Pain related to cancer treatments and diagnostic procedures: a no man’s land?

C. I. Ripamonti*, P. Bossi2, D. Santini3 & M. Fallon4

1Supportive Care in Cancer Unit, Fondazione IRCCS, Istituto Nazionale dei Tumori, Milan; 2Head and Neck Medical Oncology Unit, Fondazione IRCCS, Istituto Nazionale dei Tumori, Milan; 3Medical Oncology Unit, Università Campus Bio-Medico, Rome, Italy; 4St Columba’s Hospice Chair of Palliative Medicine, IGMM, University of Edinburgh, Edinburgh, UK

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Background: While guidelines are available for the management of cancer-related pain, little attention is given to the assessment and treatment of pain caused by treatments and diagnostic procedures in cancer patients.

Methods: We evaluated the literature on pain related to cancer treatment and diagnostic procedures within a critical analysis.

Results: The data available are sparse, suggesting that little attention has been directed at this important aspect of oncology. This points to potentially suboptimal patient management.

Conclusions: Appropriately conducted studies are necessary in order to understand the incidence and appropriate management of pain, both during and/or after oncological treatments and diagnostic procedures. At the same time, Health Care Professionals should have heightened awareness of the causes and treatment of pain with the aim of anticipating and managing pain most appropriately for each individual patient. This is clearly an important component of holistic patient care, before, during, and after oncological treatment.

Key words: pain management, cancer, oncological treatments, diagnostic procedures

introduction

Pain in cancer patients is a subjective experience in any stage of the disease, as nociceptive stimuli capable of eliciting pain are influenced by genetics, personal past history, mood, expectation, and culture.

Pain has been defined as the fifth vital sign by the American Pain Society and its daily routine assessment is emphasized by international guidelines and new regulations [1–3]. In recent years, several guidelines have been published on the assessment and management of pain in cancer patients [4–8]. So far, most attention has been focused on patients with advanced or terminal cancer, especially those in the palliative care context.

Despite published guidelines, unrelieved pain continues to be a substantial worldwide public health concern in patients with solid and haematological malignancies [9–16].

Independently of the cancer type, pain may be caused by the cancer itself, or it may result following surgery, radiotherapy (RT), chemotherapy, targeted therapy (TT), supportive care therapies, and/or diagnostic procedures. In addition, pain can be associated with other debilitating conditions or it may be unrelated to cancer. In clinical practice, pain is often the first sign of primary cancer and/or its recurrence [17, 18] and could be diagnostic of a small mass as well as of a widespread disease. However, the incidence of pain as a diagnostic cancer symptom is rarely reported.

A systematic review of the literature identifies pain prevalence that ranges from 64% in patients with metastatic, advanced, or...
terminal phase, 59% in patients on anticancer treatment, and 33% in patients after curative treatments [19]. No real difference in pain prevalence was found between patients during anticancer treatment and those in the advanced or terminal phase of the disease. At the time of cancer diagnosis, pain is present in 24%–62% of adult patients [20, 21]. Patients admitted to Oncology wards have been found to receive more appropriate analgesic therapy for cancer-related pain compared with those in other settings, such as general medicine or respiratory units [22].

In a multicentre and multidisciplinary cross-sectional study carried out on 3285 patients (55% ≥65 years) treated with analgesic therapy in the hospital setting [16], 2821 patients reported pain despite analgesic therapy; among these, 1178 (42%) patients experienced severe pain. Multiple multilevel logistic regression shows that non-reporting pain in this study is not age-related, but is associated with non-malignant pain ($P = 0.05$), a short hospitalization ($P = 0.001$), and admission to a hospital without a ’Pain-Free Hospital’ project ($P = 0.011$) [23].

Only a small amount of data exists about pain assessment and its management in cancer patients during the various invasive and non-invasive diagnostic procedures at this time or throughout a cancer illness.

Such procedures (Table 1) range from radiological imaging procedures, which necessitate the patient to remain in uncomfortable positions for a long time, invasive procedures, biopsies of soft tissues or bone, and to surgical interventions. Similarly, long-lasting pain after oncological treatments is rarely considered.

In this paper, pain caused by cancer-specific treatments or supportive treatments and also caused by the diagnostic procedure will be discussed.

