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CLINICAL PRACTICE GUIDELINES

Management of cancer pain in adult patients: ESMO Clinical Practice Guidelines†

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Incidence

Pain is common in cancer patients, particularly in the advanced stage of disease when the prevalence is estimated to be more than 70% [1], contributing to poor physical and emotional well-being. The most comprehensive systematic review indicates pain prevalence ranging from 33% in patients after curative treatment, to 59% in patients on anticancer treatment and to 64% in patients with metastatic, advanced or terminal disease [2]. Pain has a high prevalence earlier in disease in specific cancer types such as pancreatic (44%) and head and neck cancer (40%) [3].

Increased survival with either life-prolonging treatment or curative treatment results in increased numbers of patients experiencing persistent pain due to treatment or disease, or a combination of both [4]. Approximately 5%–10% of cancer survivors have chronic severe pain that interferes significantly with functioning [5].

Despite guidelines and the availability of opioids (the mainstay of moderate to severe cancer pain management), undertreatment is common.

European studies [6] confirmed these data from the United States, showing that different types of pain or pain syndromes were present in all stages of cancer (Table 1) and were not adequately treated in a significant percentage of patients, ranging from 56% to 82.3%.

According to a systematic review published in 2014 [7] using the Pain Management Index (PMI) [8], approximately one-third of patients do not receive appropriate analgesia proportional to their pain intensity (PI).

High prevalence has also been documented in haematology patients at diagnosis, during therapy and in the last month of life [9]. These data reinforce the recommendation that patients with advanced or metastatic cancer require management within an integrated system for palliative care [7]. Cancer-related pain may be presented as a major issue of healthcare systems worldwide: ∼14.1 million new cancer cases and 8.2 million deaths occurred worldwide in 2012, based on GLOBOCAN estimates [10] and incidence will be > 15 million in 2020, based on projections [11].

Assessment

Initial and ongoing assessment of pain should be an integral part of cancer care and indicates when additional comprehensive assessment is needed (Table 2). The regular self-reporting of PI with the help of validated assessment tools is the first step towards effective and individualised treatment. The most frequently used standardised scales [12] are reported in Figure 1 and are the visual analogue scale (VAS), the verbal rating scale (VRS) and the numerical rating scale (NRS).

Assessment of the pain descriptors improves the choice of therapy. Pain can be:

(i) Nociceptive: caused by ongoing tissue damage, either somatic (such as bone pain) or visceral (such as gut or hepatic pain); or
(ii) Neuropathic: caused by damage or dysfunction in the nervous system, such as in brachial plexopathy or in spinal cord compression by tumour [13].

Table 1. Non-tumour-related causes of pain in cancer patients

Acute procedural pain	Iatrogenic pain causes	Comorbidity-related pain	Pain in cancer survivors
Adjuvant setting			
– Diagnostic intervention – Lumbar puncture ± headache – Transthoracic needle biopsy – Endoscopy ± visceral dilatation – Bone marrow aspiration/biopsy – Blood sampling – Central line position – Arterial line injections – Medication of skin ulcers – Myelography and lumbar puncture – Thoracentesis	– Surgery – Chemotherapy – Hormonal therapy – Targeted therapy – Osteonecrosis of the jaw – RT – Steroids (pain due to skin lesions, peripheral neuropathy, mucositis, aseptic femoral head necrosis, infections)	– Cardiovascular – Pulmonary – Diabetic neuropathy – Vasomotor headache – Fibromyalgia – May be worsened by anticancer treatments and/or cancer-related pain – Postherpetic neuralgia – Acute thrombosis pain	– Follow-up procedures – Persisting postsurgical pain – Persisting anticancer drug-related pain – Persisting RT-related pain – Postherpetic neuralgia
Neo-adjuvant setting			
– As adjuvant setting plus diagnostic and prognostic tissue biopsy	– As adjuvant setting without surgery-related pain	– As adjuvant setting	– As adjuvant setting
Locally advanced setting			
– As adjuvant setting plus pleurodesis, tumour embolisation, suprapubic catheterisation and nephrostomy insertion	– As adjuvant setting plus cryosurgery, thermal ablation, TACE, spinal/epidural injection and opioid hyperalgesia	– As adjuvant setting	– As adjuvant setting
Metastatic setting			
– As locally advanced setting plus liver, lung or soft tissue diagnostic biopsies, wound care and movement procedural pain	– As neo-adjuvant setting	– As adjuvant setting	– As adjuvant setting plus synergistic pain effects between iatrogenic and disease-related causes in long-term cancer survivors

RT, radiotherapy; TACE, transarterial chemoembolisation.

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Table 2. Guidelines for the adequate assessment of the patient with pain at any stage of the disease

1. Assess and re-assess the pain

Causes, onset, type, site, absence/presence of radiating pain, duration, intensity, relief and temporal patterns of the pain, number of BTcPs, pain syndrome, inferred pathophysiology, pain at rest and/or moving

Presence of trigger factors and signs and symptoms associated with the pain

Presence of relieving factors

Use of analgesics and their efficacy and tolerability

Description of the pain quality:

– Aching, throbbing, pressure: often associated with somatic pain in skin, muscle and bone

– Aching, cramping, gnawing, sharp: often associated with visceral pain in organs or viscera

– Shooting, sharp, stabbing, tingling, ringing: often associated with NP caused by nerve damage

2. Assess and re-assess the patient

Clinical situation by means of a complete/specific physical examination and the specific radiological and/or biochemical investigations

Interference of pain with the patient's daily activities, work, social life, sleep patterns, appetite, sexual functioning, mood, well-being and coping

Impact of the pain, the disease and the therapy on the physical, psychological and social conditions

Presence of a caregiver, psychological status, degree of awareness of the disease, anxiety and depression and suicidal ideation, his/her social environment, QoL, spiritual concerns/needs, problems in communication, personality disorders

Presence and intensity of signs, physical and/or emotional symptoms associated with cancer pain syndromes

Presence of comorbidities (i.e. diabetic, renal and/or hepatic failure, etc.)

Functional status

Presence of opiophobia or misconception related to pain treatment

Alcohol and/or substance abuse

3. Assess and re-assess your ability to inform and to communicate with the patient and the family

Spend time with the patient and the family to understand their needs

BTcP, breakthrough cancer pain; NP, neuropathic pain; QoL, quality of life.

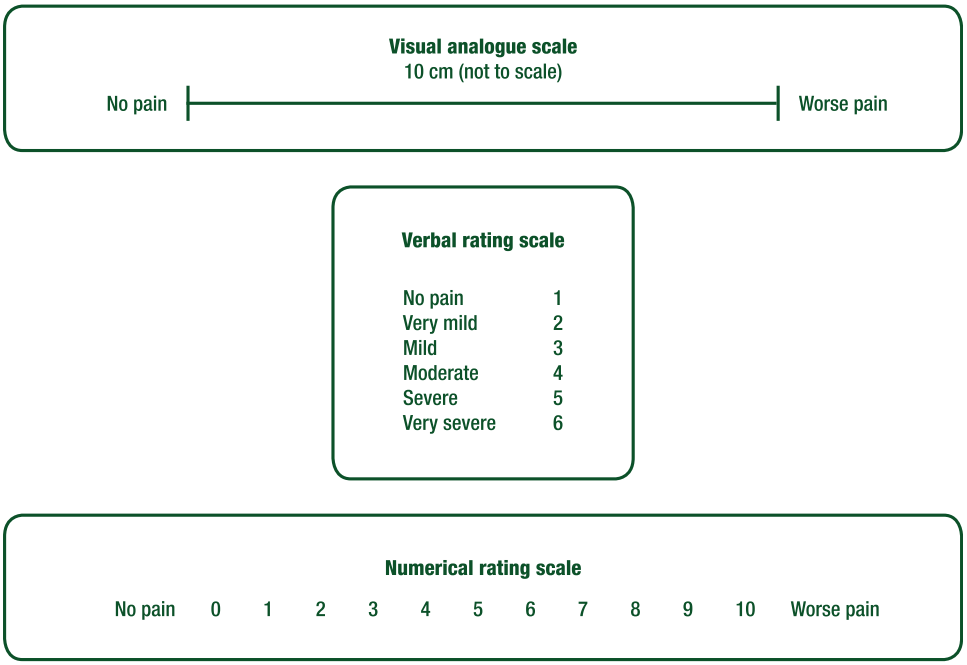

Figure 1. Validated and most frequently used pain assessment tools.

Most patients with advanced cancer have at least two types of cancer-related pain, resulting from a variety of pathophysiology [14].

Initial assessment of cancer-related pain for all patients should include:

(i) Ask a key screening question, which is not paraphrased and is used consistently. That question should be: 'What has been your worst pain in the last 24 hours on a scale of 0–10?', where 0 is no pain and 10 is the worst imaginable [15].
(ii) Monitor if the pain is < 3.
(iii) Move to a more detailed assessment if the worst pain is ≥ 3 or if the patient is distressed by pain (as per Table 2). This should also include average pain and pain 'right now'.
(iv) Administer appropriate analgesic and reassess both pain and analgesic side effects.
(v) Review analgesic regimen if side effects to prescribed analgesics are present and/or pain persists.

Recommendation:

- The intensity of pain and the treatment outcomes should be assessed regularly and consistently using the VAS or NRS using the question: 'What has been your worst pain in the last 24 hours?' [V, D].

In elderly patients, limited communicative skills and/or cognitive impairment make self-reporting of pain more difficult, although there is no evidence of clinical reduction in pain-related suffering.

When cognitive deficits are severe, observation of pain-related behaviours and discomfort (e.g. facial expression, body movements, verbalisation or vocalisations, changes in interpersonal interactions, changes in routine activity) is an alternative strategy for assessing the presence of pain (but not its intensity) [16]. Observational scales are available [16]; however, none is validated in different languages. Sensitivity to a light touch can signal neuropathic pain (NP). A detailed appraisal of the literature pertaining to pain assessment in patients with cognitive impairment is outside the scope of this guideline but, given the global challenge and projected increase in dementia, this will become increasingly important [17].

Assessment and management of pain in children are not considered in this manuscript, but guidelines have been developed by the World Health Organization (WHO) [18].

Recommendation:

- Observation of pain-related behaviours and discomfort is indicated in patients with cognitive impairment to assess the presence of pain [V, C].

Psychosocial distress is strongly associated with cancer pain and should be assessed [19]. Psychological distress may amplify pain and similarly, inadequately controlled pain may cause psychological distress [20].

Recommendation:

- The assessment of all components of suffering, such as psychosocial distress, should be considered and evaluated [II, B].

Principles of pain management

Patients must be informed about possible onset of pain at any stage of the disease, both during/after diagnostic interventions and as a consequence of cancer and/or anticancer treatments. Patients should be empowered and encouraged to communicate with the physician and/or the nurse about their suffering, the efficacy of therapy and side effects. Patient education should include information on the appropriate use of opioids; this should be set in context with other analgesic and non-pharmacological approaches [21]. Patient involvement in pain management improves both communication and pain relief through enhancing both patient understanding and physician assessment and prescribing [22, 23].

It is important to prescribe a therapy that can be managed simply by patients and families themselves. The oral route, if well tolerated, should be considered as the preferred route of administration [24, 25].

Breakthrough cancer pain (BTcP), defined as 'a transitory flare of pain that occurs on a background of relatively well-controlled baseline pain', requires careful assessment and appropriate management. Typical BTcP episodes are of moderate to severe intensity, rapid in onset (minutes) and of relatively short duration (median 30 minutes) [26].

Recommendations:

- Patients should be informed about pain and pain management and should be encouraged to take an active role in their pain management [II, B].
- The onset of pain should be prevented by means of around-the-clock (ATC) administration, taking into account the half-life, bioavailability and duration of action of different drugs [II, B].
- Analgesics for chronic pain should be prescribed on a regular basis and not on an 'as required' schedule [V, D].
- The oral route of administration of analgesic drugs should be advocated as the first choice [IV, C].

