestinal transit, mild bilateral ankle swelling and 2-kg weight gain. The dose of 5-FU in the fourth cycle was reduced by 20% and the transdermal fentanyl dose was decreased to 12.5 µg/h. The treatment was well tolerated and the patient recovered his activities with an ECOG PS of 0, regular food intake, regular intestinal functioning, no abdominal pain and no need for rescue medication. Two weeks after treatment, transdermal fentanyl was suspended and surgical intervention was planned 4–6 weeks after the last cycle.

Comment

Patients receiving chemotherapy often experience mucosal damage throughout the digestive tract; mucositis reflects a short-term, self-limited adverse effect of cancer treatments, especially in those treated with 5-FU, methotrexate, capecitabine and irinotecan.[97–102] Symptoms include painful oral ulcerations, dysphagia, odynophagia, oesophagitis, gastritis, diarrhoea, electrolyte imbalance, dehydration, malabsorption and malnutrition. In some cases, life-threatening infections and sepsis can occur.[99] Mild oral mucositis can also be very painful and worsen patients' QoL. Basic physiological needs, such as swallowing and eating, can be limited, directly influencing the success of anticancer therapies and greatly impacting clinical outcomes.[103–106]

The onset of chemotherapy-associated enteritis is acute (usually within 24–48 h after treatment) and may present with increased frequency of bowel movements, excessive gas, intestinal cramping and loosening of stool consistency. This can become severe with frequent watery stools. Nausea, vomiting, anorexia and intense abdominal pain can also occur.[99,107,108] Patients with severe intestinal mucositis frequently require hospital admission for adequate supportive care.

The National Cancer Institute Common Terminology Criteria for Adverse Events[95] grades the severity of mucositis on a scale of 0–5, based primarily on symptom severity, functional alteration and intervention requirements. Integration with patient-reported outcomes, such as the Oral Mucositis Daily Questionnaire[109] or the Patient-Reported Oral Mucositis Symptom Scale,[110] becomes critical for improving the accuracy of clinical evaluation.[5] The Multinational Association of Supportive Care in Cancer and the International Society of Oral Oncology offer specific guidelines for the treatment of oral mucositis.[101] Primarily, oral administration of systemic opioids is recommended to treat pain, whilst intravenous morphine is the preferred parental route for patients who cannot swallow. Transdermal fentanyl is another suitable option in this instance.[111]

This case illustrates the need for regular examination in patients undergoing chemotherapy and highlights that monitoring of symptom evolution is mandatory to prevent toxicity. Optimization of a patient's physical condition during perioperative treatment is essential to ensure the best possible outcomes and to support surgical aggressiveness. All approaches to iatrogenic symptom control should therefore be undertaken, including opioid therapy, even in the early stages of cancer.

Aligning the action of clinical resources and recruiting a multidisciplinary team are fundamental to addressing supportive care measures, accomplishing proposed plans and maintaining the best patient-centred care.

Case report #2

A 54-year-old man was diagnosed with bladder cancer (stage T3N2M0) in October 2021. Histological examination revealed high-grade invasive urothelial carcinoma (ypT4a, ypN3). Adjuvant chemotherapy (gemcitabine and carboplatin for three cycles) before radical cystectomy was performed and a cutaneous uretero-ileostomy *ad modum* Bricker was created.

In April 2022, the patient had persistent abdominal pain (NRS 3–4). Computed tomography (CT) revealed a large, capsuled fluid collection in the pelvis. Bilateral percutaneous drainage was performed but, at the next CT scan, fluid collection (7.8 × 5.5 cm) did not decrease and malignant ascites due to peritoneal carcinomatosis was found.

In May 2022, the patient complained of abdominal pain (NRS 6–7), nausea, vomiting and constipation and was treated at home with intramuscular ketorolac (30 mg) as needed. A clinical and radiological diagnosis of sub-obstruction was made; a nasogastric tube was placed and hydration was provided.

Rapid opioid titration with intravenous morphine (1.5 mg/10 min) was initiated to control pain, followed by continuous intravenous morphine (40 mg/24 h), dexamethasone (8 mg/24 h) and metoclopramide (10 mg/24 h). To manage transient exacerbations of pain, intramuscular butylscopolamine (20 mg, daily) and subcutaneous morphine (10 mg as needed) were provided.

In the subsequent days, the symptoms and pain remained well controlled; however, on hospital day 10, the patient complained of unrelenting severe abdominal pain (NRS 10). After swallowing of the oral water-soluble

contrast,[112] CT revealed dilatation of small bowel, multiple air-fluid levels and stoppage of the oral contrast, indicating malignant bowel obstruction (MBO).[113]

The multidisciplinary team (oncologist, gastroenterologist, nutritionist, interventional radiologist surgeon and palliative care physician) informed the patient about short-term symptomatic relief with palliative surgery (temporary laparotomic ileostomy), high probability of re-obstruction and serious complications associated with surgery. Options for limiting aggressive treatments were explored.[114,115]

After a 2-week inpatient stay, the patient wanted to return home to be with his family. He was referred to a home palliative care team, with a subcutaneous portable pump for prolonged subcutaneous administration of morphine (80 mg, daily), dexamethasone (8 mg, daily), hyoscine butylbromide (60 mg, daily) and octreotide (0.5 mg, daily). Oral transmucosal fentanyl (133 µg, up to four times daily) was prescribed for visceral BTcP. The patient died at home 20 days later.

Comment

Peritoneal carcinomatosis and MBO are common in the progression of many cancer types and demand a multidisciplinary approach for successful palliation.[116,117] Medical management for inoperable symptomatic MBO includes antimotility, antisecretory and antiemetic drugs, which aid spontaneous occlusion resolution in 30–40% of cases.[118,119]

Due to its anti-inflammatory effect, dexamethasone (4–12 mg, daily) provides central antiemetic effects and minimizes distension of the bowel wall.[120] Whilst intravenous metoclopramide (10 mg/4 h) is the first-line treatment option for partial bowel obstruction, it should be avoided in cases of complete obstruction.[119] Somatostatin analogues (e.g. octreotide) reduce peristalsis and gastroenteric secretions and may be administered by subcutaneous bolus or continuous subcutaneous infusion.[118,121] It is also important to note that peripheral µ-opioid receptor antagonists, prescribed for the management of opioid-induced constipation, are contraindicated for MBO.[122,123] Finally, for patients with intractable symptoms, immediate placement of a nasogastric tube for decompression provides relief.[124]

Routine parenteral nutrition for patients with end-stage cancer and MBO is generally discouraged, and nutrition interventions should only be initiated when the benefits to QoL and survival outweigh the risks. Multidisciplinary teams should therefore identify patients that will survive long enough to benefit from tailored parenteral nutrition and hydration.[119,125,126]

Pain was the paramount symptom in this patient; intravenous morphine was prescribed according to the European Society of Palliative Care and WHO guidelines.[127] Notably, morphine is two to three times more potent when administered parenterally and is physically compatible with other drugs commonly used in syringe drivers.