### assessment of pain

According to the ESMO guidelines, initial and ongoing assessment of pain should include additional comprehensive evaluation and a rational care plan [8]. Self-reported perceived pain intensity evaluated through validated assessment tools (i.e. visual analogue scale, numerical rating scale, and verbal rating scale) represents the first step for effective and personal intervention; this applies to all pain assessment throughout the entire course of the disease.

Consideration should be given to the possibility of pain that may occur subsequently as a result of oncological therapies, supportive therapies, or diagnostic procedures; patients can generally experience severe pain when undergoing diagnostic treatments, although it will diminish within minutes or hours. It is important, therefore, to inform the patient of such a possibility and to prescribe pre-emptive analgesia. This prevents pain and unnecessary fear in patients, which may lead to inappropriate hospitalization.

Professional and humane attention towards pain evaluation, and towards treatments that might cause pain, and good communication will strengthen the patient/physician relationship and allow the patient to appreciate that health care providers are taking a considered, holistic approach.

### Table 1. Examples of procedural cancer-related pain in different clinical settings

<table>
<thead>
<tr>
<th>Type of procedural pain</th>
<th>Pathophysiology</th>
<th>Pain therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lumbar puncture, myelography ± headache</td>
<td>Somatic and neuropathic pain</td>
<td>Local anaesthetic + pre-/post-med. with NSAIDs/ opioids; steroid for headache</td>
</tr>
<tr>
<td>Transthoracic needle biopsy</td>
<td>Somatic and visceral pain</td>
<td>Local anaesthetic + pre-/post-med. with NSAIDs/ opioids</td>
</tr>
<tr>
<td>Endoscopy ± visceral dilatation</td>
<td>Visceral pain and neuropathic autonomic pain</td>
<td>Systemic anaesthetic</td>
</tr>
<tr>
<td>Bone marrow aspiration/biopsy</td>
<td>Somatic and neuropathic pain</td>
<td>Local anaesthetic + pre-/post-med. with NSAIDs/ opioids</td>
</tr>
<tr>
<td>Blood sampling, intramuscular injections</td>
<td>Somatic and neuropathic pain</td>
<td>Local anaesthetic</td>
</tr>
<tr>
<td>Central line position, arterial line position</td>
<td>Somatic and neuropathic pain</td>
<td>Local anaesthetic + pre-/post-med. with NSAIDs/ opioids</td>
</tr>
<tr>
<td>Pleurodesis</td>
<td>Somatic and visceral pain</td>
<td>Local anaesthetic + pre-/post-med. with NSAIDs/ opioids</td>
</tr>
<tr>
<td>Tumour embolization</td>
<td>Somatic and visceral pain (depending from the site of cancer)</td>
<td>Local anaesthetic + pre-/post-med. with NSAIDs/ opioids</td>
</tr>
<tr>
<td>Suprapubic catheterization, nephrostomy insertion</td>
<td>Somatic and visceral pain</td>
<td>Local anaesthetic + pre-/post-med. with NSAIDs/ opioids</td>
</tr>
<tr>
<td>Thoracocentesis</td>
<td>Somatic and visceral pain</td>
<td>Local anaesthetic + pre-/post-med. with NSAIDs/ opioids</td>
</tr>
<tr>
<td>Medication of skin ulcers</td>
<td>Somatic and neuropathic pain</td>
<td>Local anaesthetic</td>
</tr>
<tr>
<td>Liver, lung, soft tissue diagnostic biopsies</td>
<td>Somatic and visceral pain (neuropathic in neural tissue biopsy)</td>
<td>Local anaesthetic + pre-/post-med. with NSAIDs/ opioids</td>
</tr>
<tr>
<td>Movement/procedural pain (bone/CNS/wound met) during diagnostic procedures</td>
<td>Visceral and neuropathic pain</td>
<td>Premedication with (rapid onset) opioids</td>
</tr>
</tbody>
</table>

Med., medication; CNS, central nervous system; NSAIDs, non-steroidal anti-inflammatory drugs.
**procedural cancer-related pain in different clinical settings**

**diagnostic phase**
A guideline for the management of acute pain related to operative or medical procedures was published in 1992, but this guideline is not specifically for patients with cancer [24]. Various diagnostic procedures in cancer patients, at various stages of disease, can be accompanied by substantial pain (Table 1).