The type and dose of analgesic drugs are influenced by the PI and must be promptly adjusted to reach a balance between optimal pain relief and minimum side effects. Rescue doses [as-needed (prn) doses] should be prescribed proactively for the relief of BTcP pain and to overcome end-of-dose failure. Rescue medication used for end-of-dose failure should help with calculating the daily titration of regular doses.

The oral route is preferred except when oral intake is not possible because of severe vomiting, bowel obstruction, severe dysphagia or severe confusion, and in the case of poor pain control which requires rapid dose escalation and/or in the presence of oral opioid-related adverse effects.

The WHO proposes a strategy (currently under review) for cancer pain treatment based on a sequential three-step analgesic ladder, from non-opioids to weak opioids to strong opioids, according to PI [24]. The WHO ladder recommends non-opioid analgesics as possible options at all steps; however, this is of greater relevance for the first two steps of the WHO ladder. In practical terms, this means paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs) (step 1). Opioid analgesics are the mainstay of analgesic therapy and are classified according to ability to control pain from mild to moderate (step 2) to moderate to severe intensity (step 3) [24–26]. However, some authors have suggested eliminating the second step of the analgesic ladder, with weak opioids being replaced with low doses of oral morphine [27, 28].

Analgesic drugs are only one part of cancer pain management, and an integrated approach to cancer pain management should be adopted; this should incorporate:

(i) primary antitumour treatments;
(ii) interventional analgesic therapy and
(iii) a variety of non-invasive techniques such as psychological and rehabilitative interventions [29].

Treatment of mild pain

Paracetamol and NSAIDs are universally accepted as part of the treatment of cancer pain at any stage of the WHO analgesic ladder. Several relevant systematic reviews are available regarding the efficacy of paracetamol and NSAIDs for cancer pain management, either when used alone or in combination with opioids.

Paracetamol

Paracetamol is the mainstay of the first two steps of the WHO analgesic ladder in many countries. However, a Cochrane systematic review highlights the lack of knowledge about the effectiveness of paracetamol for cancer pain [30].

NSAIDs

In 2017, Cochrane identified 11 studies of oral NSAIDs in adults with cancer pain [31]. These included 949 participants; however, no studies examined the effects of NSAIDs together with an opioid (such as morphine), although this is how they are often used. All studies were compromised by small numbers. With any NSAID, moderate or severe cancer pain was reduced to no worse than mild pain in 26%–51% of patients, after 1 or 2 weeks in 4 of the 11 studies.

Based on this 2017 Cochrane review, there is no conclusive evidence to support or refute the use of NSAIDs alone or in combination with opioids for the treatment of mild cancer pain. (There is limited evidence that some people with moderate or severe cancer pain can obtain substantial levels of benefit within 1 or 2 weeks.)

It is important to monitor and reassess the long-term use of NSAIDs or cyclo-oxygenase-2 (COX-2) selective inhibitors [32] because of their significant toxicity (e.g. gastrointestinal bleeding, platelet dysfunction and renal failure). COX-2 selective inhibitors may increase the risk of thrombotic cardiovascular adverse reactions [33] and do not reduce the risk of renal failure.

Dipyrone is another non-opioid analgesia that a recent systematic review concluded could be used for the treatment of cancer pain, alone or in combination with opioids [34].

Recommendations:

- Analgesic treatment should start with drugs indicated by the WHO analgesic ladder appropriate for the severity of pain [II, B].
- There is no significant evidence to support or refute the use of paracetamol alone or in combination with opioids for mild to moderate pain [I, C].
- There is no significant evidence to support or refute the use of NSAIDs alone or in combination with opioids for mild to moderate pain [I, C].

Treatment of mild to moderate pain

There are few options to treat mild to moderate cancer pain before moving to strong opioids such as morphine. Tramadol, dihydrocodeine and codeine are the widely available options.

Tramadol

There is widespread use of tramadol in palliative care, even though the data on its use are limited and adverse effects can be severe [27, 35, 36]. Tramadol has a potential role on step 2 of the analgesic ladder, particularly if other step 2 drugs are not tolerated, but adequate studies comparing tramadol with other step 2 drugs (e.g. codeine or dihydrocodeine) are missing.

Tramadol can have significant side effects, such as dizziness, nausea, vomiting and constipation [37]. Tramadol affects serotonin metabolism or availability, potentially leading to serotonin toxicity, particularly in the elderly, and can lower seizure thresholds. Tramadol has a much-reduced analgesic effect in cytochrome P450 2D6 (CYP2D6) poor metabolisers.

Dihydrocodeine

Dihydrocodeine is also a substrate for CYP2D6; its partial metabolism is limited in poor metabolisers and is blocked by CYP2D6 inhibitors. However, there is no evidence that such inhibition reduces its analgesic effect.

Codeine

Codeine has no or little analgesic effect until metabolised to morphine, mainly via CYP2D6. In poor metabolisers, it is therefore essentially ineffective, while in ultrarapid metabolisers, it is potentially toxic.

The second step of the WHO ladder has several controversial aspects. The first criticism concerns the absence of a definitive proof of efficacy of weak opioids. A meta-analysis of data from randomised controlled trials (RCTs) showed no significant difference between the effectiveness of non-opioid analgesics alone and non-opioids in combination with weak opioids [38]. The available studies do not demonstrate a clear difference in the effectiveness of the drugs between the first and the second step [39]. A 2014 Cochrane review of weak opioids in cancer pain including 15 studies with 721 participants, although providing newer data, was not able to help formulate recommendations [40].

The available evidence indicates that codeine is more effective against cancer pain in adults than placebo, but with increased risk of nausea, vomiting and constipation [41].

Work is evolving in the exploration of the place of step 2 in the WHO three-step ladder. Historical work with uncontrolled studies showed that the effectiveness of the second step of the WHO ladder has a time limit of 30–40 days for most patients and that the shift to the third step is mainly due to insufficient analgesia, and 'ceiling effect' with weak opioids, rather than to adverse effects [42].

Given the lack of data on effectiveness of tramadol, dihydrocodeine and codeine on cancer pain, many authors have proposed the abolition of the second step of the WHO analgesic ladder, in favour of the early use of morphine at low doses, which is not in the

current WHO guideline. The evidence base is evolving, with one study in favour of a low-dose morphine approach already reported and results from another RCT expected shortly [27, 28].

Recommendations:

- For mild to moderate pain, weak opioids such as tramadol, dihydrocodeine and codeine can be given in combination with non-opioid analgesics [III, C].
- As an alternative to weak opioids, low doses of strong opioids could be an option, although this recommendation is not currently part of WHO guidance [II, C].
- There is no evidence of increase in adverse effects from the use of low-dose strong opioids instead of the standard step 2 approach with weak opioids [II, C].

Treatment of moderate to severe pain

Strong opioids

Strong opioids are the mainstay of analgesic therapy in treating moderate to severe cancer-related pain. Although a variety of strong opioids exist and there is no superiority of one over another, morphine is the most widely available and prescribed.

In spite of the global agreement that access to opioids is essential, both access to and use of opioids remains poor in many countries. Various factors contribute to poor access and use, which is still problematic in Eastern and South Eastern Europe [43–47].

According to the last European Society for Medical Oncology–European Association of Palliative Care (ESMO–EAPC) report [48], morphine, methadone, oxycodone, hydromorphone, fentanyl, alfentanil, buprenorphine, diamorphine, levorphanol and oxymorphone are all used in Europe. In some countries, the consumption of oxycodone and patches of fentanyl and buprenorphine has increased [49], and the WHO list of essential medicines includes morphine, methadone and fentanyl patches for the management of cancer pain [36]. New combination opioid preparations are now available, e.g. oxycodone/naloxone, which have been shown to be potentially useful in reducing opioid-induced constipation (OIC).

The last Cochrane systematic review published in 2016 analysed 62 studies with 4241 participants [50] and supported the use of oral morphine as an effective analgesic for cancer pain, with a low rate (6%) of reported intolerable adverse events. Transdermal fentanyl also achieved similar rates of effective analgesia and has also been advocated as an effective and tolerable analgesic [51].

Although the non-parenteral route of administration is advocated where appropriate, patients presenting with severe pain that needs urgent relief should be treated and titrated with parenteral opioids, usually administered by the subcutaneous (s.c.) or intravenous (i.v.) route.

When converting from oral to parenteral morphine, the dose should be divided by two or three to get a roughly equianalgesic effect, but upward or downward dose adjustment may be required [52].

In general, adjustment of opioid doses is required in renal dysfunction. Accumulation of toxic metabolites can cause a variety of distressing and life-threatening symptoms, including confusion, drowsiness and hallucinations. The latter group of symptoms, known as opioid toxicity, can be associated with a terminal decline, especially in the frail patient. Smaller doses with wider dosing intervals should be used in mild renal dysfunction. Preferred opioids for patients with moderate to severe dysfunction or on dialysis are buprenorphine or fentanyl, as discussed below [53].

Recommendations:

- The opioid of first choice for moderate to severe cancer pain is oral morphine [I, A].
- The average relative potency ratio of oral to i.v. morphine is between 1:2 and 1:3 [II, A].
- The average relative potency ratio of oral to s.c. morphine is between 1:2 and 1:3 [IV, C].

Oxycodone or hydromorphone, in both immediate-release and modified-release formulations for oral administration, and oral methadone are effective alternatives to oral morphine [54].

Transdermal (t.d.) fentanyl and t.d. buprenorphine are best reserved for patients with stable opioid requirements; however, the use of lower strength t.d. fentanyl preparations in patients with unstable opioid requirements requires examination. The t.d. route is usually contraindicated during the titration phase, in opioid-naïve patients or to control BTcP [55]. t.d. fentanyl can be useful in patients with nausea, vomiting, problems with swallowing, constipation and poor compliance.

The latest Cochrane systematic review showed insufficient comparable data for meta-analysis to be undertaken; however, the evidence pointed to a significant reduction in constipation for t.d. fentanyl-treated patients compared with oral morphine [56].

Given the heterogeneity and complexities of patients with cancer pain, choice of opioid is important to achieve an optimum balance between analgesia and unwanted adverse effects. Buprenorphine has a role in the analgesic therapy of patients with renal impairment undergoing haemodialysis treatment [57]; as buprenorphine is mainly excreted in the stool, a dose reduction is not normally needed. The dose conversion from other opioids to buprenorphine can be complex; therefore, palliative care advice is recommended.

Extensive reviews [58, 59] demonstrate that oral methadone has the potential to control pain that does not respond to morphine or other opioids, because methadone shows significant incomplete cross-tolerance with other mu opioid receptor agonist analgesics. Moreover, it can be useful (instead of other opioids) when accumulation of active metabolites is the suspected cause of side effects such as myoclonus, sedation, confusion, nausea and vomiting [60]. This strategy is called opioid switching. Methadone is an effective alternative to oral morphine, oxycodone, hydromorphone and t.d. fentanyl, but because of marked inter-individual differences in the plasma half-life of methadone, attention is required when using this drug in treating chronic cancer pain. Although morphine and methadone demonstrate approximately the same analgesic potency after single-dose administration, a reduction of the equianalgesic dose by one-fourth to one-twelfth is recommended when switching from another opioid to methadone [61, 62]. Therefore, methadone is

Table 3. Relative analgesic ratios for opioid switching

Opioids	Analgesic ratio	LoE	GoR	Evaluated studies (*N*)	References
Oral morphine to oral oxycodone	1:1.5	II	B	RCTs (4); PCT (2)	[69–74]
Oral oxycodone to oral hydromorphone	1:4	II	B	RCT (1)	[75]
Oral morphine to t.d. buprenorphine[a]	75:1	IV	C	PCT (1)	[76]
Oral morphine to t.d. fentanyl[b]	100:1	III	B	PCT (4)	[77–80]
Oral morphine to oral methadone	1:5 to 1:12	III	B	PCT (6)	[61, 62, 76, 81–83]
Oral morphine to oral hydromorphone	1:5 to 1:7.5	II	B	RCT (1)	[84]

[a]Example: 60 mg oral morphine to 35 μg/h t.d. buprenorphine (equivalent to 0.8 mg/24 h).
[b]Example: 60 mg oral morphine to 25 μg/h t.d. fentanyl (equivalent to 0.6 mg/24 h).
GoR, grade of recommendation; LoE, level of evidence; PCT, uncontrolled prospective cohort trial; RCT, randomised controlled trial; t.d., transdermal.
Adapted from [68] with permission.

still considered a drug that should be administered by physicians with experience and expertise in its use.

