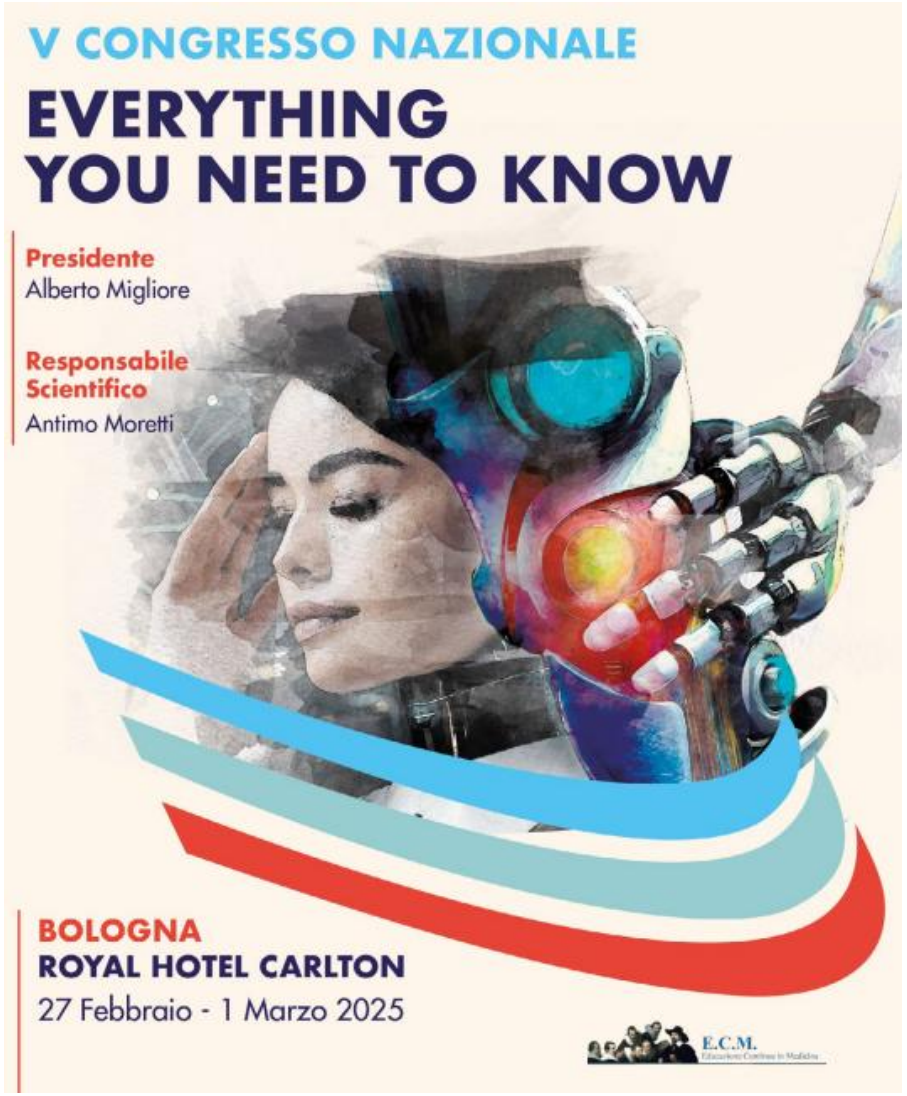


La patogenesi del dolore oncologico

V CONGRESSO NAZIONALE - G.U.I.D.A.
28 febbraio 2025

V.A. GUARDAMAGNA
Director - Palliative Care & Pain Therapy Department
IRCCS IEO - European Institute of Oncology
Milan - ITALY

Il sottoscritto Vittorio A. Guardamagna
in qualità di docente

ai sensi dell'art. 76 sul Conflitto di Interessi, pag. 34 dell'Accordo Stato del Regione del 2 Febbraio 2017

dichiara

di non aver avuto rapporti di finanziamento con soggetti portatori di interessi commerciali in campo sanitario.