Little is known about patient perception of pain during diagnostic tests, because most data are related to cancer-related pain. Moreover, procedural pain could be underestimated by physicians, because the importance of performing such invasive procedures in order to obtain a specific cancer diagnosis overcomes the perception of possible pain-related problems. Another issue concerning the reporting of pain is the possible lack of congruence between patients’ and physicians’ perceptions of pain; it is a controversial question, with some papers showing how health care providers underestimate pain reported by the patients, in particular when the intensity is severe [25, 26]. The importance of recognizing and pre-empting pain induced by medical procedures should be stressed, to avoid the development of central sensitization, a phenomenon causing an increase in the area and the response to noxious stimuli and a reduction in pain threshold [27].

As no study has been carried out to identify the most painful procedures, we will cover some examples of procedural pain in cancer patients.

One of the most frequent diagnostic procedures, bone marrow biopsy or aspiration (B MBA), is the cause of pain in ~85% of patients, and severe intensity is reported in a range varying from 8% to 35% [28–30]. Factors associated with higher perceived pain are the length of the procedure, younger age, higher body mass index, female sex, anxiety, site of examination (sternum being the most painful), information given before procedure, and physician experience [31]. Several strategies have been applied in order to alleviate pain due to B MBA, even in the absence of guidelines and without a high evidence of efficacy. Pharmacological interventions employed vary from local anaesthetic (with low efficacy when employed alone) [32], intravenous sedation with benzodiazepines and/or opioids [33–35] or with inhaled nitrous oxide [36, 37], and premedication with opioids [28, 38]. The importance of non-pharmacological intervention should be stressed, as anxiety is a key factor in pain development [31].

Lumbar puncture is often used for diagnostic purposes in haematological and central nervous system malignancies; it can be associated with a typical post-dural puncture headache, developing from hours to days after the procedure, due to leakage of cerebrospinal fluid, possibly causing compensatory intracranial vessel dilatation or increased tension on brain and meninges [39, 40]. No specific intervention has shown a high level of efficacy, apart from the preventive use of an atraumatic needle [41].

Transrectal ultrasound-guided prostate biopsy is a common procedure associated with mild to severe pain in 65%–90% of patients [42]. Periprostatic nerve blockade has been shown to be an effective measure to prevent pain due to the needle insertion through prostate capsule [43], as with topical anaesthetics and tramadol [44] or sedatives [45].

Examples of other procedures associated with pain are fine-needle aspiration cytology or biopsy of a neck mass [46], thyroid nodules [47], breast mass [48] or radionucleide injection for breast cancer lymphatic mapping [49], and percutaneous liver biopsy [50].

Diagnostic examination, even if not followed by biopsy, could also cause discomfort or overt pain. Examples include: colonoscopy (abdominal pain is reported both during bowel preparation and during the exam) [51, 52] and prostate digital examination [53].

**particular cases**
There is another area of procedural pain that is underestimated in cancer patients, but whose importance can be inferred by reports in acute or critically ill patients. It regards some procedures such as turning, wound drain removal, wound dressing changing, tracheal suctioning, placement of a central venous catheter, and femoral catheter removal, all of which have been described extensively [54]. All these procedures are carried out regularly in cancer patients in different phases of diagnosis or treatment, and the importance of recognizing associated pain should be stressed. Puntillo et al. showed clearly that the majority of patients did not receive any medication before or during a specific procedure and in particular fewer than 20% received premedication with opioids. In cancer patients, these types of procedural pain should be investigated and prevented with pharmacological and non-pharmacological intervention [55, 56].

Several diagnostic and therapeutic procedures, such as venipuncture, arterial puncture, lumbar puncture, and percutaneous venous catheter placement, may be associated with severe pain and quality-of-life decrement. For this reason, the use of topical anaesthesia may represent a significant clinical help with the aim to prevent procedural pain. In the literature, several local procedures have been described: lidocaine/tetracaine patch, lidocaine/prilocaine cream, buffered lidocaine solutions, and chloroprocaine injections [57, 58]. The lack of phase III randomised, controlled trials does not permit to prefer any of these local anaesthetic procedures.

The best-known form of breakthrough pain is incident pain due to movement, which is commonly associated with bone metastases or pathological fractures. This type of pain limits the functional activity of patients, decreasing their quality of life. It may be caused by movement such as standing, walking, sitting, turning, lifting, deep breathing, coughing, eating, dressing, or washing. The pathophysiological mechanism of bone pain elicited by movement corresponds to a mechanical allodynia (pain induced by a non-noxious stimulus, such as movement), resulting in hypersensitivity, that could require higher opioid doses than those sufficient to control basal pain.