The low cost of methadone makes it more affordable for developing countries and methadone, along with t.d. fentanyl, is included on the WHO list of essential medicines [36].

Recommendation:

- Fentanyl and buprenorphine (via the t.d. or i.v. route) are the safest opioids in patients with chronic kidney disease stages 4 or 5 (estimated glomerular filtration rate < 30 mL/min) [III, B].

After starting the prescribed initial opioid, clinical efficacy may decrease gradually with time or even suddenly, resulting in a need to increase the dose. In some cases, dose increases do not provide analgesia, and further dose increments are ineffective. Alternatively, adverse effects that are difficult to control with symptomatic therapies may occur [63].

When an opioid fails to provide adequate analgesia or causes unmanageable adverse effects, it should be discontinued, and a different opioid should be offered [64]. Opioid switching (also known as opioid rotation) is the process of substituting one opioid for another one to improve the opioid response, either by improving pain relief or by reducing the intensity of adverse effects [65].

No RCTs have investigated the efficacy of opioid switching. However, a switch to an alternative opioid is frequently used in clinical practice. This approach requires familiarity with equianalgesic doses of the different opioids.

There is no evidence that one sequence is better than another. Thus, the choice of a conversion ratio between opioids during switching should not be a mere mathematical calculation, but part of a more comprehensive assessment of opioid therapy. This should evaluate the underlying clinical situation, pain and adverse effect intensity, comorbidities and concomitant drugs and, in addition, exclude any possible pharmacokinetic factor that could limit the effectiveness of certain drugs [66]. Evidence-based recommendations from the EAPC have been developed for conversion ratios during opioid switching [67].

When switching from one opioid drug to another, dose conversion ratios can be recommended with different levels of confidence (Table 3) [61, 62, 68–84]. These conversion ratios are specific for patients for whom analgesia from the first opioid is satisfactory.

The conversion ratio from oral morphine to oral methadone is affected by previous opioid dose and varies widely from 1:5 to 1:12 or more [67]. Calculation is also complicated by the long half-life of methadone and several aspects of clinical practice (Table 3) [67] and it should be used only by experienced professionals.

Recommendation:

- A different opioid should be considered in the absence of adequate analgesia (despite opioid dose escalation) or in the presence of unacceptable opioid side effects [III, C].

For patients who cannot swallow, those with nausea and vomiting or those at the end of life who are unable to continue with oral medication because of weakness or debility, parenteral opioid administration might be necessary [85]. In some cases, the use of existing venous access may be considered.

A systematic literature review of 18 studies comparing different parenteral routes of administration for cancer pain control showed similar efficacy and tolerability of both s.c. and i.v. routes of administration and no difference in the dose used, but pain relief was faster with the i.v. route [85].

Recommendations:

- The s.c. route is simple and effective for the administration of morphine, diamorphine and hydromorphone and it should be the first-choice alternative route for patients unable to receive opioids by oral or t.d. routes [III, B].
- i.v. infusion should be considered when s.c. administration is contraindicated (peripheral oedema, coagulation disorders, poor peripheral circulation and need for high volumes and doses) [III, B].
- i.v. administration is an option for opioid titration when rapid pain control is needed [III, B].

Scheduling and titration. Opioid doses should be titrated to take effect as rapidly as possible. Titration is a process in which the opioid dose is modified speedily to achieve adequate relief of pain without unacceptable side effects. The established practice with immediate-release oral morphine every 4 hours is based only on the pharmacokinetic profile of this formulation [t_{max} (time after

administration when the maximum plasma concentration is reached) < 1 hour; $t_{1/2\beta}$ (elimination half-life) = 2–3 hours; duration of effect ~4 hours)] [68]. Immediate-release formulations are much more flexible than long-acting preparations. Individual titration of opioid should usually start at the minimum recommended dose and increase until optimum analgesia without unacceptable side effects is reached [86]. One small RCT did not show significant differences between titration with immediate- versus modified-release oral morphine [87].

In patients with severe pain, i.v. titration is strongly suggested (Table 4). i.v. administration of morphine (e.g. 1.5 mg every 10 minutes) for rapid titration in cases of severe pain has been shown to be effective within an hour in most patients [88]. The relative potency ratio of oral to i.v. morphine in patients receiving chronic treatment for cancer pain was 3:1, and the ratio is similar for oral to s.c. morphine [89].

Following the titration period, slow-release opioids can be used [86].

All patients should receive ATC dosing with provision of a rescue or breakthrough dose to manage transient exacerbations of pain. A breakthrough dose is usually equivalent to 10%–15% of the total daily dose. If more than four rescue doses per day are necessary, the baseline opioid treatment with a slow-release formulation must be adapted. Opioids with a rapid onset of analgesia and short duration are preferred as rescue medications.

Recommendations:

- Individual titration, e.g. normal-release morphine administered every 4 hours plus rescue doses (up to hourly) for BTcP, is recommended in clinical practice [IV, C].
- Immediate and slow-release oral morphine formulations can be used to titrate the dose. Titration schemes for both types of formulation should be supplemented with immediate-release oral opioids, prescribed as required for BTcP [III, B].
- The regular dose of slow-release opioids can be adjusted to take into account the total amount of rescue morphine [IV, C].

Management of opioid side effects. Many patients develop adverse effects from opioid therapy such as bowel dysfunction (e.g. constipation, bloating, incomplete evacuation, increased gastric reflux), nausea, vomiting, pruritus, respiratory depression and central nervous system (CNS) toxicities [drowsiness, cognitive impairment, confusion, hallucinations, myoclonic jerks and rarely, opioid-induced hyperalgesia (OIH)]. OIH presents as a significant escalation of pain and emergence of sensitivity to a light touch that can be generalised.

The management of opioid-induced adverse effects is an important aspect of pain management because each adverse effect requires a careful assessment and treatment strategy [90]. However, there are few studies in this area.

Opioid dose reduction can reduce the incidence and/or severity of adverse events. To achieve an opioid reduction, an additional strategy may be necessary, such as a co-analgesic, nerve block or radiotherapy (RT). Since some adverse effects may be caused by accumulation of toxic opioid metabolites, switching to another opioid agonist and/or another route may improve adverse effects. This is especially true for symptoms of CNS toxicity such as OIH/allodynia and myoclonic jerks [91].

Table 4. i.v. titration (dose finding) with morphine for severe cancer pain

RCT [88]	Initial dosage	Following dosage	Results
62 strong opioid-naïve patients PI NRS ≥ 5 Patients were randomised to receive: – i.v. morphine then IR oral morphine (dose equal to i.v. dose) (i.v. group, *N*=31) or – oral IR morphine (oral group, *N*=31)	**i.v. group:** 1.5 mg bolus every 10 min until pain relief (or adverse effects) **Oral group:** IR morphine 5 mg every 4 h in opioid-naive patients, 10 mg in patients already on weak opioids **Rescue dose:** The same dose every 1 h max	**i.v. group:** Oral IR morphine every 4 h, on the basis of the previous i.v. requirements (i.v. to p.o. conversion 1:1) **Oral group:** Follow the same scheme **Rescue dose:** The same dose every 1 h max	**Percentage of patients achieving satisfactory pain relief** After 1 h: i.v. group 84%, oral group 25% ($P<0.001$) After 12 h: i.v. group 97%, oral group 76% ($P<0.001$) After 24 h: i.v. group and oral group similar **Median morphine dosage to achieve pain relief** i.v. group: i.v. 4.5 mg (range 1.5–34.5). p.o. 8.3 mg (range 2.5–30) after stabilisation Oral group: 7.2 mg (range 2.5–15) **No significant adverse events**

IR, immediate release; i.v., intravenous; NRS, numerical rating scale; PI, pain intensity; p.o., orally (per os); RCT, randomised controlled trial.

There is little evidence for the use of methylphenidate or similar drugs in the management of opioid-induced sedation and cognitive disturbance [91, 92].

Metoclopramide and antidopaminergic drugs are used frequently for treatment of opioid-related nausea/vomiting. ESMO/Multinational Association of Supportive Care in Cancer (MASCC) have published guidelines on the use of these drugs [93].

There are no prospective, randomised studies on the treatment of opioid-induced pruritus. Antihistamines and 5-HT3 (serotonin) antagonists are commonly recommended. Opioid rotation may represent an additional choice [64, 89].

The most common manifestation of bowel dysfunction is OIC; reduction in bowel movement frequency, increased straining, incomplete evacuation and hard stools [94]. First-line treatments for OIC typically involve a combination stimulant and softer laxative, increased dietary fibre and fluid intake, along with exercise. However, more than half of patients remain constipated [95]. A newer class of agents which try to address the underlying pathophysiology of OIC are called peripherally acting mu opioid receptor antagonists (PAMORAs), such as naloxegol. Naloxegol has been approved for treatment of OIC in patients with cancer-related or non-cancer pain in the European Union (EU) [96]. Other studies are ongoing with similar drugs, such as naldemedine (S-297995) [97]. Methylnaltrexone administered by s.c. injection is available for the treatment of OIC resistant to traditional laxatives; however, data on outcomes are limited [95].

Naloxone, a short-acting opioid antagonist is administered by i.v. to reverse symptoms of accidental severe opioid overdose (e.g. respiratory depression, significant sedation) [90]; however, this is not appropriate for OIC management. The use of an oral prolonged-release (PR) combination formulation of oxycodone and naloxone is now established in practice [98]. Combined opioid/naloxone medications have been shown to reduce the risk of OIC through a range of open label, phase II and phase III studies [II, B] [99].

PR oxycodone/naloxone versus PR oral oxycodone alone was reported in a double-blind placebo-controlled trial [98] evaluating both analgesia and bowel function. Two-hundred and two opioid-stable patients (mainly non-cancer), taking 40–60 mg oxycodone daily, were randomised to either naloxone (10–40 mg daily) or placebo. The Bowel Function Inventory (BFI) was used to assess constipation. Patients taking a combined oral therapy reported significant improvements in bowel function compared with those only taking PR oral oxycodone, with no loss of analgesic efficiency. This outcome has been supported in a more recent review of literature of clinical trials and observational studies into the evidence for PR oxycodone/naloxone treating moderate to severe pain and specific impact on opioid-induced bowel dysfunction (OIBD) [99]. Thirty-eight clinical trials and observation studies were reported of which seven were undertaken with a cancer population [100–107]. Other studies reported on patient groups with direct relevance to patients with cancer (e.g. those with NP, pain in the elderly and patients with pain and refractory laxatives symptoms) [99]. Although the method of review is not explicit, the range of evidence presents PR oxycodone/naloxone as an effective treatment for moderate to severe pain and effective OIC bowel management for selected patients.

Although these studies demonstrate a growing body of evidence particularly in relation to therapies to manage OIC, the overall impact remains relatively small in terms of application to clinical practice, and further studies are needed to support these early data. Some of the study outcomes reported here include an advanced cancer population. Further elaboration of OIC can be found in the ESMO guidelines on constipation [41].