L'ICEBERG DEL DOLORE CRONICO

L’ICEBERG DEL DOLORE CRONICO

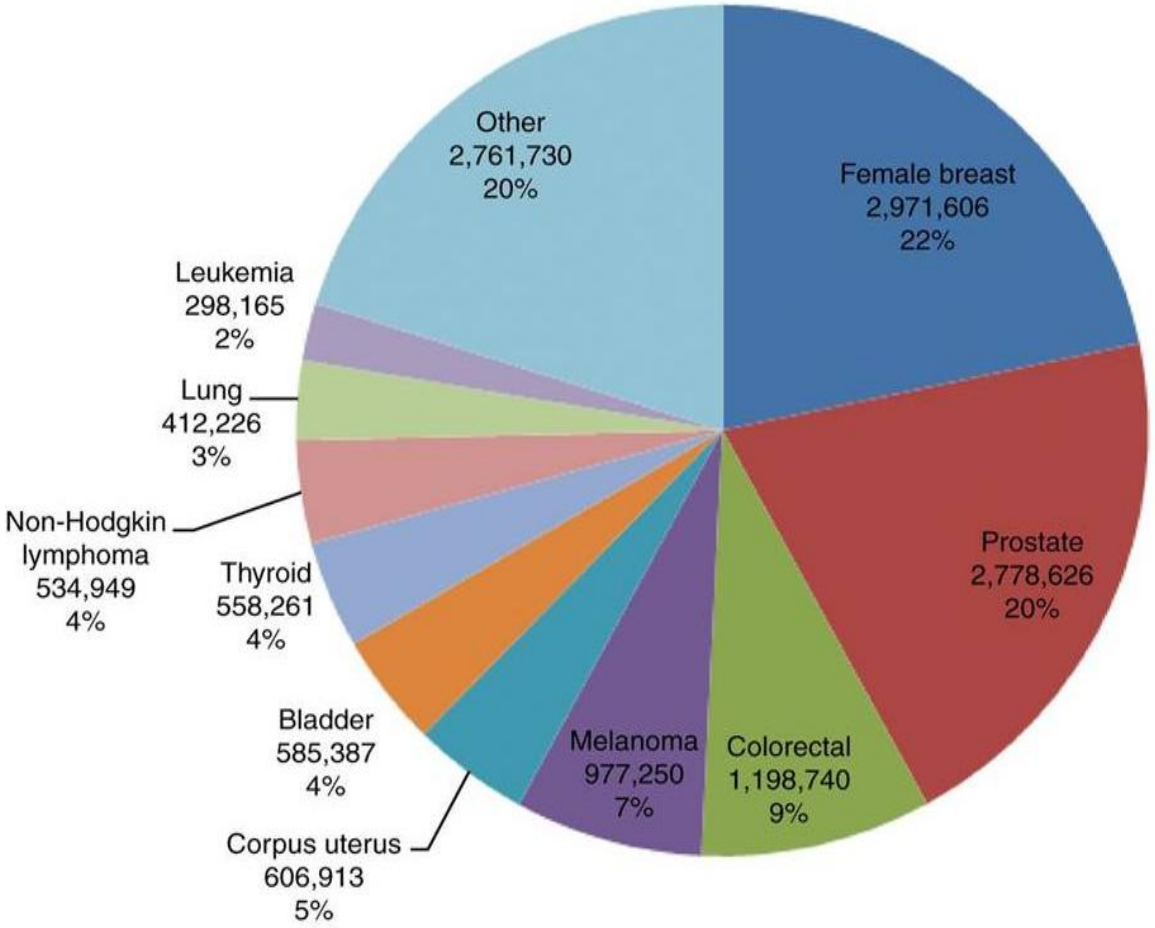
E IL DOLORE ONCOLOGICO E’
UNA «PICCOLA PUNTA DELL’ICEBERG»?

Cancer Prevalence

- In 2012, new cancer cases worldwide – 14.1 million, 8.2 million deaths, **32.6 million people living with cancer**
- By 2030, 21.7 million new cases, 13 million cancer deaths, **52.2 million survivors?**

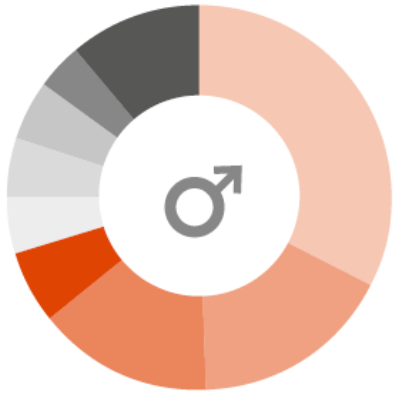
Presented By Judith Paice at 2017 ASCO Annual Meeting