When MBO is diagnosed in advanced cancer, a multidisciplinary team is required to inform medical decisions, directed at minimizing symptom burden and maximizing QoL.[127,128] For improved medical decision-making, patients and their families must be informed about available treatment options and their respective likely outcomes. Patients must be encouraged to communicate their needs so that effective symptom and pain control can be delivered in their preferred setting.[116]

Case report #3

A 78-year-old man, with a diagnosis of prostatic adenocarcinoma with pulmonary and vertebral metastases had recently discontinued active therapies on his own due to collateral effects and knowledge of disease progression at the last diagnostic investigation. Furthermore, the worsening of vision due to bilateral maculopathy and the need for urinary catheter had greatly reduced his independence.

Pain was poorly controlled with oxycodone (20 mg, twice daily), such that he avoided movement, spending most days alone in bed, lasting a period of approximately 2 months. The patient's family consulted the oncologist, who reported the case to a multidisciplinary team. The team agreed on immediate referral to home palliative care service.

At the first home visit, the patient showed a discrete performance status (Karnofsky performance score of 60) and lumbar pain (NRS 4–5) radiating to the left leg, with several episodes of BTcP. BTcP episodes (NRS 8–9) were spontaneous and mainly exacerbated by movement or walking. Additionally, the patient was especially frightened by the upcoming catheter change, which he reported to be very painful. The patient reported taking oxycodone irregularly. The Palliative Prognostic score (PaP; 2.5 points and 30-day survival probability >70%), Hospital Anxiety Scale (9 points, borderline) and Hospital Depression Scale (16 points, abnormal) were used to assess the patient.

To improve adherence to opioid treatment, transdermal fentanyl (25 µg/h) was applied and sublingual fentanyl (133 µg, up to four times daily) was prescribed for BTcP, volitional or spontaneous. Sublingual fentanyl was also recommended shortly before catheter replacement to

reduce procedural pain. Duloxetine (30 mg, once daily) was prescribed for the co-occurrence of neuropathic pain and depression in the patient, measured by the Hospital Depression Scale.

After approximately 3 weeks, the patient presented with baseline-controlled pain (NRS 1–2) and was receiving two daily intakes of TIRF on average for volitional BTcP; mood was markedly improved. Following recommendation from the palliative care physician, the patient underwent a new oncology consultation. The multidisciplinary team proposed single-shot spinal radiotherapy (D12–L1).

Comment

Sharing verified scales for the comprehensive and all-inclusive assessment of patients with cancer is essential for multidisciplinary teams. Greater interprofessional dissemination of scales validated by scientific societies, available on digital platforms, could enhance the management of patients with cancer. Consequently, training programmes for the use of validated scores and their implementation in clinical practice are critical in the future.[129,130]

In this case, an overall PaP score, derived from the Karnowski Performance score combined with five other criteria, was used to generate prognostic information. The PaP was reported in the form of a 0–17.5 numerical scale, with higher scores predicting shorter survival.[129]

The biopsychosocial model of pain emphasizes the interactions between chronic pain, anxiety and depression, which are often difficult to diagnose in patients with cancer despite their high prevalence and associated all-cause mortality.[80,131]

The Hospital Anxiety Scale and Depression Scale are unidimensional measures recommended to assess psychological distress amongst populations aged 65–80 years. They yield consistent results and show invariance regarding sex.[132] In this case, these scales simplified the assessment of depression in outpatient cancer care settings and guided treatment with duloxetine, which is also useful as an adjuvant for neuropathic pain.

Finally, regular and thorough assessment of pain, monitoring baseline and daily fluctuations, is crucial.[133] Often, greater intensity breakthrough pain episodes in the advanced stages of cancer are due to bone pain, caused by metastasis. This is responsible for both incident and movement-induced BTcP.[134] Correct management of BTcP allows for significant improvement in the QoL of these patients.[135–137]

TIRF is the treatment of choice for BTcP due to its pharmacological properties, including rapid onset, increased potency and short half-life.[4,26,138] Conversely, oral immediate-release opioids can be used to treat slow-onset or predictable BTcP.[34,35,139] Furthermore, both TIRF and oral morphine can be prescribed to manage procedural pain, administered according to their onset of action (10–15 and 30 min, respectively).[138,140]

In support of this, a Delphi expert management consensus recommended transmucosal fentanyl and oral morphine as the most appropriate drugs for procedural pain,[138] suitable for both outpatients and inpatients, whilst intravenous and subcutaneous morphine was deemed most appropriate for inpatients.[138]

Case report #4

A 44-year-old woman was diagnosed, in 2009, with epithelioid sarcoma, located primarily in the fifth left metacarpal bone. In 2012, the surgery was radicalized by amputating fifth metacarpal bones and fifth left finger. Due to a local recurrence in 2014, preoperative radiotherapy was provided prior to surgical treatment. The fourth finger and four left metacarpal bones were then amputated.

The patient received analgesic treatment with long-acting morphine (30 mg/12 h), short-acting morphine (as needed) and paracetamol (2 g, daily). However, due to the increased intensity of phantom pain (NRS 7), the treatment was modified by including oxycodone (40 mg/12 h) and short-acting morphine temporarily withdrawing from the long-acting form. Pregabalin was added and gradually increased to a dose (150 mg/8 h). Rehabilitation began with special focus on the mirror method.

Following complete resolution of phantom pain, pain medications (including pregabalin) were withdrawn 12 months after the initiation of analgesic treatment. The patient did not experience any episodes of pain and fully returned to social and professional activities. She assessed her QoL as high throughout periodic control performed by the care team (palliative care physician and oncologist).

In June 2016, the patient-reported pain in the left armpit area and the previous pain treatment schedule was gradually reinstated, achieving good pain control. No abnormalities were found in the imaging studies of the left armpit and chest.

At the end of December 2016, during a routine inspection at the palliative clinic, a painless mass approximately 5 mm in diameter was detected in the patient's left

armpit, and an urgent excision of the lesion with the surrounding tissue margin was performed. Histopathology confirmed epithelioid sarcoma and two lymph nodes 10 mm in diameter were identified upon re-examination of the thoracic CT. This prompted the multidisciplinary team to perform preoperative radiotherapy and subsequent axillary lymphadenectomies.

Due to local recurrence, the patient began to experience anxiety states and required psychological support; alprazolam (0.5 mg/8 h) was initiated, reducing their frequency and severity.

After radiotherapy and lymphadenectomy, the pain in the armpit and shoulder areas worsened (NRS 4–5), coupled by a significant reduction in shoulder joint mobility. Phantom pain worsened and BTcP appeared, often concurrent with physical activity. BTcP showed moderate-to-severe intensity (NRS 6–8), appearing suddenly, typically lasting approximately 30 min.

After increasing the dose of oxycodone (80 mg, twice daily) and pregabalin (300 mg, 150 mg and 300 mg, daily), complete control of phantom pain and good control of background pain was achieved (NRS <3). Initially, 133 µg of sublingual fentanyl was administered to treat breakthrough pain episodes. Following titration, the optimal dose was 267 µg for a maximum of 2–4 BTcP episodes throughout the day. The patient also underwent comprehensive rehabilitation, achieving significant improvement in functionality. In the following months, the patient experienced controlled pain and assessed QoL as good, with improved professional, social and family life.