Globally, there is a lack of guidelines evaluating and treating pain during procedures for cancer diagnosis and treatment; clinical trials are warranted to investigate the efficacy of specific analgesic interventions. Such studies will provide an evidence base which can contribute to the global care of patients.
stable phase (iatrogenic pain)

chemotherapy-related pain

Acute pain associated with chemotherapy infusion techniques. Pain at the site of cytotoxic infusion is a common problem. Four pain syndromes related to intravenous infusion of chemotherapeutic agents are recognized: venous spasm, chemical phlebitis, vesicant extravasation, and anthracycline-associated flare. Venous spasm causes pain that is not associated with inflammation or phlebitis, and which may be modified by application of a warm compress or reduction of the rate of infusion. Chemical phlebitis can be caused by cytotoxic medications, as well as the infusion of potassium chloride and hyperosmolar solutions. Vesicant extravasation may produce intense pain followed by desquamation and ulceration. Finally, a brief venous flare reaction is often associated with intravenous administration of the anthracycline, doxorubicin. Typically, the flare is associated with local urticaria and occasional patients report pain or stinging.

Acute pain associated with chemotherapy toxicity mucositis. Severe mucositis is an almost invariable consequence of the myeloablate chemotherapy that precedes bone marrow transplantation, but it is less common with standard intensity therapy. The cytotoxic agents most commonly associated with mucositis are: cytarabine, doxorubicin, etoposide, 5-fluorouracil, and methotrexate. Pre-treatment oral pathology, poor dental hygiene, and younger age increase the risk of chemotherapy-induced mucositis.

taxane-induced arthralgia and myalgia. Administration of paclitaxel generates a syndrome of diffuse arthralgias and myalgias in 10%–20% of patients. They are related to individual doses; associations with the cumulative dose and infusion duration are less clear. Diffuse pain in joints and muscles generally appeared 1–2 days after the infusion and lasted for a median of 4–5 days. Pain is commonly located in the back, hips, shoulders, thighs, legs, and feet. The pain is often exacerbated by weight bearing, walking, or tactile contact. Steroids may reduce tendency to myalgia and arthralgias. Evidence for targeted analgesia is lacking.

Acute herpetic neuralgia. Acute herpetic neuralgia occurs with a significantly increased incidence among cancer patients, especially those with haematological or lymphoproliferative malignancies and those receiving immunosuppressive therapies. The pain, which may be continuous or lancinating, usually resolves within 2 months. Pain persisting beyond this interval is referred to as post-herpetic neuralgia, and is often challenging to treat, therefore optimum attention to the acute phase is important.

tpalmar-plantar erythrodysesthesia syndrome. This is a painful rash of unknown pathogenesis seen in association with continuously infused 5-fluorouracil, capcitabine, liposomal doxorubicin, and paclitaxel. It is characterized by the development of a tingling or burning sensation in the palms and soles followed by the development of an erythematos rash. Management often requires the discontinuation of therapy, or symptoms may be more manageable at lower doses of therapy. Symptomatic measures are often required and treatment with pyridoxine has been reported to induce resolution of the lesions.

Pain at tumour site. After vinorelbine administration, an incident very intense pain has been reported at tumour site, in particular in patients having already received radiation treatment and in head and neck cancer subset. Premedication with ketorolac and morphine can reduce the occurrence of this symptom; otherwise, the shift to oral vinorelbine is indicated, as no acute pain has been reported with this formulation.

Supportive therapy-related pain

Table 2 summarizes some examples of pain related to supportive therapy.