Estimated number of survivors by cancer site

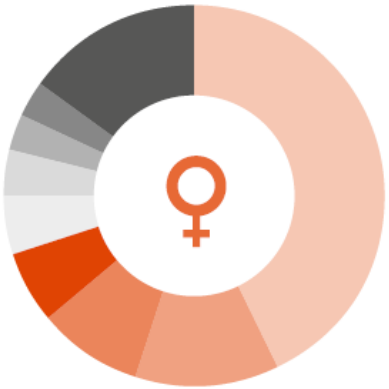


De Moor, Cancer Epidemiol Biomark Prev 2013

In Italy: AIRTUM register, 2021



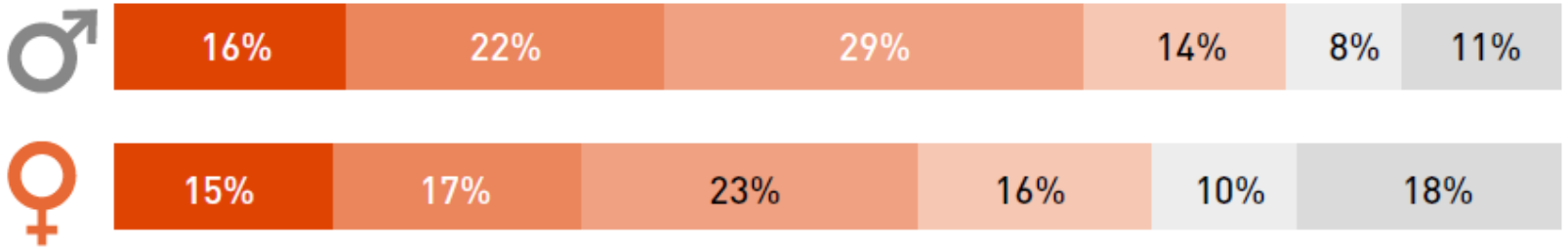
Tumore	n.	%
Prostata	563.960	33
Colon-retto-ano	280.277	17
Vescica	255.015	15
Rene e vie urinarie	97.249	6
Linfomi non-Hodgkin	82.780	5
Melanomi, cute	80.069	5
Polmone	77.159	5
Testicolo	63.395	4
Altri	187.145	11



Tumore	n.	%
Mammella	834.154	43
Colon-retto-ano	233.245	12
Tiroide	166.914	9
Utero (corpo)	122.553	6
Melanomi, cute	89.831	5
Linfomi non-Hodgkin	73.584	4
Vescica	58.608	3
Utero cervice	51.136	3
Altri	292.061	15

FIGURA 7. Proporzione di persone che vivono dopo una diagnosi di tumore in Italia nel 2020, per i tipi di tumore più frequenti e sesso

How many italians are living with cancer diagnosis nowadays?



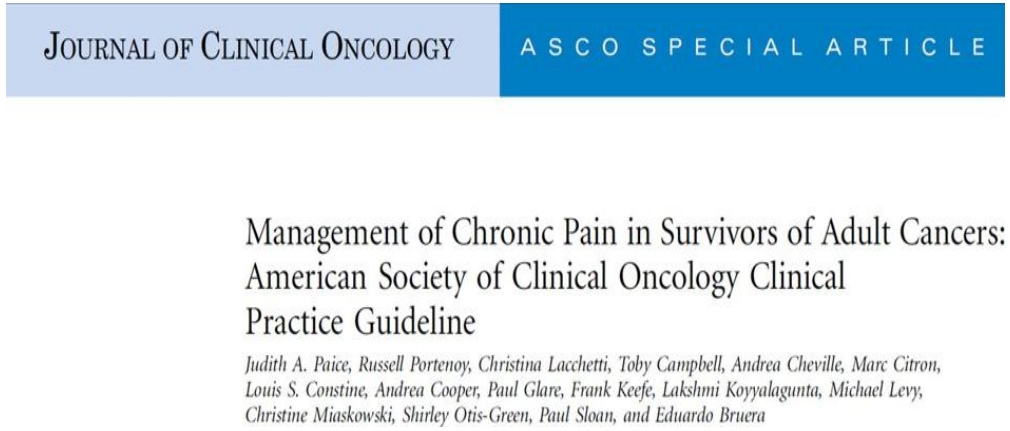
Anni dalla diagnosi	Uomini	Donne
≤ 2	267.107	286.470
2 - ≤ 5	364.582	332.759
5 - ≤ 10	497.186	449.153
10 - ≤ 15	242.308	310.314
15 - ≤ 20	138.115	201.786
>20	177.751	341.605
	1.687.049	1.922.086

3,600,000

FIGURA 8. Numero e proporzione di persone che vivono dopo una diagnosi di tumore in Italia nel 2020, per tempo dalla diagnosi e sesso

I NUMERI DEL CANCRO IN ITALIA Italia 2021. AIOM-AIRTUM. www.aiom.it

A renewed interest to pain in cancer survivors


JOURNAL OF CLINICAL ONCOLOGY ASCO SPECIAL ARTICLE

Management of Chronic Pain in Survivors of Adult Cancers: American Society of Clinical Oncology Clinical Practice Guideline

Judith A. Paice, Russell Portenoy, Christina Lacchetti, Toby Campbell, Andrea Cheville, Marc Citron, Louis S. Constine, Andrea Cooper, Paul Glare, Frank Keefe, Lakshmi Koyyalagunta, Michael Levy, Christine Miaskowski, Shirley Otis-Green, Paul Sloan, and Eduardo Bruera

Glare PA, J Clin Oncol 2014
Paice JA, J Clin Oncol 2016


JOURNAL OF CLINICAL ONCOLOGY REVIEW ARTICLE

Pain in Cancer Survivors

Paul A. Glare , Pamela S. Davies, Esmé Finlay, Amitabh Gulati, Dawn Lemanne, Natalie Moryl, Kevin C. Oeffinger, Judith A. Paice, Michael D. Stubblefield, and Karen L. Syrjala

Pain in survivors

- From short-term to chronic problem
- Define who is responsible for comprehensive pain management program and prescribing
- Maintain a multidisciplinary approach when needed
- Evaluate…

  → late effect or recurrence/second primary?