In October 2020, 267 µg of sublingual fentanyl did not provide the patient with satisfactory relief from BTcP (reduction of NRS from 7–8 to 5–6) and the dose was increased to 533 µg, achieving fast and effective reduction of breakthrough pain.

In January 2021, local radiotherapy was initiated to treat a new recurrence. This resulted in dermatological complications (such as skin wounds and oozing) and tissue restrictions, which significantly limited mobility in the shoulder joint and caused severe pain. QoL deteriorated significantly, owing to the acknowledgement of disease progression and the patient became increasingly concerned about death. The multidisciplinary team requested a psychiatric consultation for depressive symptoms and the patient was referred to palliative care staff. After acceptance of disease progression and the inevitability of death, the patient tried to enjoy each subsequent day without pain. At present, despite the lack of recovery, the patient still participates in family life, is self-reliant, and her greatest joys are the graduation and independence of her daughters and her loving and supportive husband.

Comment

Epithelioid sarcoma is a rare, slow-growing soft tissue malignancy associated with a high rate of local recurrence, metastases and mortality.[141,142] The classic variant typically occurs in young adults and tends to arise in the distal extremities.

Missed or delayed diagnosis is commonplace.[143] In high-volume, comprehensive cancer centres, patient-centric oncological pathways should be established to address this, thereby lowering morbidity and mortality rates.[144]

Limb-sparing surgery, with early reconstructive procedures and preservation of function is foundational in the treatment of most sarcomas of the forearm, hand and wrist.[145]

In the described case, progressive neoplastic disease and iatrogenic consequences of treatment manifested in various types of pain and other ailments. The appropriate selection of painkillers allowed for complete pain control, relieving it almost completely with relatively few side-effects. Although the expected durations of opioid therapies, adjuvants and non-opioid analgesics can vary and range from infrequent to long-term, the present case demonstrates that the implementation of opioid drugs is not synonymous with lifelong use. This is supported by evidence that patients with cancer are not primarily affected by opioid misuse and appropriate pain management supports avoidance of addiction, whilst maintaining full symptom control.[24,25] Even higher doses of opioid analgesics used across several months can be safely discontinued in the event of pain relief, provided that the treatment is properly administered and withdrawal is accompanied by strong clinician support.

Early and dedicated palliative care delivered by interdisciplinary teams, parallel to oncological therapies, improves health-related QoL and ameliorates symptom burden. Partnering with patients and their families is paramount to promote physical, spiritual and psychosocial well-being throughout their journey with the disease.[93,146–148]

Key highlights of cancer pain management[11,16,149]

- ✓ Always assess the presence of pain in patients with cancer.
- ✓ Identify the underlying mechanism of pain and intervene on modifiable causes.
- ✓ Assess psychological and emotional distress.

- ✓ Quantify pain periodically using validated scales.
- ✓ Select specific scales for cognitive impairment.
- ✓ Evaluate the most appropriate choice of treatment as part of the multidisciplinary team and propose it to the patient.
- ✓ Frequently reassess pain and encourage patients to use pain diaries.
- ✓ Consider the benefits of adjuvants to improve pain control.
- ✓ Assess for the presence of BTcP in patients on stable doses of opioids and offer appropriate tailored therapy, as needed.
- ✓ Change the route of opioid administration and use opioid rotation (or switching) to improve clinical outcomes.
- ✓ Assess addictive behaviour in patients using opioids.
- ✓ Gradually taper therapy when unnecessary.

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References

1. van den Beuken-van Everdingen MHJ, Hochstenbach LMJ, Joosten EAJ, Tjan-Heijnen VCG, Janssen DJA. Update on prevalence of pain in patients with cancer: systematic review and meta-analysis. *J Pain Symptom Manag*. 2016;51(6):1070–1090.e9. https://doi.org/10.1016/j.jpainsymman.2015.12.340
2. Deng D, Fu L, Zhao YX, et al. The relationship between cancer pain and quality of life in patients newly admitted to Wuhan Hospice Center of China. *Am J Hosp Palliat Care*. 2012;29(1):53–59. https://doi.org/10.1177/1049909111418636
3. Matsumura C, Yamada M, Jimaru Y, Ueno R, Takahashi K, Yano Y. Relationship between pain scores and EORTC QLQ-C15-PAL scores in outpatients with cancer pain receiving opioid therapy. *Biol Pharm Bull*. 2021;44(3):357–362. https://doi.org/10.1248/bpb.b20-00626
4. Bedard G, Davies A, McDonald R, et al. Breakthrough cancer pain: a comparison of surveys with European and Canadian patients. *Support Care Cancer*. 2015;23(3):791–796. https://doi.org/10.1007/s00520-014-2426-6
5. Bossi P, Antonuzzo A, Armento G, et al. What to do and what not to do in the management of cancer pain: a physician survey and expert recommendations. *Cancer Manag Res*. 2021;13:5203–5210. https://doi.org/10.2147/CMAR.S310651
6. Pugh TM, Squarize F, Kiser AL. A comprehensive strategy to pain management for cancer patients in an inpatient rehabilitation facility. *Front Pain Res*. 2021;2:688511. https://doi.org/10.3389/fpain.2021.688511
7. Yang B, Cui Z, Zhu X, et al. Clinical pain management by a multidisciplinary palliative care team. *Medicine*. 2020;99(48):e23312. https://doi.org/10.1097/MD.0000000000023312
8. Fernando G, Hughes S. Team approaches in palliative care: a review of the literature. *Int J Palliat Nurs*. 2019;25(9):444–451. https://doi.org/10.12968/ijpn.2019.25.9.444
9. Marinangeli F, Saetta A, Lugini A. Current management of cancer pain in Italy: expert opinion paper. *Open Med*. 2021;17(1):34–45. https://doi.org/10.1515/med-2021-0393
10. Bennett MI, Kaasa S, Barke A, Korwisi B, Rief W, Treede RD. The IASP classification of chronic pain for ICD-11: chronic cancer-related pain. *Pain*. 2019;160(1):38–44. https://doi.org/10.1097/j.pain.0000000000001363
11. Caraceni A, Shkodra M. Cancer pain assessment and classification. *Cancers*. 2019;11(4):510. https://doi.org/10.3390/cancers11040510
12. Minello C, George B, Allano G, Maindet C, Burnod A, Lemaire A. Assessing cancer pain – the first step toward improving patients' quality of life. *Support Care Cancer*. 2019;27(8):3095–3104. https://doi.org/10.1007/s00520-019-04825-x
13. Caraceni A, Cherny N, Fainsinger R, et al. Pain measurement tools and methods in clinical research in palliative care. *J Pain Symptom Manag*. 2002;23(3):239–255. https://doi.org/10.1016/S0885-3924(01)00409-2
14. Fink RM, Gallagher E. Cancer pain assessment and measurement. *Semin Oncol Nurs*. 2019;35(3):229–234. https://doi.org/10.1016/j.soncn.2019.04.003
15. Bruera E, Portenoy R. Cancer pain. In: *Assessment and Management*. Cambridge: Cambridge University Press; 2010:53–88.
16. Fallon M, Giusti R, Aielli F, et al. Management of cancer pain in adult patients: ESMO clinical practice guidelines. *Ann Oncol*. 2018;29:iv166–iv191. https://doi.org/10.1093/annonc/mdy152
17. Mercadante S, Porzio G, Adile C, et al. Pain intensity as prognostic factor in cancer pain management. *Pain Pract*. 2015;15(1):E1–E8. https://doi.org/10.1111/papr.12259
18. Hjermstad MJ, Fayers PM, Haugen DF, et al. Studies comparing numerical rating scales, verbal rating scales, and visual analogue scales for assessment of pain intensity in adults: a systematic literature review. *J Pain Symptom Manag*. 2011;41(6):1073–1093. https://doi.org/10.1016/j.jpainsymman.2010.08.016
19. Caraceni A, Cherny N, Fainsinger R, et al. Pain measurement tools and methods in clinical research in palliative care. *J Pain Symptom Manag*. 2002;23(3):239–255. https://doi.org/10.1016/S0885-3924(01)00409-2
20. Brant JM. Assessment and management of cancer pain in older adults: strategies for success. *Asia Pac J Oncol Nurs*. 2018;5(3):248–253. https://doi.org/10.4103/apjon.apjon_11_18
21. Lichtner V, Dowding D, Esterhuizen P, et al. Pain assessment for people with dementia: a systematic review of systematic reviews of pain assessment tools. *BMC Geriatr*. 2014;14(1):138. https://doi.org/10.1186/1471-2318-14-138
22. van Herk R, van Dijk M, Baar FPM, Tibboel D, de Wit R. Observation scales for pain assessment in older adults with cognitive impairments or communication difficulties. *Nurs Res*. 2007;56(1):34–43. https://doi.org/10.1097/00006199-200701000-00005
23. Kennedy AJ, Arnold RM, Childers JW. Opioids for chronic pain in patients with history of substance use disorders, part 1: assessment and initiation #311. *J Palliat Med*. 2016;19(8):888–889. https://doi.org/10.1089/jpm.2016.0076