Recommendations:

- Laxatives must be routinely prescribed for both the prophylaxis and the management of OIC [I, A].
- The use of naloxone in association with oxycodone or methylnaltrexone to control OIC may be considered [II, B].
- Naloxegol has been shown to be highly effective in OIC [II, B], but, to date, there is no specific reported experience in the cancer population.
- Metoclopramide and antidopaminergic drugs should be recommended for treatment of opioid-related nausea/vomiting [III, B].
- Psychostimulants (e.g. methylphenidate) to treat opioid-induced sedation are only advised when other methods to treat this have been tried (e.g. rationalise all medication with a sedative side effect) [II, B].
- Mu receptor antagonists (e.g. naloxone) must be used promptly in the treatment of opioid-induced respiratory depression [I, B].

Medical cannabis

An iterative approach was used starting with an electronic search of the MEDLINE database (via PubMed). The search terms ['neoplasms' (Mesh) AND 'pain' (Mesh) AND 'Cannabis' (Mesh)] were used. Citation tracking and a search for all related eligible articles in PubMed identified 22 items with no eligible RCT in the last 5 years for medical cannabis in cancer pain.

Another PubMed search was carried out without the MESH thesaurus with following search terms [('cannabis' OR 'cannabinoids' OR 'medical cannabis' OR 'cannabis sativa' OR 'sativex') AND 'cancer pain']. Results showed 46 items with five eligible clinical trials found by direct searching and cross-references.

Two prior randomised, double-blind phase II/III studies demonstrated the analgesic effects of nabiximols [an extract of *Cannabis sativa* containing two potentially therapeutic cannabinoids (D9-tetrahydrocannabinol (27 mg/mL) and cannabidiol (25 mg/mL)] in advanced cancer patients with pain not fully alleviated by opioid therapy [108–110]. Both studies enrolled patients with baseline scores ≥ 4 on a 0–10-point average daily pain NRS, despite ongoing treatment with opioids. The primary efficacy endpoint, i.e. 30% response rate on an average daily pain NRS, was similar for nabiximols and placebo (treatment effect, $P = 0.59$). However, a secondary continuous responder analysis of average daily pain demonstrated that the proportion of patients reporting analgesia was greater for nabiximols than placebo overall ($P = 0.035$), specifically in the low-dose ($P = 0.008$) and medium-dose ($P = 0.039$) groups. In the low-dose group, results were similar for mean average pain ($P = 0.006$), mean worst pain ($P = 0.011$) and mean sleep disruption ($P = 0.003$). Confirmatory studies by Fallon et al. [111] describe two phase III, double-blind, randomised, placebo-controlled trials in advanced cancer patients with average pain NRS scores ≥ 4 and ≤ 8 at baseline, despite optimised opioid therapy. In Study 1, patients were randomised to nabiximols or placebo, and then self-titrated study

medications over a 2-week period per effect and tolerability, followed by a 3-week treatment period. In Study 2, all patients self-titrated nabiximols over a 2-week period. Patients with a $\geq$ 15% improvement from baseline in pain score were then randomised 1:1 to nabiximols or placebo, followed by a 5-week treatment period.

The primary efficacy endpoint in average daily pain NRS scores was not met in either study. Nabiximols did not demonstrate superiority to placebo in reducing self-reported pain.

Another phase III, double-blind, randomised, placebo-controlled trial in the same population with similar intervention, showed analogue results with nabiximols not superior to placebo on the primary efficacy endpoint [112].

For advanced cancer patients with pain not fully alleviated by opioid therapy, the additive effect of nabiximols to the ongoing opioid treatment remains unclear. There is a need for further double-blind, placebo-controlled clinical trials with large sample sizes in order to establish the optimal dosage and efficacy of different cannabis-based therapies [II, D].

BTcP

There is no unanimous consensus on definition and characteristics of BTcP. Two Delphi surveys published in 2016 defined BTcP as a transient pain exacerbation that can occur in patients with stable and adequately controlled background pain not necessarily treated with opioids [113]. However, the current agreement defines BTcP as an episode of severe pain that occurs in patients receiving a stable opioid regimen for persistent pain sufficient to provide at least mild sustained analgesia. There are many underlying neurobiological causes of BTcP. The reported prevalence of BTcP varies significantly according to a recent systematic review that included 19 studies; the overall pooled prevalence was 59%, with the lowest prevalence reported in studies in outpatient clinics (39%) and the highest prevalence reported in studies conducted in the hospice setting (80%) [114]. The lack of validation of BTcP tools has been a limitation; however, an assessment tool for BTcP has been validated [115]. The simple clinical algorithm for the diagnosis of BTcP, proposed by Davies et al. [116], continues to be widely used in practice (Figure 2).

Use of drugs as needed is the conventional treatment of BTcP. There is a major gap in the knowledge of the role of non-opioid analgesics and non-pharmacological approaches to manage BTcP.

Oral opioids, particularly oral morphine, have been the mainstay approach for the management of BTcP. However, the pharmacokinetic and pharmacodynamic profiles of oral opioids (onset of analgesia: 20–30 minutes; peak analgesia: 60–90 minutes; duration of effect: 3–6 hours) do not tend to mirror the temporal characteristics of most BTcP episodes, resulting in delayed or ineffective analgesia and in ongoing adverse effects. Different formulations have been developed to provide fast pain relief with fentanyl, delivered by non-invasive routes: oral, transmucosal buccal tablet, sublingual tablet, buccal soluble film, sublingual and intranasal spray. Several placebo-controlled RCTs have demonstrated the efficacy of all available transmucosal fentanyl formulations for BTcP [117, 118]. These products called rapid-onset opioids (ROOs) provide an effect clinically observable 10–15 minutes after drug administration. As these products have been tested only in opioid-tolerant patients, the current recommendation is only for patients receiving doses of oral morphine equivalents of at least 60 mg. Two meta-analyses [119, 120] and several systematic reviews [121, 122] have shown a clinical role for all transmucosal fentanyl formulations in BTcP, but there is no evidence for the superiority of any particular formulation.

Dosing recommendations have been developed for the transmucosal formulations as a group, and these share a low initial dose followed by dose titration to an effective dose. Some non-comparative trials suggest that the tolerability and the safety of an initial dose of a transmucosal formulation are proportionate to the baseline opioid dose, even in elderly patients, patients in the home care setting and in patients receiving a high dose of opioids [123–125]. A randomised, controlled, non-blinded study carried out in a sample of 82 cancer patients with BTcP receiving strong opioids supported fentanyl buccal tablets (FBTs) in doses proportional to the baseline opioid dose; however, further evidence is required to confirm that this approach should be routinely recommended.

The concept of using fentanyl sublingual tablets instead of s.c. morphine was explored in a double-blind, randomised, non-inferiority trial [126]. At the chosen standard doses of both drugs, non-inferiority was not demonstrated.

Recommendations:

- Immediate-release opioids should be used to treat BTcP that is opioid-responsive and for which background cancer pain management has been optimised [I, A].
- Transmucosal fentanyl formulations (oral, buccal, sublingual and intranasal) have a role in unpredictable and rapid-onset BTcP [I, A].
- There are indications for standard normal-release oral opioids (e.g. morphine) that include a slow-onset BTcP or a pre-emptive administration of oral opioids ~30 minutes before a predictable BTcP triggered by known events [II, B].

Bone pain

Treatment of bone pain should always take into consideration the use of analgesic drugs (Figure 3). In addition, external beam RT (EBRT), radioisotopes and targeted therapy given in association with analgesics have an important role in bone pain management (Figure 4).

EBRT

RT is highly effective in the management of metastatic bone pain and in metastatic spinal cord compression (mSCC) [127]. Numerous randomised, prospective trials show improvements in pain relief in 60%–80% of patients after RT, with complete responses (no pain and no increase in analgesic requirements) in up to 30% [128]. The American Society for Radiation Oncology (ASTRO) reviewed randomised, published trials on RT for painful bone metastases and found pain relief equivalence for different regimens, including 3 Gy in 10 fractions, 4 Gy in 6 fractions, 4 Gy in 5 fractions and 8 Gy single dose [129]. These data are consistent with sequential meta-analyses which have failed to show an advantage for doses greater than a single dose of 8 Gy for pain relief. Although the rate of retreatment after single doses

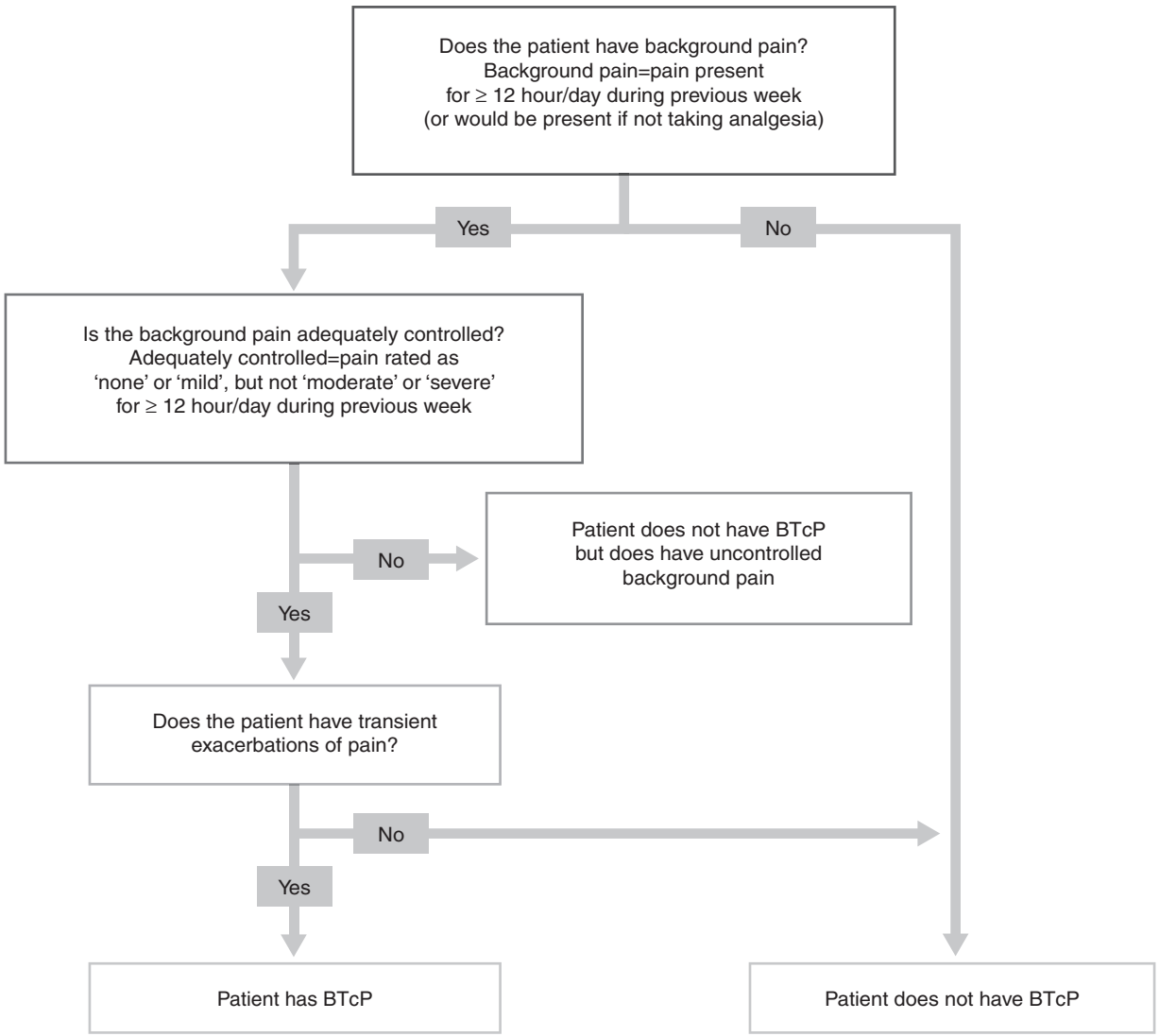

Figure 2. The assessment of BTcP.
BTcP, breakthrough cancer pain.
Reprinted with permission from [116].

is higher, 20% compared with 8%, these data are not systematic; overall, an 8 Gy single dose should be considered the regimen of choice for patients with painful bone metastases, optimising patient and carer experience. The single dose is also more cost-effective, even when re-irradiation is included [130]. Retreatment of recurrent bone pain has been studied in a large randomised trial comparing 8 Gy single dose with 20–26 Gy in 5 fractions [131]. This trial confirmed the efficacy of retreatment with a single dose and showed no disadvantage; therefore, 8 Gy single dose should also be considered the schedule of choice in re-irradiation.

