Disclosure

No Conflicts of Interest to declare
Incidence of pain in cancer patients

- 33% in patients after curative treatment
- 59% in patients on anticancer treatment
- 64% in patients with metastatic, advanced, or terminal disease

No difference in pain prevalence was found between patients on anticancer treatment and those in an advanced or terminal phase of the disease.
Pain during natural history of cancer

**Clinical settings**
- Neoadjuvant
- Adjuvant
- Locally advanced
- Metastatic
- Advanced
- End-of-life
- Survivors

**Causes**
- Acute Procedural Pain
- Iatrogenic Pain
- Co-morbidity-related pain
- Metastatic pain
- End-of-life pain
- Pain in cancer survivors
ESMO Recommendations

-Assessment of patients with pain-

• The intensity of pain and the treatment outcomes should be regularly assessed using 1. visual analogue scales (VAS), or 2. verbal rating scale (VRS) or 3. the numerical rating scale (NRS) \((V, D)\)

• Observation of pain-related behaviours and discomfort is indicated in patients with cognitive impairment to assess the presence of pain \((\text{expert and panel consensus})\)

• The assessment of all components of suffering such as psychosocial distress should be considered and evaluated \((II, B)\)
Validated assessment tools for the assessment of pain

**Visual analogue scale**

- No pain
- 10 cm
- Worst pain

**Verbal scale pain**

- No pain: 1
- Very mild: 2
- Mild: 3
- Moderate: 4
- Severe: 5
- Very severe: 6

**Numerical scale**

- No pain: 0
- 1
- 2
- 3
- 4
- 5
- 6
- 7
- 8
- 9
- 10
- Worst pain
# 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 and radiation, duration, intensity, relief and temporal patterns of the pain, number of breakthrough pains, pain syndrome, inferred pathophysiology, pain at rest and/or moving
- presence of the trigger factors and the signs and symptoms associated with the pain
- presence of the relieving factors
- use of analgesics and their efficacy and tolerability
- require the 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 neuropathic pain caused by nerve damage*

## 2. Assess and re-assess the patient

- The clinical situation by means of a complete/specific physical examination and the specific radiological and/or biochemical investigations
- The presence of interference of pain with the patient's daily activities, work, social life, sleep patterns, appetite, sexual functioning, mood, well-being, coping
- The impact of the pain, the disease and the therapy on the physical, psychological, and social conditions
- The presence of a caregiver, the psychological status, the degree of awareness of the disease, anxiety and depression and suicidal ideation, his/her social environment, quality of life, spiritual concerns/needs, problems in communication, personality disorders, depression and anxiety disorders
- The presence and intensity of signs, physical and/or emotional symptoms associated with cancer pain syndromes
- The presence of co-morbidities (i.e. diabetic, renal and/or hepatic failure etc)
- The functional status
- The presence of opioidophobia or misconception related to pain treatment
- The alcohol and/or substance abuse

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

- Take time to spend with the patient and the family to understand their needs
ESMO Recommendations
-Principles of pain management-

• Patients should be informed about pain and pain management and be encouraged to take an active role in their pain management (II, B)

• Analgesic for chronic pain should be prescribed on a regular basis and not on “as required” schedule (V, D)

• The oral route of administration of the analgesic drugs should be advocated as the 1st choice (IV, C)

• Rescue dose of medications (as required or p.r.n) other than the regular basal therapy must be prescribed for breakthrough pain episodes (V, D)

• The analgesic treatment should start with drugs indicated by the WHO analgesic ladder appropriate for the severity of pain (II, B)
Treatment of cancer pain

**STRONG RECOMMENDATION**

MILD PAIN

STEP 1
NRS 1-3

NSAIDs-
PARACETAMOL


WEAK RECOMMENDATION

MILD-MODERATE PAIN

STEP 2
NRS 4-6

WEAK OPIOIDS +/-
NSAIDs-
PARACETAMOL

Periodical reassessment of cancer pain. Use rescue medications. If pain not controlled do not change opioid but go on the next step.

STRONG RECOMMENDATION

MODERATE-SEVERE PAIN

STEP 3
NRS 7-10

STRONG OPIOIDS +/-
NSAIDs- PARACETAMOL

Increase the dose of opioid every day, considering the number of opioid rescue doses used, till pain control or side effects.