24. Dalal S, Bruera E. Pain management for patients with advanced cancer in the opioid epidemic era. *Am Soc Clin Oncol Educ Book*. 2019;39:24–35. https://doi.org/10.1200/EDBK_100020
25. Scarborough BM, Smith CB. Optimal pain management for patients with cancer in the modern era. *CA Cancer J Clin*. 2018;68(3):182–196. https://doi.org/10.3322/caac.21453
26. Davies AN, Dickman A, Reid C, Stevens AM, Zeppetella G. The management of cancer-related breakthrough pain: recommendations of a task group of the Science Committee of the Association for Palliative Medicine of Great Britain and Ireland. *Eur J Pain*. 2009;13(4):331–338. https://doi.org/10.1016/j.ejpain.2008.06.014
27. Deandrea S, Corli O, Consonni D, Villani W, Greco MT, Apolone G. Prevalence of breakthrough cancer pain: a systematic review and a pooled analysis of published literature. *J Pain Symptom Manag*. 2014;47(1):57–76. https://doi.org/10.1016/j.jpainsymman.2013.02.015
28. Raj SX, Thronaes M, Brunelli C, Hjermstad MJ, Klepstad P, Kaasa S. A cross-sectional study on prevalence of pain and breakthrough pain among an unselected group of outpatients in a tertiary cancer clinic. *Support Care Cancer*. 2014;22(7):1965–1971. https://doi.org/10.1007/s00520-014-2178-3
29. Zucco F, Bonezzi C, Fornasari D. Breakthrough cancer pain (BTcP): a synthesis of taxonomy, pathogenesis, therapy, and good clinical practice in adult patients in Italy. *Adv Ther*. 2014;31(7):657–682. https://doi.org/10.1007/s12325-014-0130-z
30. Mercadante S, Cuomo A. Breakthrough cancer pain: ten commandments. *Value Health*. 2016;19(5):531–536. https://doi.org/10.1016/j.jval.2016.03.002
31. Portenoy RK, Payne D, Jacobsen P. Breakthrough pain: characteristics and impact in patients with cancer pain. *Pain*. 1999;81(1):129–134. https://doi.org/10.1016/S0304-3959(99)00006-8
32. Davies A, Buchanan A, Zeppetella G, et al. Breakthrough cancer pain: an observational study of 1000 European oncology patients. *J Pain Symptom Manag*. 2013;46(5):619–628. https://doi.org/10.1016/j.jpainsymman.2012.12.009
33. Mercadante S, Portenoy RK. Breakthrough cancer pain: twenty-five years of study. *Pain*. 2016;157(12):2657–2663. https://doi.org/10.1097/j.pain.0000000000000721
34. Løhre ET, Thronæs M, Klepstad P. Breakthrough cancer pain in 2020. *Curr Opin Support Palliat Care*. 2020;14(2):94–99. https://doi.org/10.1097/SPC.0000000000000494
35. Davies AN, Elsner F, Filbet MJ, et al. Breakthrough cancer pain (BTcP) management: a review of international and national guidelines. *BMJ Support Palliat Care*. 2018;8(3):241–249. https://doi.org/10.1136/bmjspcare-2017-001467
36. Gibbins J, Bhatia R, Forbes K, Reid CM. What do patients with advanced incurable cancer want from the management of their pain? A qualitative study. *Palliat Med*. 2014;28(1):71–78. https://doi.org/10.1177/0269216313486310
37. Mayahara M, Wilbur J, O'Mahony S, Breitenstein S. E-Pain reporter. *J Palliat Care*. 2017;32(2):77–84. https://doi.org/10.1177/0825859717722466
38. Oldenmenger WH, Baan MAG, van der Rijt CCD. Development and feasibility of a web application to monitor patients' cancer-related pain. *Support Care Cancer*. 2018;26(2):635–642. https://doi.org/10.1007/s00520-017-3877-3
39. te Boveldt N, Vernooij-Dassen M, Leppink I, Samwel H, Vissers K, Engels Y. Patient empowerment in cancer pain management: an integrative literature review. *Psychooncology*. 2014;23(11):1203–1211. https://doi.org/10.1002/pon.3573
40. Holmes MM, Lewith G, Newell D, Field J, Bishop FL. The impact of patient-reported outcome measures in clinical practice for pain: a systematic review. *Qual Life Res*. 2017;26(2):245–257. https://doi.org/10.1007/s11136-016-1449-5
41. Valenta S, Spirig R, Miaskowski C, Zaugg K, Spichiger E. Testing a pain self-management intervention by exploring reduction of analgesics' side effects in cancer outpatients and the involvement of family caregivers: a study protocol (PEINCA-FAM). *BMC Nurs*. 2018;17(1):54. https://doi.org/10.1186/s12912-018-0323-x
42. Chen J, Ou L, Hollis SJ. A systematic review of the impact of routine collection of patient reported outcome measures on patients, providers and health organisations in an oncologic setting. *BMC Health Serv Res*. 2013;13:211. https://doi.org/10.1186/1472-6963-13-211
43. Kotronoulas G, Kearney N, Maguire R, et al. What is the value of the routine use of patient-reported outcome measures toward improvement of patient outcomes, processes of care, and health service outcomes in cancer care? A systematic review of controlled trials. *J Clin Oncol*. 2014;32(14):1480–1501. https://doi.org/10.1200/JCO.2013.53.5948
44. World Health Organization. *Cancer Pain Relief: With a Guide to Opioid Availability*. 2nd ed. World Health Organization; 1996. https://apps.who.int/iris/handle/10665/37896. Accessed March 16, 2023.
45. Batistaki C, Graczyk M, Janecki M, Lewandowska AA, Moutinho R, Vagdatli K. Relationship between breakthrough cancer pain, background cancer pain and analgesic treatment – case series and review of the literature. *Drugs Context*. 2022;11:2022-9-4. https://doi.org/10.7573/dic.2022-9-4
46. Cascella M, Monaco F, Nocerino D, et al. Bibliometric network analysis on rapid-onset opioids for breakthrough cancer pain treatment. *J Pain Symptom Manag*. 2022;63(6):1041–1050. https://doi.org/10.1016/j.jpainsymman.2022.01.023