Stereotactic body RT (SBRT) has emerged as a new treatment option that permits the administration of very high ablative doses—typically in single doses of 10–16 Gy, or hypofractionated schedules: 27 Gy in 3 fractions or 40 Gy in 5 fractions. This technique enables delivery of high doses per fraction, while safely avoiding high doses to critical normal tissues such as the vertebrae or the spinal cord [132].

Recommendations:

- All patients with painful bone metastases should be offered EBRT and the prescription should be 8 Gy single dose [I, A].
- Patients with recurrent bone pain after previous irradiation should be offered re-irradiation with a further dose of 8 Gy [I, A].
- SBRT should be considered for patients with oligometastases having good performance status and well-controlled primary sites, preferably within clinical trials [V, D].

mSCC

Spinal cord compression is an oncological emergency [133]. Pain accompanies mSCC in 95% of patients, and usually precedes the diagnosis by days to months. Pain can be local (back or neck pain), radicular or both. Patients with established neurological deficits have a poor prognosis for recovery; thus, early diagnosis confirmed on magnetic resonance imaging (MRI) and prompt therapy is critical [134].

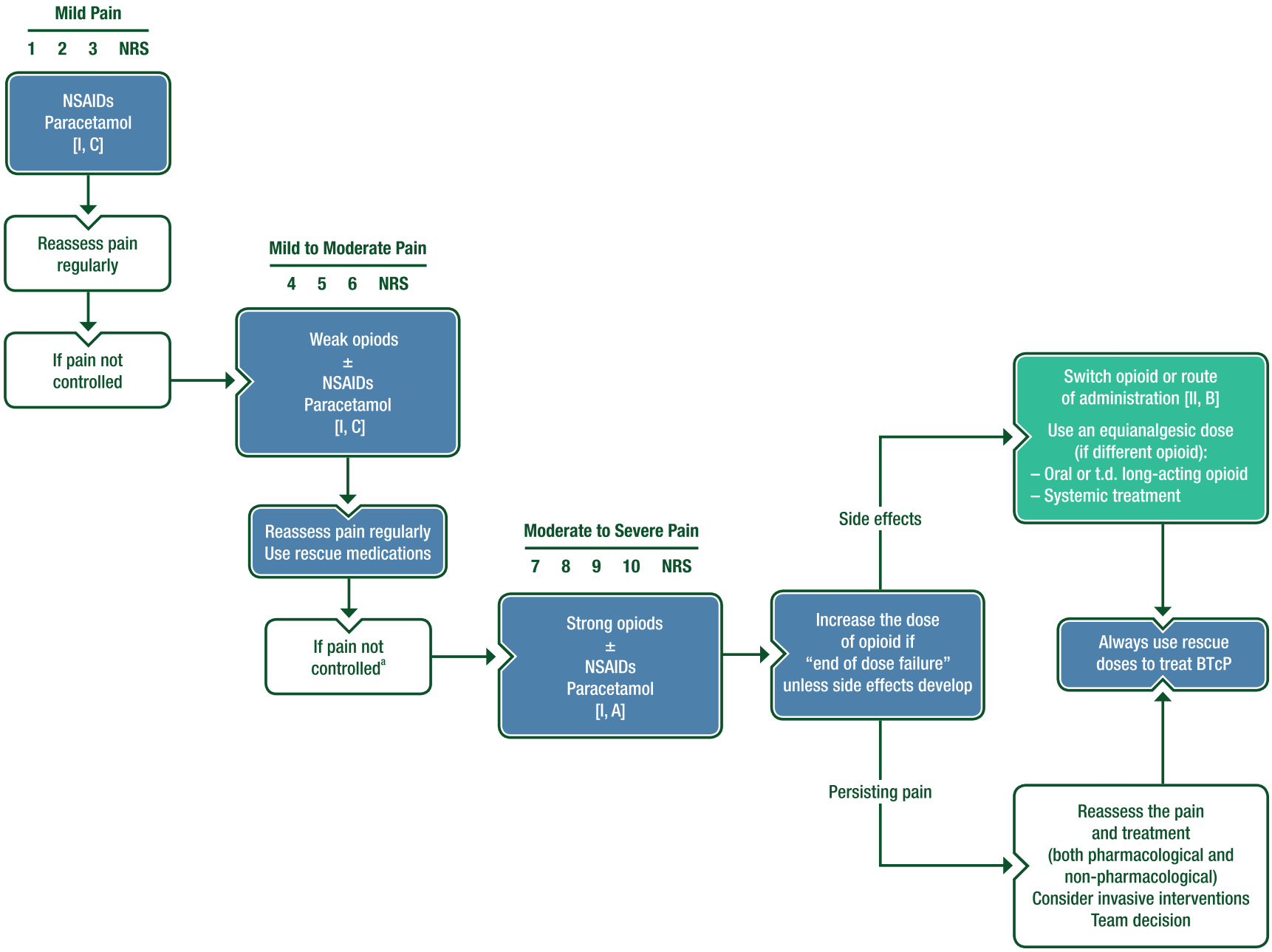

Figure 3. Treatment of cancer pain.
[a]Do not switch between weak opioids.
BTcP, breakthrough cancer pain; NRS, numerical rating scale; NSAID, nonsteroidal anti-inflammatory drug; t.d., transdermal.

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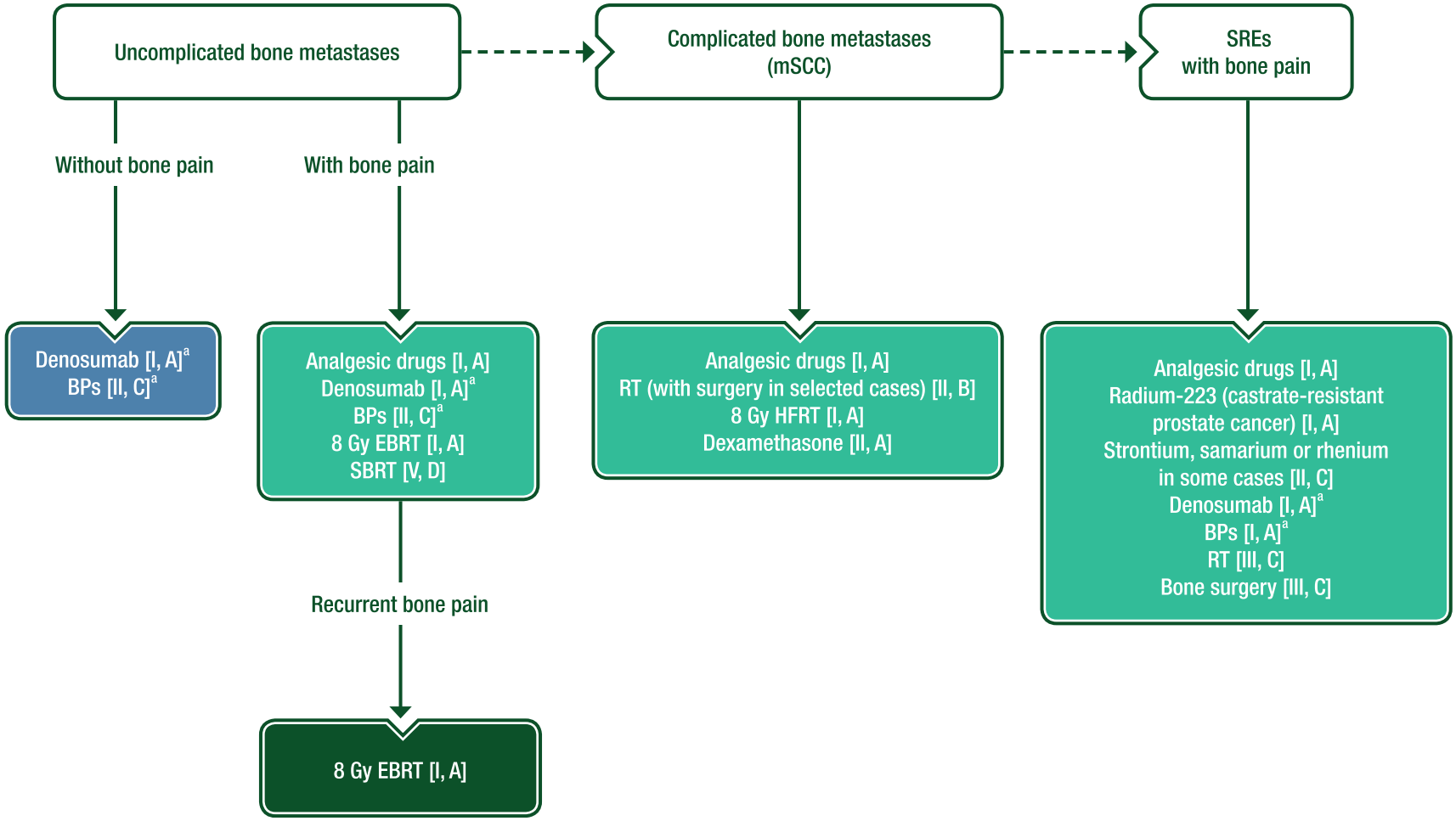

Figure 4. Treatment of pain due to bone metastases.
[a]Preventive dental measures are necessary before starting administration [III, A].
BP, biphosphonate; EBRT, external beam radiotherapy; HFRT, hypofractionated radiotherapy; mSCC, metastatic spinal cord compression; RT, radiotherapy; SBRT, stereotactic body radiotherapy; SRE, skeletal-related event.

Steroids should be given immediately when the clinical and radiological diagnosis of mSCC is confirmed. Dexamethasone is the most frequently used drug. No study to date has compared high-dose with moderate-dose dexamethasone; dexamethasone (16 mg/day) remains the most often used prescription, although doses ranging from moderate (8 mg/day) to ultra-high levels (36–96 mg/day preceded by a bolus of 10–100 mg i.v.) have been advocated. The steroids are usually tapered over 2 weeks [134].

Surgery is indicated in patients with spinal instability, an unknown primary requiring histology, recurrence after previous RT and solitary sites of compression, particularly in the setting of oligometastases in patients with good performance status and a well-controlled primary site. Postoperative RT should follow [127, 133].

RT is the first-line treatment for the majority of patients with mSCC; it provides back pain relief in 50%–58% of cases. There is now good evidence, including three phase III trials, that hypofractionated RT (HFRT) schedules, e.g. 20 Gy in 5 fractions or 8 Gy in 2 fractions, are as effective as more prolonged schedules [133, 135]. For patients who have a longer predicted life expectancy (> 6 months), higher dose schedules may be considered [136]. The median survival in these clinical trials is 4–6 months. A recent large randomised phase III trial has shown that 8 Gy in a single dose is as effective as 20 Gy in 5 fractions in this setting for pain control, quality of life (QoL) and neurological outcome [137].

Recommendations:

- Early diagnosis and prompt therapy are powerful predictors of outcome in mSCC [I, A].
- The majority of patients with mSCC should receive RT alone but surgery should be considered for selected cases [II, B].
- HFRT regimens, including a single dose of 8 Gy, can be considered the schedule of choice [I, A] while more protracted RT regimens may be used in selected mSCC patients with a predicted longer life expectancy [I, B].
- Dexamethasone should be prescribed in patients with mSCC [II, A] in a dose of 8–16 mg daily [III, B].