  → change during time (intensity, frequency, charact)

Glare PA, J Clin Oncol 2014

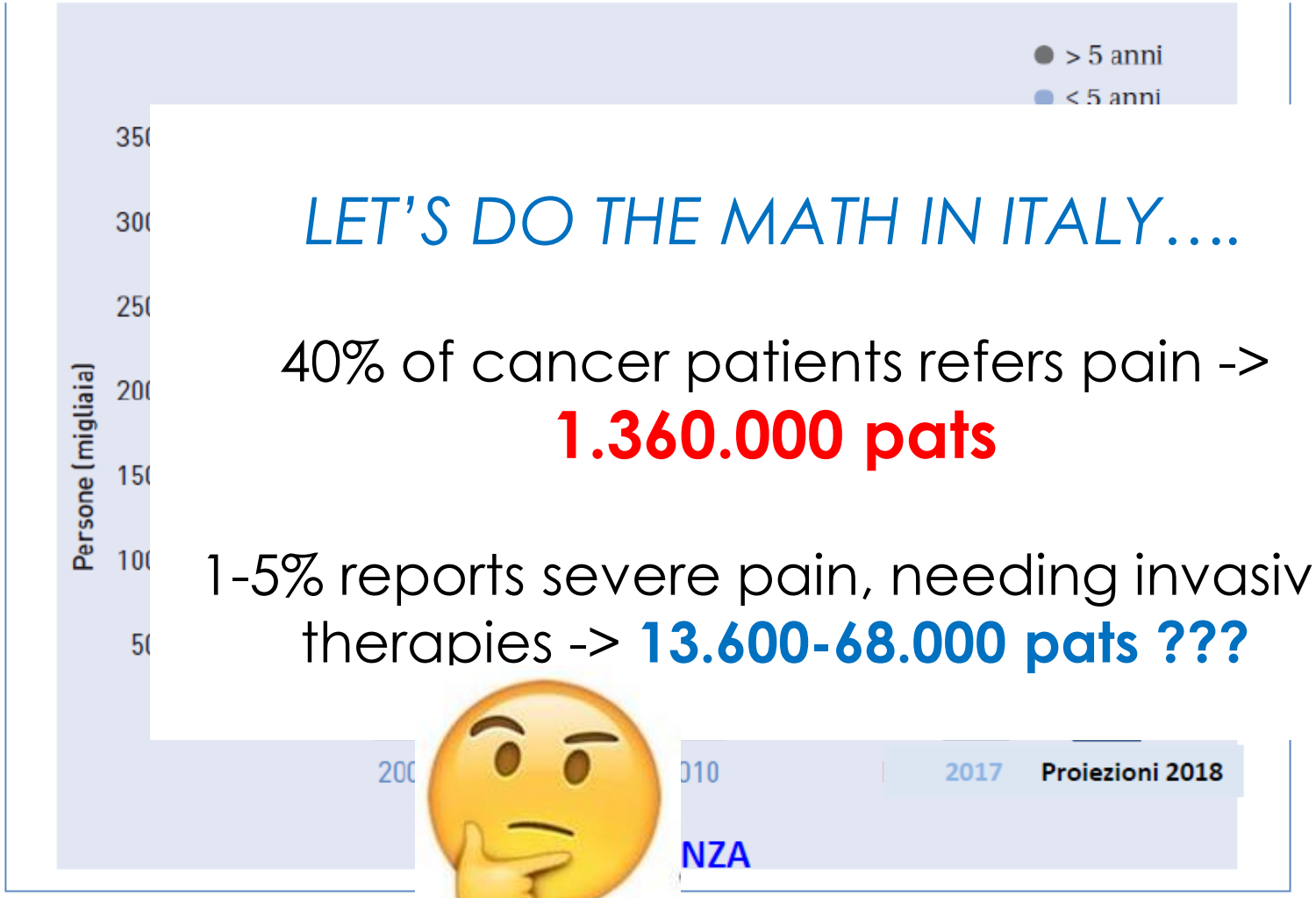
PREVALENCE OF CANCER PAIN

- 55% in patients **on** anticancer treatment
- 39% in patients **after** curative treatment
- 66% in patients **with metastatic**, advanced, or terminal disease

No changes in prevalence of pain across treatment journey.
Moreover, moderate to severe pain (NRS > 4) = 38% of the pts

Van den Beuken. Ann Oncol 2007
Marieke HJ. J Pain Sympt Manag 2016

How many italians are living with cancer diagnosis nowadays?