47. Fan R, Li X, Yang S, et al. Retrospective observational study on the characteristics of pain and associated factors of breakthrough pain in advanced cancer patients. *Pain Res Manag*. 2022;2022:11. https://doi.org/10.1155/2022/8943292
48. Brant JM, Wujcik D, Dudley WN, et al. Shared decision-making in managing breakthrough cancer pain in patients with advanced cancer. *J Adv Pract Oncol*. 2022;13(1):19–29. https://doi.org/10.6004/jadpro.2022.13.1.2
49. US FDA. Transmucosal Immediate-Release Fentanyl (TIRF) Medicines. https://www.fda.gov/drugs/information-drug-class/transmucosal-immediate-release-fentanyl-tirf-medicines. Accessed September 3, 2022.
50. Mercadante S. Treating breakthrough pain in oncology. *Expert Rev Anticancer Ther*. 2018;18(5):445–449. https://doi.org/10.1080/14737140.2018.1443813
51. Schug SA, Ting S. Fentanyl formulations in the management of pain: an update. *Drugs*. 2017;77(7):747–763. https://doi.org/10.1007/s40265-017-0727-z
52. Park H, Otte A, Park K. Evolution of drug delivery systems: from 1950 to 2020 and beyond. *J Control Release*. 2022;342:53–65. https://doi.org/10.1016/j.jconrel.2021.12.030
53. Nalamachu S, Gudin J. Characteristics of analgesic patch formulations. *J Pain Res*. 2020;13:2343–2354. https://doi.org/10.2147/JPR.S270169
54. Dupoiron D, Duarte R, Carvajal G, Aubrun F, Eldabe S. Rationale and recent advances in targeted drug delivery for cancer pain: is it time to change the paradigm? *Pain Physician*. 2022;25(3):E414–E425.
55. Stoicea N, Fiorda-Diaz J, Joseph N, et al. Advanced analgesic drug delivery and nanobiotechnology. *Drugs*. 2017;77(10):1069–1076. https://doi.org/10.1007/s40265-017-0744-y
56. Marthick M, McGregor D, Alison J, Cheema B, Dhillon H, Shaw T. Supportive care interventions for people with cancer assisted by digital technology: systematic review. *J Med Internet Res*. 2021;23(10):e24722. https://doi.org/10.2196/24722
57. WHO. Monitoring and evaluating digital health interventions. https://www.who.int/publications/i/item/9789241511766. Accessed October 31, 2022.
58. Sundararaman LV, Edwards RR, Ross EL, Jamison RN. Integration of mobile health technology in the treatment of chronic pain. *Reg Anesth Pain Med*. 2017;42(4):488–498. https://doi.org/10.1097/AAP.0000000000000621
59. Pombo N, Garcia N, Bousson K, Spinsante S, Chorbev I. Pain assessment–can it be done with a computerised system? A systematic review and meta-analysis. *Int J Environ Res Public Health*. 2016;13(4):415. https://doi.org/10.3390/ijerph13040415
60. Boceta J, Samper D, de la Torre A, Sánchez-de la Rosa R, González G. Usability, acceptability, and usefulness of an mHealth app for diagnosing and monitoring patients with breakthrough cancer pain. *JMIR Cancer*. 2019;5(1):e10187. https://doi.org/10.2196/10187
61. Adam R, Bond CM, Burton CD, de Bruin M, Murchie P. Can-Pain-a digital intervention to optimise cancer pain control in the community: development and feasibility testing. *Support Care Cancer*. 2021;29(2):759–769. https://doi.org/10.1007/s00520-020-05510-0
62. Bamgboje-Ayodele A, Smith A 'Ben,' Short CE, et al. Barriers and facilitators to the availability of efficacious self-directed digital health tools for adults living with cancer and their caregivers: a systematic literature review and author survey study. *Patient Educ Couns*. 2021;104(10):2480–2489. https://doi.org/10.1016/j.pec.2021.03.012
63. Pantano F, Manca P, Armento G, et al. Breakthrough cancer pain clinical features and differential opioids response: a machine learning approach in patients with cancer from the IOPS-MS study. *JCO Precis Oncol*. 2020;4:1339–1349. https://doi.org/10.1200/PO.20.00158
64. Cascella M, Crispo A, Esposito G, et al. Multidimensional statistical technique for interpreting the spontaneous breakthrough cancer pain phenomenon. A secondary analysis from the IOPS-MS study. *Cancers*. 2021;13(16):4018. https://doi.org/10.3390/cancers13164018
65. Cuomo A, Cascella M, Vittori A, Baciarello M, Badino M, Bignami E. Telemedicine for managing cancer pain. A great opportunity to be exploited for clinical and research purposes. *Pain Physician*. 2022;25(6):E886–E888.
66. Cascella M, Coluccia S, Grizzuti M, et al. Satisfaction with telemedicine for cancer pain management: a model of care and cross-sectional patient satisfaction study. *Curr Oncol*. 2022;29(8):5566–5578. https://doi.org/10.3390/curroncol29080439
67. Cascella M, Coluccia S, Monaco F, et al. Different machine learning approaches for implementing telehealth-based cancer pain management strategies. *J Clin Med*. 2022;11(18):5484. https://doi.org/10.3390/jcm11185484
68. Cascella M, Schiavo D, Grizzuti M, et al. Implementation of a hybrid care model for telemedicine-based cancer pain management at the Cancer Center of Naples, Italy: a cohort study. *In Vivo*. 2023;37(1):385–392. https://doi.org/10.21873/invivo.13090
69. Shrestha S, Bhuvan KC, Blebil AQ, Teoh SL. Pharmacist involvement in cancer pain management: a systematic review and meta-analysis. *J Pain*. 2022;23(7):1123–1142. https://doi.org/10.1016/j.jpain.2022.02.002