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**Side effects**

- Reasses the pain intensity and its causes
- Consider the type and/or doses of adjuvants
- Consider opioid or route of opioid administration switching
- Consider invasive interventions
- Team decision

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**Persisting Pain**

- Use always rescue doses to treat Breakthrough Pain

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**Adjuvant drugs such as corticosteroids, anticonvulsants, antidepressants, should be considered at any step when necessary**
ESMO Recommendations
-Treatment of mild pain-

• Paracetamol and/or a non-steroidal anti-inflammatory drug are effective for treating mild pain (I, A)

• Paracetamol and/or a non-steroidal anti-inflammatory drug are effective for treating all intensities of pain, at least in the short term and unless contraindicated (I, A)

• For mild to moderate pain, weak opioids such as codeine, tramadol and dihydrocodeine should be given in combination with non opioid analgesics (III, C)

• As an alternative to weak opioids consider low doses of strong opioids in combination with non-opiod analgesics (III, C)
The opioid of first choice for moderate to severe cancer pain is oral morphine (IV, D).

The average relative potency ratio of oral to intravenous morphine is between 1:2 and 1:3 (II, A) and oral to subcutaneous morphine is between 1:2 and 1:3 (IV, C).

In the presence of renal impairment all opioids should be used with caution and at reduced doses and frequency (IV, C).

Fentanyl and buprenorphine via transdermal route or intravenously are the safest opioids of choice in patients with chronic kidney disease stages 4 or 5 (estimated glomerular filtration rate <30 ml/min) (IV, C).

Individual titration of dosages by means of normal release morphine administered every 4 hours plus rescue doses (up to hourly) for BTP are recommended in clinical practice (V, C).

The regular dose of slow release opioids can then be adjusted to take into account the total amount of rescue morphine (IV, C).
ESMO Recommendations

-Breakthrough pain-

• Immediate release formulation of opioids must be used to treat exacerbations of controlled background pain (I, A)

• Immediate release oral morphine is appropriate to treat predictable episodes of breakthrough pain (i.e. pain on moving, on swallowing etc.) when administered at least 20 min before such potential painful trigger actions (II, A)

• Intravenous opioids; buccal, sublingual, intranasal fentanyl drug delivery have a shorter onset of analgesic activity in treating BTP episodes in respect to oral morphine (I, A)
ESMO Recommendations
-Management of opioid side effects-

• Laxatives has to be routinely prescribed for both the prophylaxis and the management of opioid-induced constipation (I, A)

• Metoclopramide and antidopaminergic drugs should be recommended for treatment of opioid related nausea/vomiting (III, B)
Treatment of pain due to bone metastases

Zoledronic acid, denosumab or pamidronate (only in breast cancer) (plus calcium and vitamin D supplementation) should be given, in addition to antalgic radiotherapy. These drugs showed to delay SREs and to reduce pain. Patients should undergo a preventive dental screening by dentistry prior to initiation the therapy with one of the drug. The optimal duration of these drugs is not completely defined.

USE ANALGESIC THERAPY

Uncomplicated bone metastases

YES

Bone pain?

NO

Zoledronic acid, denosumab, or pamidronate should be given also in absence of pain. These drugs demonstrated to delay SRE and the appearance of pain.

Radiotherapy and/or surgery should be promptly considered, when appropriate. Zoledronic acid, denosumab, or pamidronate should be given because showed to delay the first and subsequent SREs. USE ANALGESIC THERAPY

Complicated bone metastases (spinal cord compression or impending fracture)?

YES

The same strategies suggested for uncomplicated bone metastases with or without bone pain

NO

YES

Previous SRE: radiotherapy, bone surgery

NO

YES

Zoledronic acid, denosumab, or pamidronate should be given because showed to delay the subsequent SREs.
ESMO Recommendations
-Radiotherapy/Radioisotope – Bone pain-