LET'S DO THE MATH IN ITALY….

40% of cancer patients refers pain ->
1.360.000 pats

1-5% reports severe pain, needing invasive therapies -> **13.600-68.000 pats ???**

* 6% della popolazione italiana

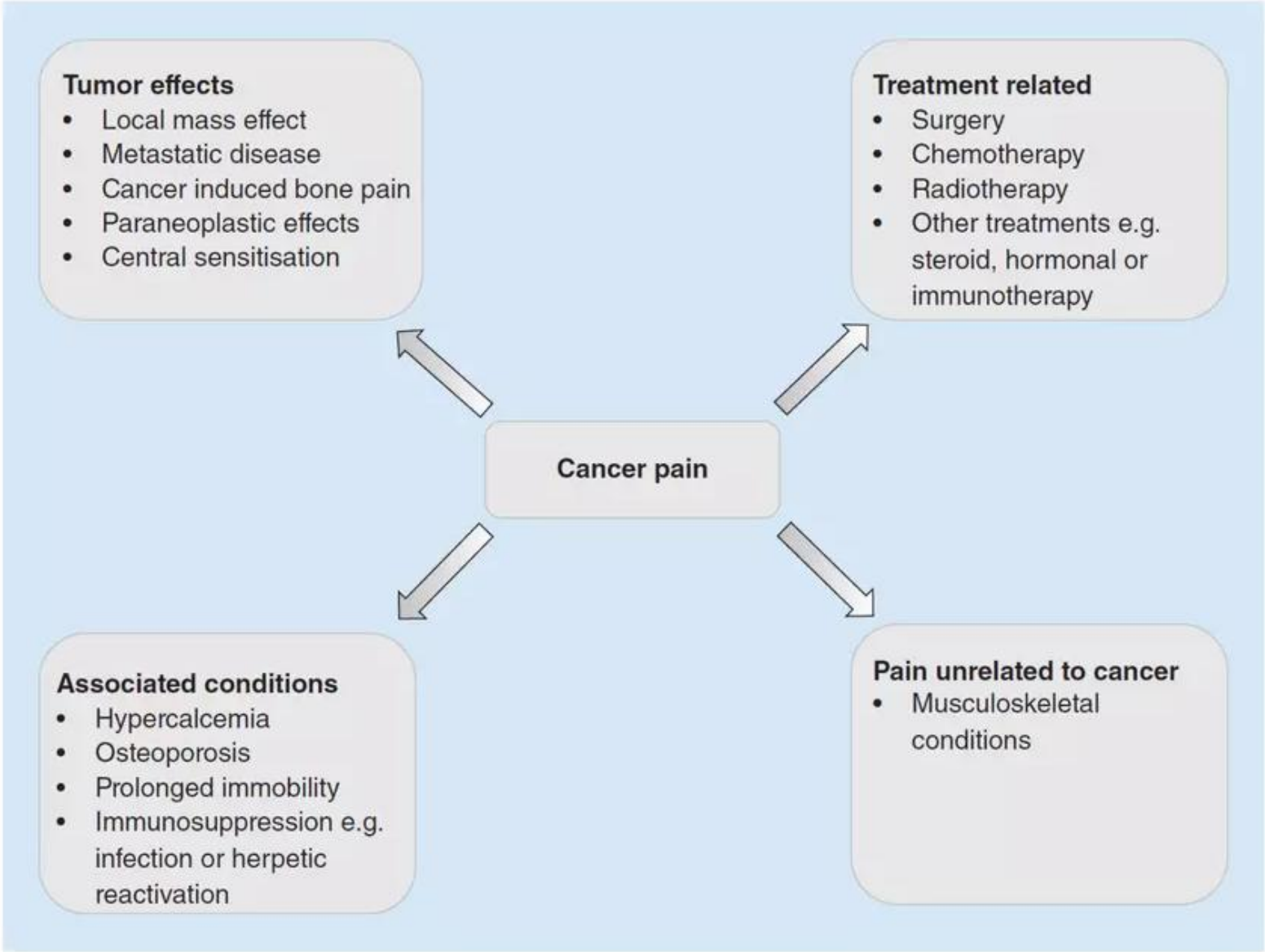
I NUMERI DEL CANCRO IN ITALIA Italia 2018. AIOM-AIRTUM. www.aiom.it

Dolore NEL Cancro

O

Dolore DA Cancro?