70. Zhang L, Ren XY, Huang HX, et al. Development of the practice of pharmaceutical care for cancer pain management in outpatient clinics using the Delphi method. *Front Pharmacol*. 2022;13:840560. https://doi.org/10.3389/fphar.2022.840560
71. Aman MM, Mahmoud A, Deer T, et al. The American Society of Pain and Neuroscience (ASPN) best practices and guidelines for the interventional management of cancer-associated pain. *J Pain Res*. 2021;14:2139–2164. https://doi.org/10.2147/JPR.S315585
72. Allano G, George B, Minello C, Burnod A, Maindet C, Lemaire A. Strategies for interventional therapies in cancer-related pain – a crossroad in cancer pain management. *Support Care Cancer*. 2019;27(8):3133–3145. https://doi.org/10.1007/s00520-019-04827-9
73. Silverman JE, Gulati A. An overview of interventional strategies for the management of oncologic pain. *Pain Manag*. 2018;8(5):389–403. https://doi.org/10.2217/pmt-2018-0022
74. Cheville AL, Moynihan T, Herrin J, Loprinzi C, Kroenke K. Effect of collaborative telerehabilitation on functional impairment and pain among patients with advanced-stage cancer. *JAMA Oncol*. 2019;5(5):644. https://doi.org/10.1001/jamaoncol.2019.0011
75. López-Sendín N, Alburquerque-Sendín F, Cleland JA, Fernández-de-las-Peñas C. Effects of physical therapy on pain and mood in patients with terminal cancer: a pilot randomized clinical trial. *J Altern Complement Med*. 2012;18(5):480–486. https://doi.org/10.1089/acm.2011.0277
76. Maldonado E, Thalla N, Nepaul S, Wisotzky E. Outcome measures in cancer rehabilitation: pain, function, and symptom assessment. *Front Pain Res*. 2021;2:692237. https://doi.org/10.3389/fpain.2021.692237
77. Pyszora A, Budzyński J, Wójcik A, Prokop A, Krajnik M. Physiotherapy programme reduces fatigue in patients with advanced cancer receiving palliative care: randomized controlled trial. *Support Care Cancer*. 2017;25(9):2899–2908. https://doi.org/10.1007/s00520-017-3742-4
78. Cheville AL, Basford JR. Role of rehabilitation medicine and physical agents in the treatment of cancer-associated pain. *J Clin Oncol*. 2014;32(16):1691–1702. https://doi.org/10.1200/JCO.2013.53.6680
79. Lussier D, Huskey AG, Portenoy RK. Adjuvant analgesics in cancer pain management. *Oncologist*. 2004;9(5):571–591. https://doi.org/10.1634/theoncologist.9-5-571
80. Wang YH, Li JQ, Shi JF, et al. Depression and anxiety in relation to cancer incidence and mortality: a systematic review and meta-analysis of cohort studies. *Mol Psychiatry*. 2020;25(7):1487–1499. https://doi.org/10.1038/s41380-019-0595-x
81. Caruso R, Nanni MG, Riba M, et al. Depressive spectrum disorders in cancer: prevalence, risk factors and screening for depression: a critical review. *Acta Oncol*. 2017;56(2):146–155. https://doi.org/10.1080/0284186X.2016.1266090
82. Naser AY, Hameed AN, Mustafa N, et al. Depression and anxiety in patients with cancer: a cross-sectional study. *Front Psychol*. 2021;12:585534. https://doi.org/10.3389/fpsyg.2021.585534
83. Ruano A, García-Torres F, Gálvez-Lara M, Moriana JA. Psychological and non-pharmacologic treatments for pain in cancer patients: a systematic review and meta-analysis. *J Pain Symptom Manag*. 2022;63(5):e505–e520. https://doi.org/10.1016/j.jpainsymman.2021.12.021
84. Syrjala KL, Jensen MP, Mendoza ME, Yi JC, Fisher HM, Keefe FJ. Psychological and behavioral approaches to cancer pain management. *J Clin Oncol*. 2014;32(16):1703–1711. https://doi.org/10.1200/JCO.2013.54.4825
85. Ahmed E. Antidepressants in patients with advanced cancer: when they're warranted and how to choose therapy. *Oncology*. 2019;33(2):62–68.
86. Benyamin R, Trescot AM, Datta S, et al. Opioid complications and side effects. *Pain Physician*. 2008;11(Suppl. 2):S105–S120.
87. Mitra R, Jones S. Adjuvant analgesics in cancer pain: a review. *Am J Hosp Palliat Med*. 2012;29(1):70–79. https://doi.org/10.1177/1049909111413256
88. Mercadante S, Arcuri E, Santoni A. Opioid-induced tolerance and hyperalgesia. *CNS Drugs*. 2019;33(10):943–955. https://doi.org/10.1007/s40263-019-00660-0
89. Mercadante S. Opioid analgesics adverse effects: the other side of the coin. *Curr Pharm Des*. 2019;25(30):3197–3202. https://doi.org/10.2174/1381612825666190717152226
90. Derry S, Wiffen PJ, Häuser W, et al. Oral nonsteroidal anti-inflammatory drugs for fibromyalgia in adults. *Cochrane Database Syst Rev*. 2017;3:CD012332. https://doi.org/10.1002/14651858.CD012332.pub2
91. Lovell MR, Phillips JL, Luckett T, et al. Effect of cancer pain guideline implementation on pain outcomes among adult outpatients with cancer-related pain. *JAMA Netw Open*. 2022;5(2):e220060. https://doi.org/10.1001/jamanetworkopen.2022.0060
92. Ferrell BR, Temel JS, Temin S, et al. Integration of palliative care into standard oncology care: American Society of Clinical Oncology clinical practice guideline update. *J Clin Oncol*. 2017;35(1):96–112. https://doi.org/10.1200/JCO.2016.70.1474
93. Haun MW, Estel S, Rücker G, et al. Early palliative care for adults with advanced cancer. *Cochrane Database Syst Rev*. 2017;(6):CD011129. https://doi.org/10.1002/14651858.CD011129.pub2