<table>
<thead>
<tr>
<th>Type of supportive therapy</th>
<th>Pathophysiology</th>
<th>Pain therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone and muscular pain related to growth factors for white cells (G-CSF, peg-formulations)</td>
<td>Somatic pain</td>
<td>Pre-/post-med. with NSAIDs/opioids</td>
</tr>
<tr>
<td>Acute phase with fever and bone/muscular pain induced by parental bisphosphonates or denosumab</td>
<td>Somatic pain</td>
<td>Pre-/post-med. with NSAIDs/opioids</td>
</tr>
<tr>
<td>Steroid therapy (aseptic head femoral necrosis)</td>
<td>Somatic and neuropathic pain</td>
<td>Therapy with NSAIDs/opioids; bisphosphonates/cord decompression</td>
</tr>
<tr>
<td>Steroid/NSAID therapy (acute gastritis)</td>
<td>Visceral pain</td>
<td>Proton pump inhibitors; antacids; prokinetics</td>
</tr>
<tr>
<td>Parenteral iron/potassium supplementation</td>
<td>Local somatic pain and phlebitis</td>
<td>Local anaesthetic</td>
</tr>
<tr>
<td>Parenteral bisphosphonates in metastatic setting causing osteonecrosis of the jaw</td>
<td>Somatic and neuropathic pain</td>
<td>Therapy with NSAIDs/opioids; antibiotics; local anaesthetics; local surgery</td>
</tr>
<tr>
<td>Opioid hyperalgesia</td>
<td>Neuropathic pain</td>
<td>Opioid rotation</td>
</tr>
<tr>
<td>Prosthesis in bone metastases</td>
<td>Somatic and neuropathic pain</td>
<td>Therapy with NSAIDs/opioids; contracture relieving; revaluation of the prosthesis</td>
</tr>
</tbody>
</table>

Med., medication; NSAIDs, non-steroidal anti-inflammatory drugs.
parental bisphosphonate acute phase reaction and osteonecrosis of the jaw. Acute systemic inflammatory reactions in different anatomical sites, characterized by fever, influenza-like symptoms, myalgia, arthralgia, bone pain, nausea, vomiting, abdominal pain, eye pain, fatigue, nasopharyngitis, and oedema, are commonly observed after intravenous administration of last generation bisphosphonates (BPs) in patients with bone metastases, as well as in patients with hormone-induced osteoporosis [80, 81]. At present, few data are available on denosumab acute inflammatory reactions.

Myalgia has been reported in 25%–30% of patients receiving the first dose of pamidronate or zoledronic acid [82, 83]. Accompanying bone pain has also been reported in over half of patients after the first administration and is less frequent during subsequent infusions [81, 83]. Musculoskeletal pain may occur also without fever and usually starts within 12–72 h after infusion, resolving completely within 48–72 h. Commonly, it is experienced as a generalized discomfort, or local pain involving the back, spines, ribs, and lower limbs, not necessarily near the site of metastases. Severe pain limiting daily activity and lasting several days has been described in a minority of patients; it may provoke acute gait disturbance in elderly patients [84]. However, patients must be informed regarding the possible onset of pain or the worsening of pre-existing pain. Pain relief is generally achieved with the administration of non-steroidal anti-inflammatory drugs (NSAIDs) and acetaminophen [85]. Patients on regular analgesic opioid therapy can use the drugs already prescribed at higher doses. Premedication with acetaminophen or ibuprofen [83] or with 4 mg of intravenous dexamethasone (Ripamonti, ongoing study) may help to reduce the intensity and incidence of pain caused by BPs. However, patients on long-term NSAIDs are more sensitive to the effects of superadded inflammatory changes, probably because they have other medical problems associated with chronic pain and/or inflammation [81].

Osteonecrosis of the jaw (ONJ) is an adverse event reported in patients receiving BPs and RANKL inhibitors, such as denosumab [86–88]. Recent recommendations for ONJ include a conservative approach with intermittent prophylactic antibiotic therapy and rinses with oral chlorhexidine and debridement [89]; moreover, a careful sequestrum removal is recommended [90–92]. No data are available on the incidence of pain in patients with ONJ, although in many cases pain is the first sign of this complication.

Granulocyte colony-stimulating factor (G-CSF) bone-related pain. G-CSF and its long-term action form pegfilgrastim which may induce bone pain that can result in discontinuation of the growth factor, reducing chemotherapy dose intensity, and consequently the patients’ survival. Pain is reported in 26%–71% of patients, with 5%–24% of patients reporting pain intensity >5 on a 1–10 numerical rating scale [93–96]. Kirshner et al. [95] carried out a phase III randomized, placebo-controlled clinical trial to assess the efficacy of naproxen 500 mg twice per day in reducing the incidence and severity of pegfilgrastim-induced bone pain, on the day of pegfilgrastim and continuing for 5–8 days after. The study shows that naproxen significantly reduced pegfilgrastim-induced bone pain by 22% over the whole 5 days of the course, with an absolute difference of 10%. Even with the preventative use of naproxen, >60% of patients still experienced some pain (19% severe pain). Future trials with other agents to prevent G-CSF-induced bone pain are needed.

targeted/biological therapy-related pain

TTs have been acquiring greater room in the strategic management of several neoplasms in recent years. There is a growing body of data about their toxicity, but, surprisingly, very few trials reported the presence and intensity of pain associated with these toxicities. Along with the wider use and longer survival associated with these agents, the prevalence of pain as an effect of TT will increase. Table 3 depicts some potential causes of TT pain toxicities.