CANCER PAIN

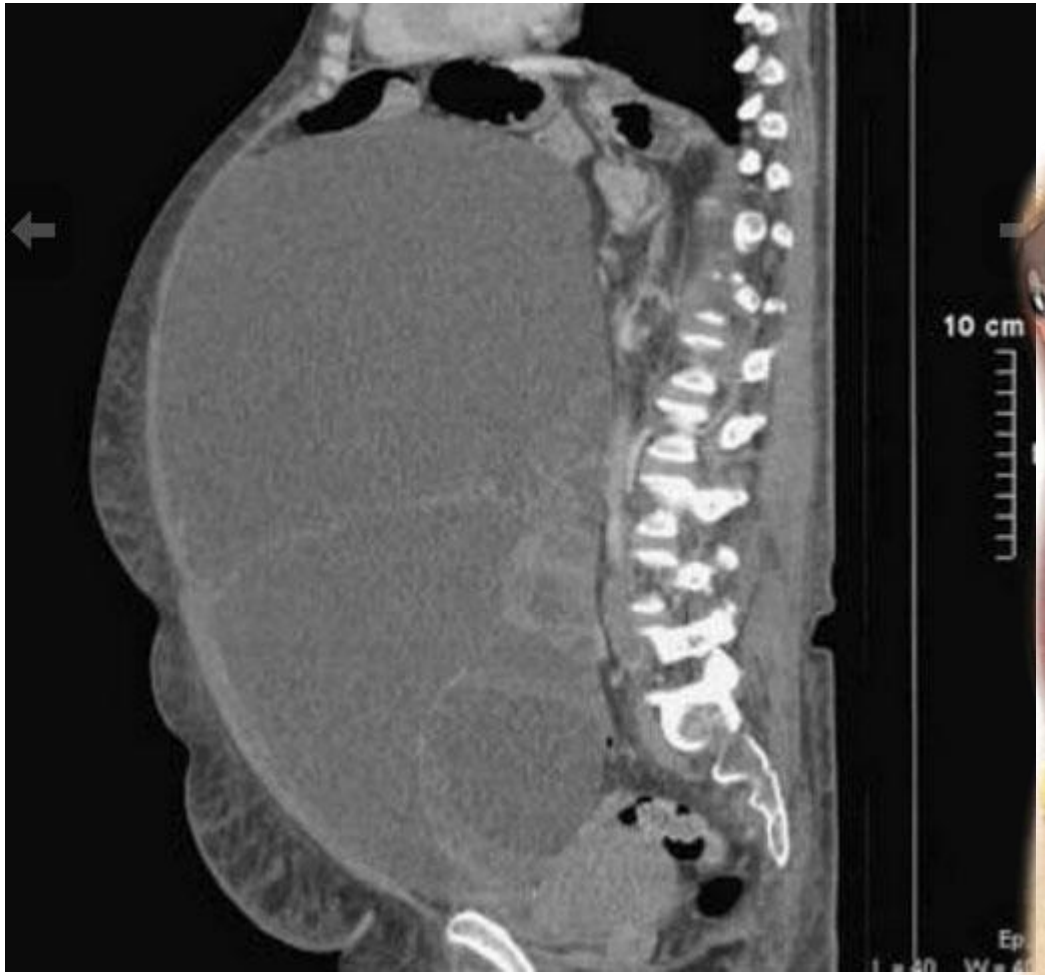


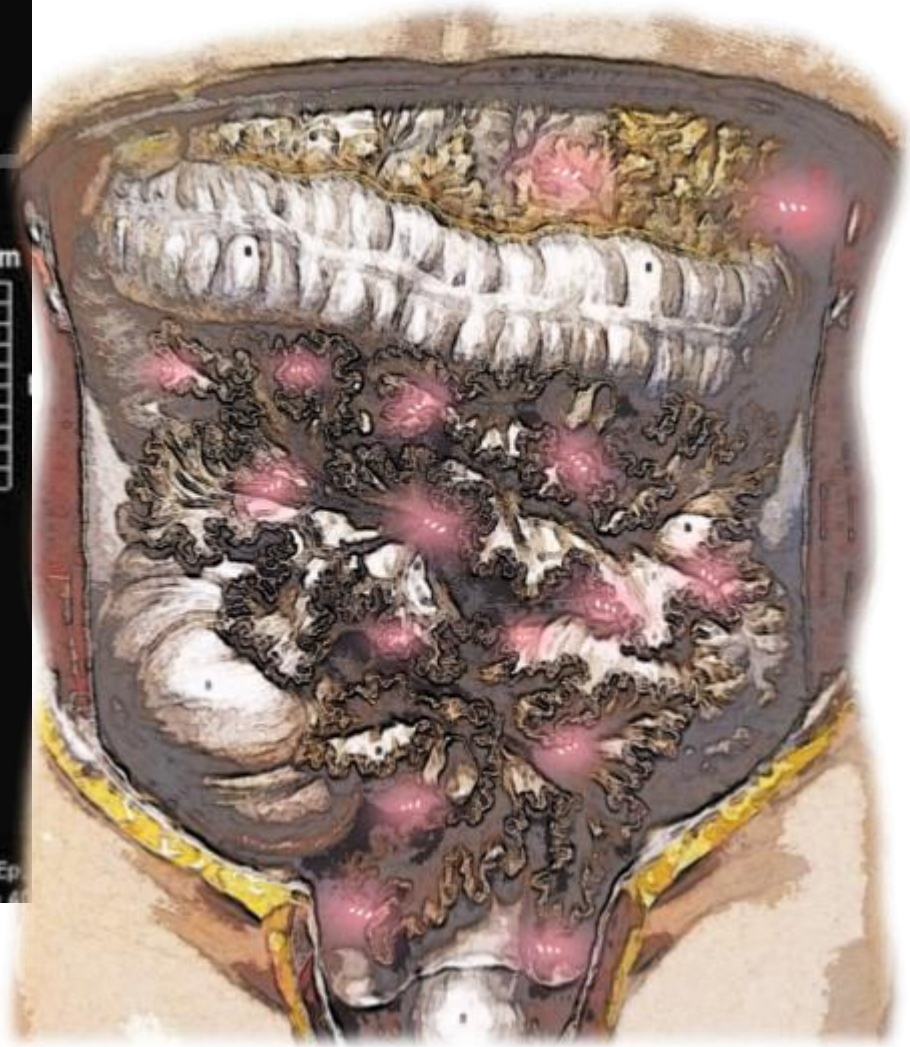
Magee D, Pain Manag 2019

Chronic pain syndromes directly related to cancer

Nociceptive pain syndromes: visceral

Hepatic distention syndrome
Midline retroperitoneal syndrome
Chronic intestinal obstruction
Peritoneal carcinomatosis
Malignant perineal pain
Adrenal pain syndrome
Ureteric obstruction