94. Chapman EJ, Edwards Z, Boland JW, et al. Practice review: evidence-based and effective management of pain in patients with advanced cancer. *Palliat Med*. 2020;34(4):444–453. https://doi.org/10.1177/0269216319896955
95. US Department of Health and Human Services. Common Terminology Criteria for Adverse Events . Version 5.0. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf. Accessed October 31, 2022.
96. Lewis SJ, Heaton KW. Stool form scale as a useful guide to intestinal transit time. *Scand J Gastroenterol*. 1997;32(9):920–924. https://doi.org/10.3109/00365529709011203
97. Cinausero M, Aprile G, Ermacora P, et al. New frontiers in the pathobiology and treatment of cancer regimen-related mucosal injury. *Front Pharmacol*. 2017;8:354. https://doi.org/10.3389/fphar.2017.00354
98. Jamali J, Dayo A, Adeel A, Qureshi Y, Khan T, Begum S. A survey on gastrointestinal adverse drug reactions of doxorubicin and cyclophosphamide combination therapy. *J Pak Med Assoc*. 2018;68(6):926–928.
99. Benson AB, Ajani JA, Catalano RB, et al. Recommended guidelines for the treatment of cancer treatment-induced diarrhea. *J Clin Oncol*. 2004;22(14):2918–2926. https://doi.org/10.1200/JCO.2004.04.132
100. Meyerhardt JA, Mayer RJ. Systemic therapy for colorectal cancer. *N Engl J Med*. 2005;352(5):476–487. https://doi.org/10.1056/NEJMra040958
101. Elad S, Cheng KKF, Lalla RV, et al. MASCC/ISOO clinical practice guidelines for the management of mucositis secondary to cancer therapy. *Cancer*. 2020;126(19):4423–4431. https://doi.org/10.1002/cncr.33100
102. McQuade RM, al Thaalibi M, Nurgali K. Impact of chemotherapy-induced enteric nervous system toxicity on gastrointestinal mucositis. *Curr Opin Support Palliat Care*. 2020;14(3):293–300. https://doi.org/10.1097/SPC.0000000000000515
103. Pulito C, Cristaudo A, La Porta C, et al. Oral mucositis: the hidden side of cancer therapy. *J Exp Clin Cancer Res*. 2020;39(1):210. https://doi.org/10.1186/s13046-020-01715-7
104. Sougiannis AT, VanderVeen BN, Davis JM, Fan D, Murphy EA. Understanding chemotherapy-induced intestinal mucositis and strategies to improve gut resilience. *Am J Physiol Gastrointest Liver Physiol*. 2021;320(5):G712–G719. https://doi.org/10.1152/ajpgi.00380.2020
105. Basile D, di Nardo P, Corvaja C, et al. Mucosal injury during anti-cancer treatment: from pathobiology to bedside. *Cancers*. 2019;11(6):857. https://doi.org/10.3390/cancers11060857
106. Al-Rudayni AHM, Gopinath D, Maharajan MK, Menon RK. Impact of oral mucositis on quality of life in patients undergoing oncological treatment: a systematic review. *Transl Cancer Res*. 2020;9(4):3126–3134. https://doi.org/10.21037/tcr.2020.02.77
107. Elad S, Karis KFC, Cheng KF, et al. MASCC/ISOO clinical practice guidelines for the management of mucositis secondary to cancer therapy. *Cancer*. 2020;126(19):4423–4431. https://doi.org/10.1002/cncr.33100
108. Duncan M, Grant G. Oral and intestinal mucositis – causes and possible treatments. *Aliment Pharmacol Ther*. 2003;18(9):853–874. https://doi.org/10.1046/j.1365-2036.2003.01784.x
109. Stiff PJ, Erder H, Bensinger WI, et al. Reliability and validity of a patient self-administered daily questionnaire to assess impact of oral mucositis (OM) on pain and daily functioning in patients undergoing autologous hematopoietic stem cell transplantation (HSCT). *Bone Marrow Transplant*. 2006;37(4):393–401. https://doi.org/10.1038/sj.bmt.1705250
110. Kushner JA, Lawrence HP, Shoval I, et al. Development and validation of a patient-reported oral mucositis symptom (PROMS) scale. *J Can Dent Assoc*. 2008;74(1):59.
111. Tassinari D, Sartori S, Tamburini E, et al. Transdermal fentanyl as a front-line approach to moderate-severe pain: a meta-analysis of randomized clinical trials. *J Palliat Care*. 2009;25(3):172–180.
112. Wan Bahrum WFI bin, Hardy J, Foster K, Good P. Oral water-soluble contrast (Gastrografin) for malignant bowel obstruction: open label pilot study. *BMJ Support Palliat Care*. 2022:bmjspcare-2021-003444. https://doi.org/10.1136/bmjspcare-2021-003444
113. Anthony T, Baron T, Mercadante S, et al. Report of the Clinical Protocol Committee: development of randomized trials for malignant bowel obstruction. *J Pain Symptom Manag*. 2007;34(1):S49–S59. https://doi.org/10.1016/j.jpainsymman.2007.04.011
114. Rami Reddy SR, Cappell MS. A systematic review of the clinical presentation, diagnosis, and treatment of small bowel obstruction. *Curr Gastroenterol Rep*. 2017;19(6):28. https://doi.org/10.1007/s11894-017-0566-9
115. Paul Olson TJ, Pinkerton C, Brasel KJ, Schwarze ML. Palliative surgery for malignant bowel obstruction from carcinomatosis. *JAMA Surg*. 2014;149(4):383. https://doi.org/10.1001/jamasurg.2013.4059
116. Madariaga A, Lau J, Ghoshal A, et al. MASCC multidisciplinary evidence-based recommendations for the management of malignant bowel obstruction in advanced cancer. *Support Care Cancer*. 2022;30(6):4711–4728. https://doi.org/10.1007/s00520-022-06889-8
117. Bleicher J, Lambert LA. A palliative approach to management of peritoneal carcinomatosis and malignant ascites. *Surg Oncol Clin N Am*. 2021;30(3):475–490. https://doi.org/10.1016/j.soc.2021.02.004