Dermatological adverse events are frequently reported by patients treated with epidermal growth factor receptor (EGFR) inhibitors or multi-targeted tyrosine-kinase inhibitors (TKI), in a range varying from 75% to 85% [97, 98]. The Multinational Association of Supportive Care in Cancer (MASCC) proposed a new grading scale for EGFR inhibitor toxicities [99]; pain is a component of assessment in determining the grade of papulo-pustular eruption, nail changes, erythema, and mucositis. Dermatological pain by EGFR inhibitors is due to the activation of nociceptive fibres by the action of the drug in basal keratinocytes [100]. In chemotherapy-induced toxicities, palmar-plantar erythrosaesthesia syndrome (hand–foot syndrome) is reported with multiple tyrosine-kinase inhibitors, in particular sunitinib and sorafenib, even with a slightly different clinical presentation and a possible dissimilar pathogenesis [101]. The pain is burning, causing reduction in activities of daily living and quality of life.

Oral mucositis related to TT has not been elucidated in its pathophysiological mechanisms, but a different process from mucositis due to chemotherapy is expected [102]. Moreover, a different pain type and intensity could be hypothesized according to the mechanism of action of TT. Mucositis-associated pain has been reported both with EGFR inhibitors [103] and with multi-targeted TKI and mammalian target of rapamycin (mTOR) inhibitors [104]. This specific pain has both neuropathic and nociceptive components, so therapeutic intervention should target both these aspects.

There is a strong need for well-conducted trials analysing pathophysiology, epidemiology, prevention, and treatment of TT-related pain.
radiotherapy-related pain

RT is potentially painful in both acute and late phase cancer (Table 4). In the acute phase, inflammation of the mucosa or the skin, flare effects, and procedural pain are the main determinants of RT-induced pain.

Mucositis may afflict all the irradiated area, in particular the gastrointestinal tract, from oral cavity to anal tract. In particular, head and neck patients treated with chemoradiation suffer from mucositis in >90% of cases, which is associated often with high intensity pain in oral cavity and pharynx, especially during swallowing [105], interfering with oral alimentation. Updated MACC mucositis guidelines suggest the use of transdermal fentanyl and 2% morphine or 0.5% doxepin mouthwashes for the treatment of this symptom [106], whose control is, however, insufficient [107]. Acute radiation enteritis occurs in as many as 50% of patients receiving abdominal or pelvic RT. Involvement of the small intestine can present with cramping abdominal pain associated with nausea and diarrhoea [108]. Pelvic RT can cause a painful proctocolitis, with tenesmoid pain associated with diarrhoea, mucus discharge, and bleeding [108, 109].

Pain flare effect is quite common in patients irradiated for bone metastasis, consisting of a temporary, acute increase of pain in radiated areas [110, 111]. This pain is treated with breakthrough analgesics, and no preventive intervention, except from steroids in the phase II study, has been investigated [112].

Some examples of procedural pain induced by RT include brachytherapy, or movement of the patients with bone metastasis in order to perform radiation to the affected tract. Brachytherapy has a recognized role mainly in the treatment of some types of genito-urinary cancer and is associated with multi-factorial pain [113, 114]. Analgesia can be provided with local–regional anaesthesia, sedation, systemic opioids, and NSAIDs [114–116].

As a late effect, RT has been associated with pain syndromes after several treatments.