Targeted therapy and bone pain

Radioisotopes. In selected patients with multiple osteoblastic bone metastases, radioisotope therapy can be highly effective in achieving pain relief in multiple sites. Radioisotope treatment using strontium, samarium or rhenium has been investigated in a systematic review [138]. The results showed only a small beneficial effect on pain control in the short and medium term (1–6 months), with no modification of the analgesics used but relatively frequent adverse effects including leukopaenia and thrombocytopaenia.

A randomised trial has evaluated the effect of radium-223 (an alpha emitter releasing short-range radiation, with little bone marrow toxicity) in patients with castrate-resistant prostate cancer. This trial has shown improvements in skeletal-related events (SREs), including pain and QoL, as well as survival, and radium-223 is now the radioisotope treatment of choice for prostate cancer [139].

Recommendations:

- In castrate-resistant prostate cancer patients, radium-223 is effective in reducing SREs, decreasing pain and improving survival [I, A].
- Radioisotope therapy with strontium, samarium or rhenium can be effective in some cases but may cause bone marrow toxicity [II, C].

Bisphosphonates. Bisphosphonates (BPs) form part of the standard therapy for hypercalcaemia and the prevention of SREs in metastatic cancer. The evidence supporting the analgesic efficacy of BPs is weak in patients with bone pain due to bone metastases from solid tumours, predominantly breast and prostate, and also for multiple myeloma, particularly in the short term [140]. BPs should always be used in conjunction with analgesics. One randomised trial has shown that a 4 mg i.v. infusion of ibandronate gives equivalent overall pain relief to single-dose RT in prostate cancer [141]. Preventive dental measures to prevent osteonecrosis of the jaw (ONJ) are required before starting BP treatment [142]. After the first i.v. infusions of BP, a pain flare may be observed, requiring additional use of analgesics.

Recommendations:

- BPs may be considered as part of the therapeutic regimen for the treatment of patients with bone metastases in patients with a good prognosis [II, C].
- BPs should be considered especially when pain is not localised or RT is not readily accessible [II, C].
- Preventive dental measures are necessary before starting BP administration [III, A].

Denosumab. Denosumab, a targeted receptor activator of nuclear factor kappa B ligand (RANKL) inhibitor, is an effective treatment for bone metastases, delaying SREs. Two trials in prostate and breast cancer showed that denosumab was more effective than zoledronate, but this has not been confirmed in other solid tumour types [143, 144].

In a combined analysis in solid tumours, denosumab was more effective than zoledronate, delaying the return of moderate or severe pain by an additional 3 months [145]. A systematic review has confirmed that the main effect of denosumab and bisphosphonates is in delaying the onset of pain rather than acting as an analgesic for established pain [140].

The prescription of denosumab should be started after preventive dental measures are taken [146].

Recommendations:

- Denosumab is indicated as an alternative to BPs for the treatment of patients with metastatic bone disease from solid tumours and myeloma [I, A].
- Denosumab is effective in delaying bone pain recurrence [II, C].
- Preventive dental measures are necessary before starting denosumab administration [III, A].

Cancer-related NP (Figure 5)

Neuropathic cancer pain arises as a direct consequence of a cancer-induced injury to the somatosensory system. This type of neuropathic cancer pain must be distinguished from other NPs, e.g. due to cancer treatment [147]. Nerve fibrosis after RT, chemotherapy (ChT)-induced or postsurgical NPs are prominent

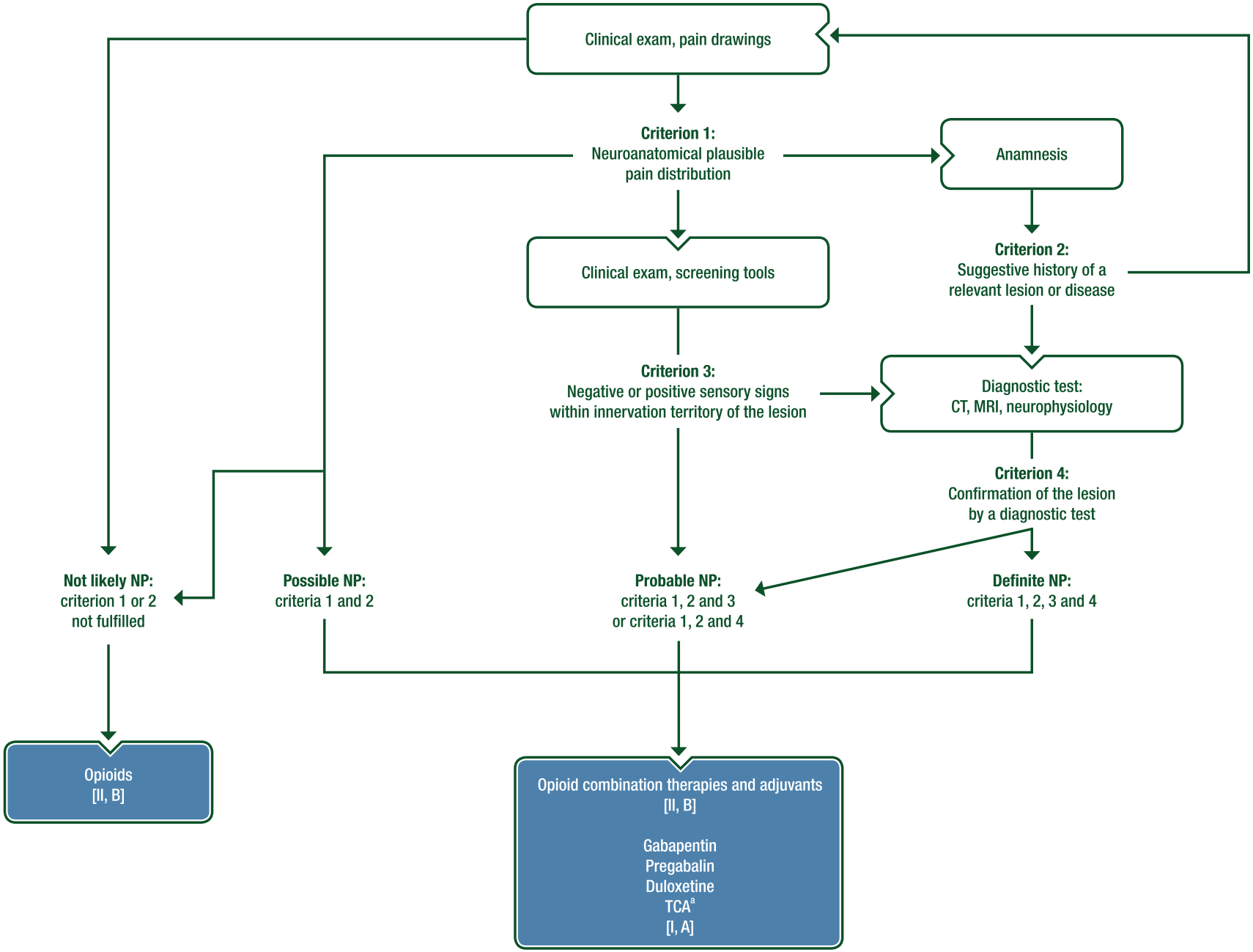

Figure 5. Assessment and treatment of cancer-related NP.
[a]Doses ≤ 75 mg/day.
CT, computed tomography; MRI, magnetic resonance imaging; NP, neuropathic pain; TCA, tricyclic antidepressant.

examples. In a systematic review, the overall prevalence of a neuropathic mechanism varied from 19% to 39.1% among 13 683 patients with cancer pain. Notably, the proportion of pain caused by cancer treatment was higher in NP compared with all types of cancer pain [148].

A probable or definite NP can be identified using the revised definition and grading system proposed by the Neuropathic Pain Special Interest Group (NeuPSIG) of the International Association for the Study of Pain (IASP) [149].

This NP grading system is based on four criteria:

Criterion 1: neuroanatomical plausible pain distribution;

Criterion 2: suggestive history of a relevant lesion or disease;

Criterion 3: negative or positive sensory signs within innervation territory of the lesion; and

Criterion 4: confirmation of the lesion by a diagnostic test.

A probable NP can be diagnosed if criteria 1, 2 and 3 or criteria 1, 2 and 4 are present. A definite NP is based on the presence of all four criteria.

When extrapolating treatment findings from studies in patients with NP to patients with cancer-related NP, there is evidence from systematic reviews that both tricyclic antidepressants (TCAs) and anticonvulsant drugs are effective in the management of NP. The number needed to treat (NNT) for these drugs is 3–7.7 [150, 151].

In cancer patients with NP, non-opioid and opioid analgesics may be combined with TCAs or anticonvulsants. The efficacy and tolerability of the therapy should be monitored over time. A narrative analysis from eight studies including five RCTs concluded, on the basis of 370 complete patient datasets, that adjuvants improved pain control within 4–8 days when added to opioids for cancer-related NP, with the strongest evidence supporting gabapentin [152, 153]. However, a pain reduction greater than 1 point, on a 0–10 NRS, was unlikely for that type of combination therapy while, in contrast, an increase in adverse events was likely [154]. Other adjuvants such as steroids should be considered in the case of nerve compression. There is a strong recommendation against the use of levetiracetam and mexiletine in NP [155].

Recommendations:

- Cancer-related NP can be treated using opioid combination therapies and carefully dosed adjuvants, when opioids alone provide insufficient pain relief [II, B].
- Patients with NP should be given either a TCA or an anticonvulsant and be monitored for side effects [I, A].
- Gabapentin, pregabalin, duloxetine and TCA (doses $\leq$ 75 mg/day) are strongly recommended as single agents for NP first-line treatment [I, A].
- Interventional treatments of NP are based on weak or inconclusive evidence and should be restricted to patients with NP syndromes other than those related to cancer [II, C].

Ketamine is a N-methyl-D-aspartate (NMDA) antagonist which has been used as an adjunct in challenging cancer pain, in particularly in NP. The preclinical evidence points to an indication of 'central wind-up' which can be tested at the bedside. RCTs carried out to date on the benefit of ketamine as an adjuvant to opioids in NP have been negative. The evidence has been of very low quality, meaning that it does not provide a reliable indication of the likely effect, and the likelihood that the effect will be substantially different is high [156]. However, there may be subgroups of patients with cancer-related NP for whom ketamine could be helpful, such as those with central sensitisation and 'clinical wind-up', for whom it is reasonable to hypothesise a more specific analgesic target for ketamine [157].

Recommendation:

- There is a lack of evidence to support the routine use of ketamine in cancer NP [II, D].

Preclinical work suggests that patients with central sensitisation, presenting as 'central wind-up', are the potential target population and clinical research should be concentrated on this group. This remains an area of research and at present no clinical recommendation can be given for routine use in cancer pain [II, D].

Invasive management of refractory pain

Surgical or oncological treatment of cancer can be effective in controlling cancer-related pain but can also be the cause of pain. About 10% of cancer patients have pain that is difficult to manage with oral or parenteral analgesic drugs. Interventional techniques include nerve blocks, neurolytic blocks (including spinal neurolytic blocks and cordotomy) and intrathecal (i.t.) drug delivery (spinal or epidural) [158]. Patients refractory to all conventional strategies and/or with dose-limiting, analgesic-related side effects may achieve pain control with interventional techniques when used alone or, more frequently, in combination with systemic therapy. Two prospective comparative trials between oral and spinal morphine have compared the analgesics and tolerability of morphine administered orally or by epidural [159, 160].

An improvement in pain control as well as in adverse effects was shown by switching from oral to epidural infusion of morphine [159]. However, Kalso et al. showed no significant benefits, either in efficacy or in adverse effects, by administering morphine via the epidural route compared with the s.c. route. The authors concluded that the co-administration of local anaesthetic agents, alpha-2-adrenergic agonists or NMDA antagonists may significantly improve the quality of epidural analgesia compared with the s.c. route [159].