• All patients with painful bone metastases should be evaluated for external beam RT and the dose prescription should be 8-Gy single-dose (IA)
• Higher doses and protracted fractionations can be reserved only to selected cases (IIB)
• Stereotactic body radiosurgery should be used for fit patients included into clinical trials (VD)
• Early diagnosis and prompt therapy are powerful predictors of outcome in MSCC (IA). The majority of patients with MSCC should receive RT alone and surgery should be reserved only to particular cases (IIB)
• Hypofractionated RT regimen can be considered the approach of choice (IA), while more protracted RT regimens can be used in selected MSCC patients with a long life expectancy (IIIB)
• Dexamethasone should be prescribed in patients with MSCC (IIA) at medium dose (IIIB)
• Radioisotope treatment can be evaluated in selected patients with multiple osteoblastic bone metastases (IIC)
ESMO Recommendations
-Bisphosphonates/denosumab – Bone pain-

• Bisphosphonates should be considered as part of the therapeutic regimen for the treatment of patients with/without pain due to metastatic bone disease (II, B)

• Denosumab should be considered as a valid alternative of BPs for the treatment of patients with/without pain due to metastatic bone disease from solid tumors (I, A)

• The role of denosumab in delaying bone pain occurrence is promising but deserves further evidence (III, B)

• Preventive dental measures are necessary before starting bisphosphonates/denosumab administration (III, A)
Assessment and treatment of neuropathic pain

Semantic descriptor of neuropathic pain

- **Allodinia**: pain caused by a stimulus which normally does not provoke pain
- **Causalgia**: continuous burning pain, allodinia and hyperpathia in succession or a traumatic nervous lesion; disturbed vasomotor functions are often intercurrent, as well as, later on, disturbances to trophism
- **Central pain**: pain associated with a lesion of the central nervous system
- **Dysesthesia**: unpleasant sensation of tingling, stabbing or burning whether spontaneous or provoked
- **Hyperesthesia**: increase in sensitivity to specific stimuli
- **Hyperalgesia**: increased response to a stimulus which is normally painful
- **Hyperpathia**: painful syndrome characterised by increased reaction to a stimulus, especially a repetitive stimulus
- **Paresthesia**: abnormal sensation, either spontaneous or evoked.

Assessment tools for neuropathic pain

- **Assessment tools**
  - Neuropathic Pain scale
  - Neuropathic Pain Symptom Inventory
- **Assessment and screening tools**
  - Scale of pain LANSS
  - Neuropathic Pain Questionnaire
  - Questionnaire DN4

Clinical assessment of neuropathic pain

- Compression, dislocation, stretching of:
  (peripheral nerves, nervous roots
  plexies, nevrasse, cerebral centres)
- **Neoplastic infiltration** (sensitive nervous structures)
- **Iatrogenic causes** (neuropathy caused by anticancer treatments: drugs, RT, surgery)

Neuropathic pain?

- **Yes**: Non opioids +/- Strong opioids +/- Amitriptyline 25-75 mg/day or Gabapentin 300-3600 mg/day
  RT for neuropathic pain due to bone metastases
- **No**: Reassess neuropathic component in mixed pain or search neuropathic mimicking pain
ESMO Recommendations
-Management of neuropathic pain-

• Patients with neuropathic pain should be treated with non opioid and opioid drugs (III, B)

• Patients with neuropathic pain should be given either a tricyclic antidepressant or an anticonvulsant and subjected to side effects monitoring (I, A)

• In patients with neropathic pain due to bone metastases RT at the dose of 20 Gy in 5 fractions should be considered (II, B)
Intrathecal infusion for refractory cancer pain

INTRATHECAL (IT) single short trial
somatic or neuropathic pain

Trial with IT CATHETER

IT implantable Pump

*Choice of drugs according type of pain

Epidural Catheter
- Tunneled or with implantable system
  - somatic or neuropathic pain

Spinal Catheter
- Tunneled or with implantable system
  - somatic or neuropathic pain

Life expectancy < 3 months

Life expectancy > 3 months

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ESMO Recommendations
-Invasive management of refractory pain-

• Intraspinal techniques monitored by a skilled team, should be included as part of cancer pain management strategy but avoiding widespread use (II, B)

• Celiac plexus block 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 six months (II, B)
Conclusions

• Only a few RCTs performed
• Further well done studies on large samples of patients are needed

• Assess and re-assess the pain, the patients and our ability to communicate

• Prescribe a personalized therapy

• Consider pharmacologic ± non pharmacological intervention