Radiation fibrosis syndrome may consist of several symptoms and signs resulting from progressive fibrotic tissue sclerosis: cervico-thoracic pain due to neck muscle weakness, shoulder pain, painful cervical dystonia, and trismus [117]. Osteoradionecrosis of the jaw is a serious adverse event occurring after irradiation of head and neck that can be initially asymptomatic, with the patient developing pain only later, thus delaying diagnosis [118]. Chest wall pain or brachial plexopathy after irradiation for thoracic cancers is generally mild, but in some patients receiving higher doses may be so severe as to require opioids [119, 120]. Adjuvant RT has been associated with increased multi-factorial pain in breast cancer survivors [121]. Radiation treatments for gynaecological cancers may cause vaginal stenosis and reduced vaginal secretions associated with dyspareunia [122]. Urethral pain is a possible late effect in long-term prostate cancer survivors, with risk directly proportional to RT dose to urethra and if brachytherapy is added to external RT [123].

hormonal therapy-related pain

aromatase inhibitor-associated bone and musculoskeletal effects. Aromatase inhibitors (AIs) are used widely in breast cancer, both in the adjuvant setting and in advanced disease treatment. Musculoskeletal symptoms, including bone demineralization with significantly increased rates of osteopenia, osteoporosis and fractures, arthralgias, and myalgias, are important side-effects that can lead to discontinuation of therapy with AIs [124–127].

AIs inhibit estrogen production in postmenopausal women, and the rapid decreases in estrogen may provide a direct nociceptive stimulus for joint pain and/or remove the protective anti-nociceptive role of estrogen [128].

In the major phase III clinical trials that compared AIs with tamoxifen, the reported incidence of musculoskeletal symptoms ranged from 5% to 36% [129–132]. However, case series have reported an even higher incidence of these symptoms in up to 61% of AI-treated women, causing high non-adherence rates and worsening of quality of life [133–135].

Recommendations for the management of joint symptoms include pharmacological and non-pharmacological interventions, and also switching to a different AI. No large study has focused on the optimal management of AI-induced arthralgia. The majority of patients in the phase III not-pre-planned retrospective analyses had received some kind of treatment of their joint symptoms consisting typically of NSAIDs or other analgesics. Other

Table 4. Causes of acute and late radiotherapy-related pain

<table>
<thead>
<tr>
<th>Radiation therapy-related pain</th>
<th>Acute phase</th>
<th>Late phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute mucosal inflammation: stomatitis, pharyngitis, oesophagitis, enteritis, proctitis, etc.</td>
<td>Pain flare effect</td>
<td>Radiation fibrosis syndrome</td>
</tr>
<tr>
<td>Radiation dermatitis</td>
<td>Procedural pain: brachytherapy; implantation of ‘fiducial markers’ in an organ for image-guided radiotherapy; passive mobilization of bone metastatic patient during simulation and treatment</td>
<td>Osteoradionecrosis of the jaw</td>
</tr>
<tr>
<td>Pain flare effect</td>
<td>Procedural pain: brachytherapy; implantation of ‘fiducial markers’ in an organ for image-guided radiotherapy; passive mobilization of bone metastatic patient during simulation and treatment</td>
<td>Chest wall pain</td>
</tr>
<tr>
<td>Diarrhoea, mucus discharge, and bleeding</td>
<td>Abdominal pain due to bowel spasms</td>
<td>Oesophageal stricture</td>
</tr>
<tr>
<td>Painful proctocolitis, with tenesmoid pain associated with diarrhoea</td>
<td>Urethral pain</td>
<td>Abdominal pain due to bowel spasms</td>
</tr>
<tr>
<td>Painful proctocolitis, with tenesmoid pain associated with diarrhoea</td>
<td>Dyspareunia</td>
<td>Anal stricture</td>
</tr>
</tbody>
</table>

Table 5. Common post-cancer surgery-related pain syndromes

<table>
<thead>
<tr>
<th>Type of post-surgical pain</th>
<th>Main associations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast surgery pain syndromes</td>
<td>Either from wide local excision, breast-conserving surgery, or radical mastectomy. Particularly common with axillary dissection</td>
</tr>
<tr>
<td>Post-radical neck dissection</td>
<td>Poor predictive factors</td>
</tr>
<tr>
<td>Post-thoracotomy</td>
<td>Poor predictive factors</td>
</tr>
<tr>
<td>Post-operative frozen shoulder</td>
<td>Post-thoracotomy and post-mastectomy at particular risk</td>
</tr>
<tr>
<td>Phantom pain syndromes</td>
<td>After limb amputation</td>
</tr>
<tr>
<td>Post-surgical pelvic floor myalgia</td>
<td>Poor predictive factors</td>
</tr>
</tbody>
</table>
reports have also described the effects of acetaminophen and opioids. At present, the use of opioids has not been supported by solid prospective data. Low-dose corticosteroids were also reported to be effective, but the toxicity profile makes them an inappropriate choice for the treatment of AI-induced arthralgia. A large prospective randomized, placebo-controlled trial to evaluate vitamin D supplementation in AI-induced arthralgia has recently been completed (NCT00263185). Duloxetine, a serotonin and norepinephrine reuptake inhibitor, reduced musculoskeletal pain in an open-label phase II study [136]. Other antidepressants and anticonvulsants, often used in the treatment of chronic pain disorders, have not been investigated in AI-related symptoms. Effective management of these symptoms is essential to enhance adherence to therapy, improve outcomes, and decrease breast cancer recurrence.