Intrathecal drug delivery

Spinal opioids work by binding to the mu receptor in the substantia gelatinosa and can be administered epidurally or by the i.t. route via percutaneous catheters, tunnelled catheters or implantable programmable pumps (Figure 6). The i.t. route of analgesics delivery leads to decreased opioid consumption: if the opioid is delivered via the oral and epidural route, the doses are 300 [160] and 24 [161] times higher, respectively, than the same i.t. dose. Generally, this direct delivery to the i.t. space and the lower doses required lead to fewer systemic side effects and better analgesia. The i.t. route of opioid administration should be considered in patients experiencing pain in various locations: head and neck, upper and lower extremities and trunk, although it is more likely to be useful for pain below the diaphragm. The fully implanted systems offer less risk of infection and need lower maintenance than the

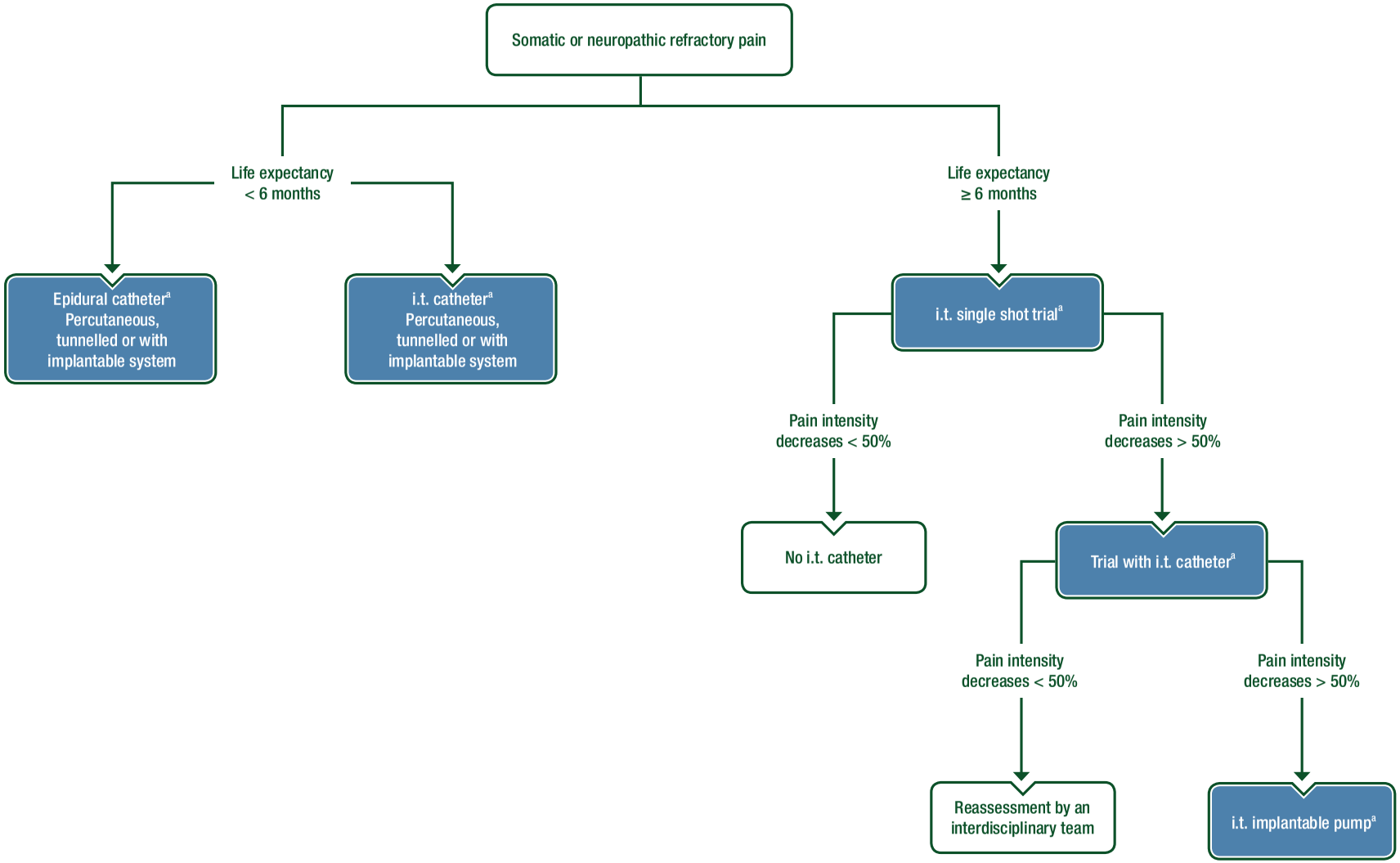

Figure 6. Management of refractory pain by i.t. drug delivery.
[a]Choice of drugs according to the type of pain.
i.t., intrathecal.

percutaneous route, but the positioning is more complex [158]. These interventional strategies are not appropriate in patients with infections, coagulopathy or very short life expectancy. Many authors [158, 162] support the use of a trial of intraspinal analgesia using a temporary epidural or spinal catheter or even single shot bolus to determine efficacy before pump implantation. When compared with epidural, i.t. drug delivery presents fewer catheter problems, smaller drug dose requirement and fewer adverse effects. In addition, it gives better pain control and decreased risk of infection. i.t. administration has the advantage of being less affected by the presence of extensive epidural metastasis and morphine, ziconotide and baclofen are the drugs most used, sometimes with local anaesthetics (bupivacaine 0.125%–0.25%) [163]. Limited evidence supports the use of subanaesthetic doses of ketamine, an NMDA antagonist, in intractable pain.

i.t. drug delivery or epidural administration of opioids may be useful in patients with:

(i) inadequate pain relief despite systemic opioid escalating doses and appropriate adjuvant analgesia;
(ii) non-effective response to switching the opioid or the route of administration, as well as when side effects increase because of dose escalation; and
(iii) life expectancy >6 months justifies the use of an implantable i.t. pump but only after a trial using a temporary epidural or spinal catheter or bolus dose of local anaesthetic and opioid [164].

Recommendation:

- Intraspinal techniques delivered and monitored by a skilled team should be included as part of the cancer pain management strategy [II, B].

Peripheral nerve block

Peripheral nerve blocks or plexus blocks can be used when pain occurs in the field of one or more peripheral nerves, or if pain is caused by complications such as pathological fracture or vascular occlusion [164]. However, a peripheral nerve block as the principal pain treatment is very rare, and they are always used together with systemic combined analgesia and in combination with the multimodal approach applied to all cancer pain. The use of neurolytic agents on peripheral nerves can lead to neuritis; therefore, for patients with good prognosis, this can result in symptoms more difficult to control than the original pain [165].

Neurolytic blockade

Neurolytic blocks should be limited to those patients with short life expectancy because they usually produce a block lasting 3–6 months. These blocks can be used for the sympathetic system as well as for spinal neurolytic purposes for somatic pain. For the sympathetic system, neurolytic blocks should be considered as adjuvants to decrease the use of oral and/or parenteral analgesics because the visceral pain mechanisms are complex and change with progression of the disease. This technique is used for the superior hypogastric plexus block or ganglion impar block, when pelvic pain or perineal pain of visceral origin is present, respectively. Spinal neurolytic blocks are very helpful and an inexpensive 'one off' means of helping pain which is localised to a few dermatomes and can be easily repeated if the effect is short-lasting [163].

Neurolysis of coeliac plexus

Coeliac plexus block (CPB) is useful when pain is of visceral aetiology only, and due to cancer in the upper abdomen or pancreas; it leads to pain control and, frequently, to a decrease in the total amount of systemic drugs and their side effects [166]. The technique used to carry out CPB (anterior or posterior approach; amount and concentration of neurolytic agent and time) may affect the results and the duration of the analgesic effect. One new way to carry out this kind of CPB is represented by echo-endoscope guidance, placed in the stomach just below the cardia [167]. CPB should be carried out in the presence of visceral pain and only if the clinical condition of the patient is not poor. Previous studies have suggested that when there is evidence of disease outside the pancreas, such as coeliac or portal adenopathy, or both, the success rate of this block decreases significantly [168].

Recommendation:

- CPB appears to be safe and effective for the reduction of pain in patients with pancreatic cancer, with a significant advantage over standard analgesic therapy until 6 months [II, B].

Spinal neurolytic blocks

Spinal neurolytic blocks are very helpful for focal pain in a small number of dermatomes. For example, it is useful in patients with perineal pain with pelvic cancer (e.g. recurrence of rectal cancer with local infiltration) or chest wall pain related to localised rib metastasis or referred abdominal pain from mesothelioma in a limited number of dermatomes, especially if the pain is one-sided. Spinal neurolytic blocks should also be considered for de-afferentation pain, such as that seen in peripheral nerve plexus tumour infiltration and destruction. Spinal neurolytic technique is a highly skilled pain intervention which has been described in various cancer pain management textbooks [169]. Neurolytic blocks are usually effective for 2–4 months and can be repeated in the event of recurrence of pain. Informed consent, explaining the side effects of this neuroablative technique including numbness or dysaesthesia, is a key when considering spinal neurolytic or any other neuroablative block. Epidural neurolytic blocks have been described in the literature; however, the benefit is limited and difficult to predict [170]. It may be applicable only to those patients in the terminal stages of cancer-related pain.

Spinal cord stimulation for cancer-related pain

Spinal cord stimulation is a well-established neuromodulation technique for chronic NP, for example, for failed back surgery syndrome and complex regional pain syndrome. This treatment is recommended by the United Kingdom (UK)'s National Institute for Health and Clinical Excellence (NICE) [171]. There has been significant improvement in the technology (hardware and the programming algorithm including electrical wave forms and frequency) and it is now applicable to alleviate severe NP of either malignant or non-malignant causes. For cancer-related pain, especially if the cancer is slow growing, there is potential benefit from spinal cord stimulation if pain is difficult to control with pharmacological options. It is now possible to carry out MRI scans if required, because of MRI-compatible spinal cord stimulation equipment. The concern with spinal cord stimulation in

cancer-related pain is related to the possible extension of the pain to other areas not covered by the stimulator and the possibility of neurological deficit. There are many published case series suggesting significant benefit, but a recent Cochrane systematic review suggested need for further high-quality studies in this field [172].

Spinal cord stimulation should be included as part of the overall pain management strategy, to be managed by a multidisciplinary team (MDT) with skill in this type of intervention. It is expected that it will be applicable in only a very small number of cases.

Cordotomy for cancer-related pain

Cordotomy for cancer-related pain has been described in the literature from the early 1900s, initially as an open surgical technique, but from the 1960s as a percutaneous technique. The technique has been further refined with the evolution of technology involving X-ray imaging facilities and radiofrequency machines, allowing a reliable heat lesion in the spinothalamic tract. High cervical cordotomy is effective for unilateral cancer-related pain below the C4 (fourth cervical) dermatomes, i.e. pain below the shoulder. The mesothelioma framework published in 2007 by the UK's Department of Health [173] recommended availability of cervical cordotomy for mesothelioma-related chest wall pain, if otherwise uncontrolled with conventional medical management. Another good indication is incident pain (movement-related pain), for example related to pathological fractures in the long bone, pubic rami or pelvis related to local metastatic disease. Surgical treatment is often preferred for these fractures, but some patients have had surgical treatment including RT and still have ongoing intractable pain. This type of pain does not respond well to opioids, as patients have very little or no pain at rest. A systematic review published in 2014 confirmed a high success rate (80%) for patients in the early postoperative period [174]. However, no RCTs were included in this systematic review. This review advised setting up a national cordotomy registry that was set up in 2014 and now has more than 200 cases prospectively recorded post-cordotomy in the UK. The registry demonstrated the safety and efficacy of this technique, and the data should be published soon. There is also a prospective case series of 45 patients undergoing cordotomy at the authors' institutes; 80% of patients reported > 75% pain relief at 4-week follow-up [175]. Cordotomy should be offered in a MDT setting with palliative medicine, oncology and pain medicine teams to support the care pathway. In the case of patients who are unable to tolerate percutaneous cervical cordotomy because of the intractable nature of pain and the incapacity to lie supine in theatre, surgical cordotomy remains an option. This is carried out by neurosurgeons and is likely to be helpful [176]. Cordotomy has very rarely been reported to help intractable pain unrelated to cancer in a terminally ill patient [177].