118. Obita GP, Boland EG, Currow DC, Johnson MJ, Boland JW. Somatostatin analogues compared with placebo and other pharmacologic agents in the management of symptoms of inoperable malignant bowel obstruction: a systematic review. *J Pain Symptom Manag*. 2016;52(6):901–919.e1. https://doi.org/10.1016/j.jpainsymman.2016.05.032
119. Laval G, Marcelin-Benazech B, Guirimand F, et al. Recommendations for bowel obstruction with peritoneal carcinomatosis. *J Pain Symptom Manag*. 2014;48(1):75–91. https://doi.org/10.1016/j.jpainsymman.2013.08.022
120. Feuer DJ, Broadley KE. Corticosteroids for the resolution of malignant bowel obstruction in advanced gynaecological and gastrointestinal cancer. *Cochrane Database Syst Rev*. 2000;2:CD001219. https://doi.org/10.1002/14651858.CD001219
121. Mercadante S, Porzio G. Octreotide for malignant bowel obstruction: twenty years after. *Crit Rev Oncol Hematol*. 2012;83(3):388–392. https://doi.org/10.1016/j.critrevonc.2011.12.006
122. Pergolizzi Jr JV, Christo PJ, LeQuang JA, Magnusson P. The use of peripheral μ-opioid receptor antagonists (PAMORA) in the management of opioid-induced constipation: an update on their efficacy and safety. *Drug Des Devel Ther*. 2020;14:1009–1025. https://doi.org/10.2147/DDDT.S221278
123. Viscusi ER. Clinical overview and considerations for the management of opioid-induced constipation in patients with chronic noncancer pain. *Clin J Pain*. 2019;35(2):174–188. https://doi.org/10.1097/AJP.0000000000000662
124. Lilley EJ, Scott JW, Goldberg JE, et al. Survival, healthcare utilization, and end-of-life care among older adults with malignancy-associated bowel obstruction. *Ann Surg*. 2018;267(4):692–699. https://doi.org/10.1097/SLA.0000000000002164
125. Naghibi M, Smith TR, Elia M. A systematic review with meta-analysis of survival, quality of life and cost-effectiveness of home parenteral nutrition in patients with inoperable malignant bowel obstruction. *Clin Nutr*. 2015;34(5):825–837. https://doi.org/10.1016/j.clnu.2014.09.010
126. Bruera E, Hui D, Dalal S, et al. Parenteral hydration in patients with advanced cancer: a multicenter, double-blind, placebo-controlled randomized trial. *J Clin Oncol*. 2013;31(1):111–118. https://doi.org/10.1200/JCO.2012.44.6518
127. Tuca A, Guell E, Martinez-Losada E, Codorniu N. Malignant bowel obstruction in advanced cancer patients: epidemiology, management, and factors influencing spontaneous resolution. *Cancer Manag Res*. 2012;4:159–169. https://doi.org/10.2147/CMAR.S29297
128. Fahy BN. Palliative care for the surgical oncologist: embracing the pallitative care physician within. *Surgery*. 2013;153(1):1–3. https://doi.org/10.1016/j.surg.2012.06.002
129. Simmons CPL, McMillan DC, McWilliams K, et al. Prognostic tools in patients with advanced cancer: a systematic review. *J Pain Symptom Manag*. 2017;53(5):962–970.e10. https://doi.org/10.1016/j.jpainsymman.2016.12.330
130. Dantigny R, Ecarnot F, Economos G, Perceau-Chambard E, Sanchez S, Barbaret C. Knowledge and use of prognostic scales by oncologists and palliative care physicians in adult patients with advanced cancer: a national survey (ONCOPRONO study). *Cancer Med*. 2022;11(3):826–837. https://doi.org/10.1002/cam4.4467
131. Cohen SP, Vase L, Hooten WM. Chronic pain: an update on burden, best practices, and new advances. *Lancet*. 2021;397(10289):2082–2097. https://doi.org/10.1016/S0140-6736(21)00393-7
132. Julian LJ. Measures of anxiety: State-Trait Anxiety Inventory (STAI), Beck Anxiety Inventory (BAI), and Hospital Anxiety and Depression Scale-Anxiety (HADS-A). *Arthritis Care Res*. 2011;63(S11):S467–S472. https://doi.org/10.1002/acr.20561
133. Mercadante S, Valle A, Porzio G, et al. Relationship between background cancer pain, breakthrough pain, and analgesic treatment: a preliminary study for a better interpretation of epidemiological and clinical studies. *Curr Med Res Opin*. 2013;29(6):667–671. https://doi.org/10.1185/03007995.2013.792247
134. Husic S, Imamovic S, Matic S, Sukalo A. Characteristics and treatment of breakthrought pain (BTcP) in palliative care. *Med Arch*. 2017;71(4):246–250. https://doi.org/10.5455/medarh.2017.71.246-250
135. Mazzotta M, Filetti M, Piras M, Mercadante S, Marchetti P, Giusti R. Patients' satisfaction with breakthrough cancer pain therapy: a secondary analysis of IOPS-MS study. *Cancer Manag Res*. 2022;14:1237–1245. https://doi.org/10.2147/CMAR.S353036
136. Cuomo A, Cascella M, Forte CA, et al. Careful breakthrough cancer pain treatment through rapid-onset transmucosal fentanyl improves the quality of life in cancer patients: results from the BEST multicenter study. *J Clin Med*. 2020;9(4):1003. https://doi.org/10.3390/jcm9041003
137. Kang JH, Koh SJ, Oh SY, et al. Interference with daily functioning by breakthrough pain in patients with cancer. *Support Care Cancer*. 2020;28(11):5177–5183. https://doi.org/10.1007/s00520-020-05329-9
138. Villegas Estévez FJ, López Alarcón MD, Beato C, Sanz-Yagüe A, Porta-Sales J, Morera López RM. Procedural pain in patients with cancer: a Delphi expert management consensus. *BMJ Support Palliat Care*. 2021:bmjspcare-2020-002668. https://doi.org/10.1136/bmjspcare-2020-002668
139. Suresh NV, Harris J, Chorath K, et al. Clinical practice guidelines in the management of breakthrough cancer pain: a systematic review using the appraisal of guidelines for research and evaluation (AGREE II) instrument. *Pain Manag Nurs*. 2022;23(4):411–417. https://doi.org/10.1016/j.pmn.2022.02.010

140. Mercadante S. Pharmacotherapy for breakthrough cancer pain. *Drugs*. 2012;72(2):181–190. https://doi.org/10.2165/11597260-000000000-00000
141. Persitz J, Beit Ner E, Chechik I, Keren T, Avisar E. Epithelioid sarcoma of the hand: a wolf in sheep's clothing. *J Plast Surg Hand Surg*. 2021;55(2):96–104. https://doi.org/10.1080/2000656X.2020.1838914
142. Pai K, Pai S, Sripathi H, Saha P, Rao P. Epithelioid sarcoma: a diagnostic challenge. *Indian J Dermatol Venereol Leprol*. 2006;72(6):446. https://doi.org/10.4103/0378-6323.29343
143. Hwang JS, Fitzhugh VA, Kaushal N, Beebe KS. Epithelioid sarcoma: an unusual presentation in the distal phalanx of the toe. *Am J Orthop*. 2012;41(5):223–227.
144. Taberna M, Gil Moncayo F, Jané-Salas E, et al. The multidisciplinary team (MDT) approach and quality of care. *Front Oncol*. 2020;10:85. https://doi.org/10.3389/fonc.2020.00085
145. Lazerges C. Soft tissue sarcomas of the forearm, wrist and hand. *Hand Surg Rehabil*. 2017;36(4):233–243. https://doi.org/10.1016/j.hansur.2016.12.010
146. Temel JS, Greer JA, Muzikansky A, et al. Early palliative care for patients with metastatic non–small-cell lung cancer. *N Engl J Med*. 2010;363(8):733–742. https://doi.org/10.1056/NEJMoa1000678
147. Ghabashi EH, Sharaf BM, Kalaktawi WA, Calacattawi R, Calacattawi AW. The magnitude and effects of early integration of palliative care into oncology service among adult advanced cancer patients at a tertiary care hospital. *Cureus*. 2021;13(5):e15313. https://doi.org/10.7759/cureus.15313
148. Shoemaker L, McInnes S. Starting a palliative care program at a Cancer Center. In: *The Comprehensive Cancer Center*. Springer International Publishing; 2022:107–120. https://doi.org/10.1007/978-3-030-82052-7_12
149. WHO. WHO's cancer pain ladder for adults. https://www.who.int/publications/i/item/9789241550390. Accessed March 16, 2023.