surgery-related pain

Table 5 summarizes the common post-cancer surgery-related pain syndromes.

conclusions

The small amount of data in the literature on pain related to oncological treatments and diagnostic procedures suggest that little attention has been given to this important aspect of oncology and the underestimation of pain leads to suboptimal management of patients.

There are different reasons for such underperformance in cancer patients’ management, ranging from low importance given to symptoms assumed to be transient in patients presenting with a good general condition and undergoing life-saving treatments, to an inadequate knowledge of cancer-related pain or pain caused by oncological therapies, as well as diagnostic procedures, pain assessment, and treatment.

Barriers and misconceptions exist towards the use of analgesic drugs, especially towards opioids, by both patients and health care professionals. Often cancer patients are afraid of developing addictions to painkillers, whereas physicians are reluctant to prescribe such drugs.

Further studies are necessary in order to understand the incidence of pain during and after oncological treatments as well as diagnostic procedures. At the same time, the Health Care Professionals must be educated regarding the causes of pain, with the aim to assess and recognize patients’ suffering and to prevent and treat it in a personalized way.

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We would like to dedicate this paper to the memory of our great teachers—Prof. Vittorio Ventafredda and Prof. Geoffrey Hanks.

disclosure

The authors have declared no conflicts of interest.

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Dairy products and pancreatic cancer risk: a pooled analysis of 14 cohort studies


1Department of Epidemiology, Mailman School of Public Health, Columbia University, New York; 2Department of Epidemiology, Harvard School of Public Health, Boston; 3Department of Biostatistics, Harvard School of Public Health, Boston; 4Division of Cancer Epidemiology and Genetics, National Cancer Institute, NIH, DHHS, Bethesda; 5Division of Epidemiology and Community Health, School of Public Health, Masonic Cancer Center, University of Minnesota, Minneapolis; 6Division of Cancer Etiology, School of Public Health, Mailman School of Public Health, 722 w 168th St, New York, NY 10019, USA. 7Department of Biostatistics, School of Public Health and Health Services, George Washington University, Washington, DC; 8Division of Epidemiology and Population Health, Albert Einstein College of Medicine, Bronx, USA; 9Department of Epidemiology and Biostatistics, School of Public Health, University of Toronto, Toronto, Canada; 10Department of Epidemiology and Community Health, School of Public Health, University of Massachusetts, Amherst; 11Department of Epidemiology, University of California, Los Angeles; 12Epidemiology Research Program, American Cancer Society, Atlanta, USA; 13Department of Social and Preventive Medicine, University at Buffalo, State University of New York, Buffalo; 14Division of Network Medicine, Department of Medicine, Brigham and Women’s Hospital and Harvard Medical School, Boston; 15Department of Social and Preventive Medicine, University of Montreal, Montreal; 16Dalla Lana School of Public Health, University of Toronto, Toronto, Canada; 17Department of Epidemiology and Biostatistics, School of Public Health and Health Services, George Washington University, Washington, DC; 18Department of Epidemiology and Community Health, School of Public Health, University of British Columbia, Vancouver, Canada; 19Department of Nutrition, Harvard School of Public Health, Boston, USA; 20Department of Chronic Disease Prevention, National Institute for Health and Welfare, Helsinki, Finland; 21Division of Network Medicine, Department of Medicine, Brigham and Women’s Hospital and Harvard Medical School, Boston.

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Pancreatic cancer has few early symptoms, is usually diagnosed at late stages, and has a high case-fatality rate. Identifying modifiable risk factors is crucial to reducing pancreatic cancer morbidity and mortality. Prior studies have suggested that specific foods and nutrients, such as dairy products and constituents, may play a role in pancreatic carcinogenesis. In this study, we examine the association between dairy product consumption and pancreatic cancer risk in 14 cohort studies with 2308 cases of pancreatic cancer.

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