Recommendation:

- Cordotomy should be available to patients with otherwise poorly controlled cancer-related pain [V, C].

End-of-life pain

Data suggest that 53%–70% of patients with cancer-related pain require an alternative route for opioid administration in the months and hours before death [71]. On some occasions, as patients are nearing death, pain is perceived to be refractory. Pain is often accompanied by other symptoms such as dyspnoea, agitation, delirium and anxiety, any of which can exacerbate underlying central pain mechanisms.

A careful assessment of physical and non-physical suffering underpins decisions about the most appropriate therapeutic intervention(s).

In deciding that pain is refractory, the clinician must, after careful assessment of physical pain and total suffering, perceive that the further application of standard interventions (including appropriate simple interventional techniques) as described above is either:

(i) incapable of providing adequate relief;
(ii) associated with excessive and intolerable acute or chronic morbidity; or
(iii) unlikely to provide relief.

In this situation, sedation may be the only therapeutic option capable of providing adequate relief. The justification of sedation, which should be a rare intervention for pain, is that it is an appropriate and proportionate goal.

However, before administering sedative drugs, all possible causes of suffering must be carefully assessed and evaluated by means of a multidisciplinary specialist approach which includes also psychiatric, psychological and pastoral care personnel.

Commonly used agents include opioids, neuroleptics, benzodiazepines, barbiturates and propofol. Irrespective of the agent or agents selected, administration initially requires dose titration to achieve adequate relief, followed subsequently by provision of ongoing therapy to ensure maintenance of effect. Patients should be monitored continuously for pain during the sedation process. If the team frequently uses sedation for pain relief, procedures should be reviewed to ensure that all other options are being considered first. If sedation is used frequently by a team, then the team should review practices.

Pain that becomes generalised and/or escalates rapidly in the existing location should be investigated immediately. Some patients with end-of-life pain have been misdiagnosed with having refractory or total pain, when in fact the pain has been induced by opioids, known as OIH [178].

OIH can be associated with a general sensitivity to a simple light touch as well as a marked increase in pre-existing pain. Patient history may reveal a recent, rapid titration of opioid and/or a deterioration in organ function, particularly renal function, with a rapid accumulation of opioid toxic metabolites. Management of OIH is based on an opioid reduction and/or opioid switch and appropriate hydration [178].

Methodology

These Clinical Practice Guidelines reviewed the published data and showed the lack of high-quality RCTs in the setting of cancer-related pain. This highlights the necessity for improved study design and a consensus approach to reporting of outcomes. Such improvements should lead to more robust evidence to determine appropriate level of evidence (LoE) and grade of recommendation (GoR).

Table 5. Summary of recommendations

Assessment

- The intensity of pain and the treatment outcomes should be assessed regularly and consistently using the VAS or NRS and the worst pain question [V, D]
- Observation of pain-related behaviours and discomfort is indicated in patients with cognitive impairment to assess the presence of pain [V, C]
- The assessment of all components of suffering such as psychosocial distress should be considered and evaluated [II, B]

Principles of pain management

- Patients should be informed about pain and pain management and should be encouraged to take an active role in their pain management [II, B]
- The onset of pain should be prevented by means of ATC administration, taking into account the half-life, bioavailability and duration of action of different drugs [II, B]
- Analgesics for chronic pain should be prescribed on a regular basis and not on an 'as required' schedule [V, D]
- The oral route of administration of analgesic drugs should be advocated as the first choice [IV, C]

Treatment of mild pain

- Analgesic treatment should start with drugs indicated by the WHO analgesic ladder appropriate for the severity of pain [II, B]
- There is no significant evidence to support or refute the use of paracetamol alone or in combination with opioids for mild to moderate pain [I, C]
- There is no significant evidence to support or refute the use of NSAIDs alone or in combination with opioids for mild to moderate pain [I, C]

Treatment of mild to moderate pain

- For mild to moderate pain, weak opioids such as tramadol, dihydrocodeine and codeine can be given in combination with non-opioid analgesics [III, C]
- As an alternative to weak opioids, low doses of strong opioids could be an option but is not included in WHO guidance [II, C]
- There is no evidence of increase in adverse effects from the use of low-dose strong opioids instead of the standard step 2 approach with weak opioids [II, C]

Treatment of moderate to severe pain

Strong opioids

- The opioid of first choice for moderate to severe cancer pain is oral morphine [I, A]
- The average relative potency ratio of oral to i.v. morphine is between 1:2 and 1:3 [II, A]
- The average relative potency ratio of oral to s.c. morphine is between 1:2 and 1:3 [IV, C]
- Fentanyl and buprenorphine (via the t.d. or i.v. route) are the safest opioids in patients with chronic kidney disease stages 4 or 5 (estimated GFR < 30 mL/min) [III, B]
- A different opioid should be considered in the absence of adequate analgesia (despite opioid dose escalation) or in the presence of unacceptable opioid side effects [III, C]
- The s.c. route is simple and effective for the administration of morphine, diamorphine and hydromorphone and it should be the first-choice alternative route for patients unable to receive opioids by oral or t.d. route [III, B]
- i.v. infusion should be considered when s.c. administration is contraindicated (peripheral oedema, coagulation disorders, poor peripheral circulation and need for high volumes and doses) [III, B]
- i.v. administration is an option for opioid titration when rapid pain control is needed [III, B]

Scheduling and titration

- Individual titration, e.g. normal-release morphine administered every 4 h plus rescue doses (up to hourly) for BTcP, is recommended in clinical practice [IV, C]
- Immediate and slow-release oral morphine formulations can be used to titrate the dose. Titration schemes for both types of formulation should be supplemented with immediate-release oral opioids, prescribed as required for BTcP [III, B]
- The regular dose of slow-release opioids can be adjusted to take into account the total amount of rescue morphine [IV, C]

Management of opioid side effects

- Laxatives must be routinely prescribed for both the prophylaxis and the management of OIC [I, A]
- The use of naloxone (in association with oxycodone) or methylnaltrexone to control OIC may be considered [II, B]
- Naloxegol has been shown to be highly effective in OIC [II, B], but, to date, there is no specific reported experience in the cancer population
- Metoclopramide and antidopaminergic drugs should be recommended for treatment of opioid-related nausea/vomiting [III, B]
- Psychostimulants (e.g. methylphenidate) to treat opioid-induced sedation are only advised when other methods to treat this have been tried (e.g. if it is not possible to rationalise all medication with a sedative side effect) [II, B]
- Mu receptor antagonists (e.g. naloxone) must be used promptly in the treatment of opioid-induced respiratory depression [I, B]

Continued

Table 5. *Continued*

BTcP

- Immediate-release opioids should be used to treat BTcP that is opioid-responsive and for which background cancer pain management has been optimised [I, A]
- Transmucosal fentanyl formulations (oral, buccal, sublingual and intranasal) have a role in unpredictable and rapid-onset BTcP [I, A]
- There are indications for standard normal-release oral opioids (e.g. morphine) that include a slow-onset BTcP or a pre-emptive administration of oral opioids ~30 minutes before a predictable BTcP triggered by known events [II, B]

Bone pain

EBRT

- All patients with painful bone metastases should be offered EBRT and the prescription should be 8 Gy single dose [I, A]
- Patients with recurrent bone pain after previous irradiation should be offered re-irradiation with a further dose of 8 Gy [I, A]
- SBRT should be considered for patients with oligometastases having good performance status and well-controlled primary sites, preferably within clinical trials [V, D]

mSCC

- Early diagnosis and prompt therapy are powerful predictors of outcome in mSCC [I, A]
- The majority of patients with mSCC should receive RT alone but surgery should be considered for selected cases [II, B]
- HFRT regimens, including a single dose of 8 Gy, can be considered the schedule of choice [I, A] while more protracted RT regimens may be used in selected mSCC patients with a predicted longer life expectancy [I, B]
- Dexamethasone should be prescribed in patients with mSCC [II, A] in a dose of 8–16 mg daily [III, B]

Targeted therapy and bone pain

- In castrate-resistant prostate cancer patients, radium-223 is effective in reducing SREs, decreasing pain and improving survival [I, A]
- Radioisotope therapy with strontium, samarium or rhenium can be effective in some cases but may cause bone marrow toxicity [II, C]
- BPs may be considered as part of the therapeutic regimen for the treatment of patients with bone metastases in patients with a good prognosis [II, C]
- BPs should be considered especially when pain is not localised or RT is not readily accessible [II, C]
- Preventive dental measures are necessary before starting BP administration [III, A]
- Denosumab is indicated as an alternative to BPs for the treatment of patients with metastatic bone disease from solid tumours and myeloma [I, A]
- Denosumab is effective in delaying bone pain recurrence [II, C]
- Preventive dental measures are necessary before starting denosumab administration [III, A]

Cancer-related NP

- Cancer-related NP can be treated using opioid combination therapies and carefully dosed adjuvants, when opioids alone provide insufficient pain relief [II, B]
- Patients with NP should be given either a TCA or an anticonvulsant and be monitored for side effects [I, A]
- Gabapentin, pregabalin, duloxetine and TCA (doses $\leq$ 75 mg/day) are strongly recommended as single agents for NP first-line treatment [I, A]
- Interventional treatments of NP are based on weak or inconclusive evidence and should be restricted to patients with NP syndromes other than those related to cancer [II, C]
- There is a lack of evidence to support the routine use of ketamine in cancer NP [II, D]

Invasive management of refractory pain

- Intraspinal techniques delivered and monitored by a skilled team should be included as part of the cancer pain management strategy [II, B]
- CPB appears to be safe and effective for the reduction of pain in patients with pancreatic cancer, with a significant advantage over standard analgesic therapy until 6 months [II, B]
- Cordotomy should be available to patients with otherwise poorly controlled cancer-related pain [V, C]

ATC, around-the-clock; BP, bisphosphonate; BTcP, breakthrough cancer pain; CPB, coeliac plexus block; EBRT, external beam radiotherapy; GFR, glomerular filtration rate; HFRT, hypofractionated radiotherapy; i.v., intravenous; mSCC, metastatic spinal cord compression; NP, neuropathic pain; NRS, numerical rating scale; NSAID, nonsteroidal anti-inflammatory drug; OIC, opioid-induced constipation; RT, radiotherapy; SBRT, stereotactic body radiotherapy; s.c., subcutaneous; SRE, skeletal-related event; TCA, tricyclic antidepressant; t.d., transdermal; VAS, visual analogue scale; WHO, World Health Organization.

These Clinical Practice Guidelines were developed in accordance with the ESMO standard operating procedures for Clinical Practice Guidelines development http://www.esmo.org/Guidelines/ESMO-Guidelines-Methodology. The relevant literature has been selected by the expert authors. A summary of recommendations is provided in Table 5. LoE and GoR have been applied using the system shown in Table 6. Statements without grading were considered justified standard clinical practice by the experts and the ESMO Faculty. This manuscript has been subjected to an anonymous peer review process.

Table 6. Levels of evidence and grades of recommendation (adapted from the Infectious Diseases Society of America-United States Public Health Service Grading System[a])

	Levels of evidence
I	Evidence from at least one large randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomised trials without heterogeneity
II	Small randomised trials or large randomised trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case–control studies
V	Studies without control group, case reports, expert opinions
	Grades of recommendation
A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, . . .), optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

[a]By permission of the Infectious Diseases Society of America [179].

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