10 cm

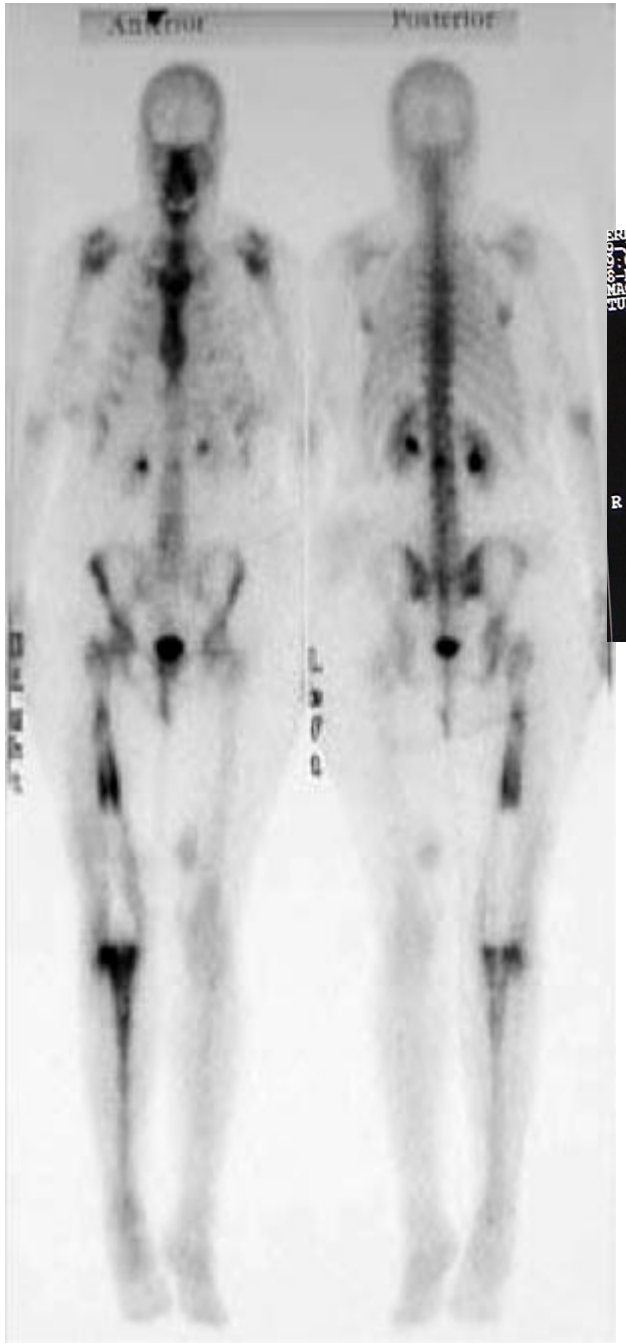


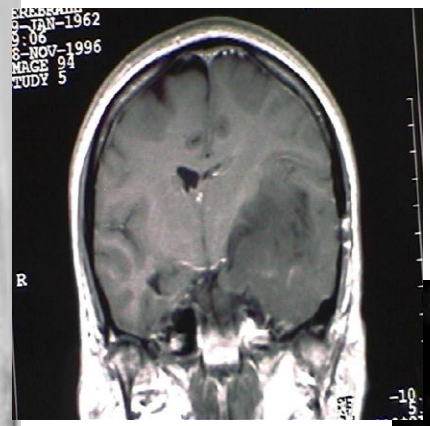

Rectum
Anal cancer

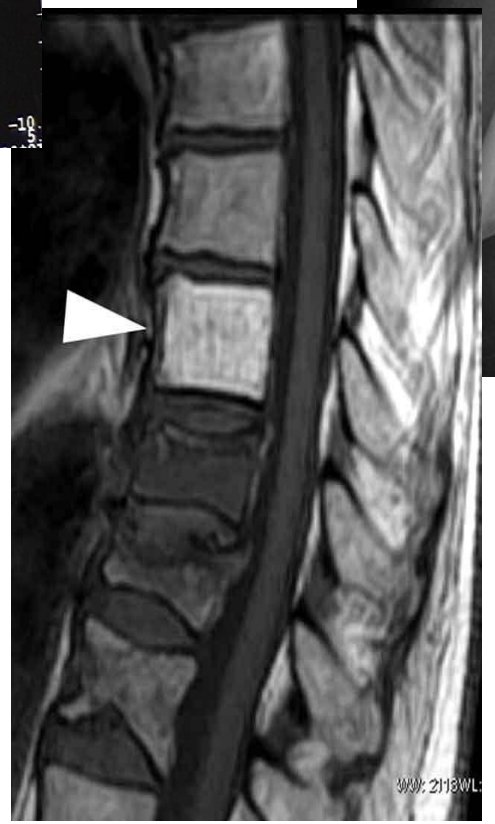
Chronic pain syndromes directly related to cancer

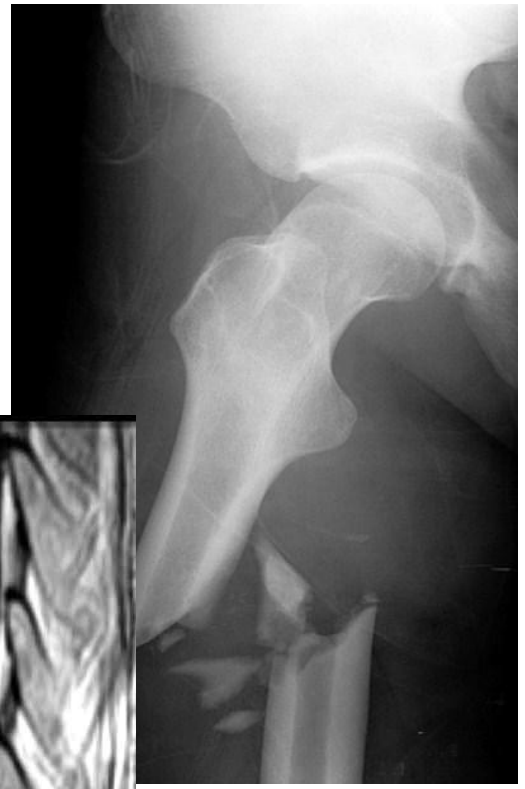
Nociceptive pain syndromes: somatic

Tumor-related bone pain: • **Multifocal bone pain** • **Vertebral syndromes** • **Pain syndromes related to pelvis and hip** • **Base of skull metastases**
Tumor-related soft tissue pain
Paraneoplastic pain syndromes


Anterior
Posterior


-JAN-1962
:06
-NOV-1996
MAGE 91
TUDY 5
R





BM are the most common cause of cancer-related pain[1,2] that can affect patient's QoL

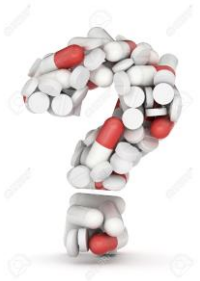
70 to 85% of prostate or breast cancer patients and 30% to 40% of lung cancer patients present bone met during the course of their illness

Treatment: multiple approaches (RT, surgery, CT, BP, NSAIDS, opioids)[3]

Bone cancer pain is one of the most dfficult of all chronic pains to fully control. **Why?**

1.BM are not limited to a single site
-Efficacy of analgesics are limited by significant AEs
-Somatic+neuropathic component[2]
2.SREs are frequent pain-producing complications associated with BM

Trattare il bone cancer PAIN: perché ci confonde così tanto?



[1]*Coleman RE. et al. Clin Cancer Res 2006*
[2]*Mercadante S. Pain 1997*
[3]*Ripamonti C. et al. Ann Oncol 2012*

Pain related to bone metastases has a multifactorial etiopathogenesis

International Journal of *Molecular Sciences*

MDPI

Review

Bone Pain in Cancer Patients: Mechanisms and Current Treatment

Renata Zajączkowska [1,*], Magdalena Kocot-Kępska [2,*], Wojciech Leppert [3] and Jerzy Wordliczek [1]

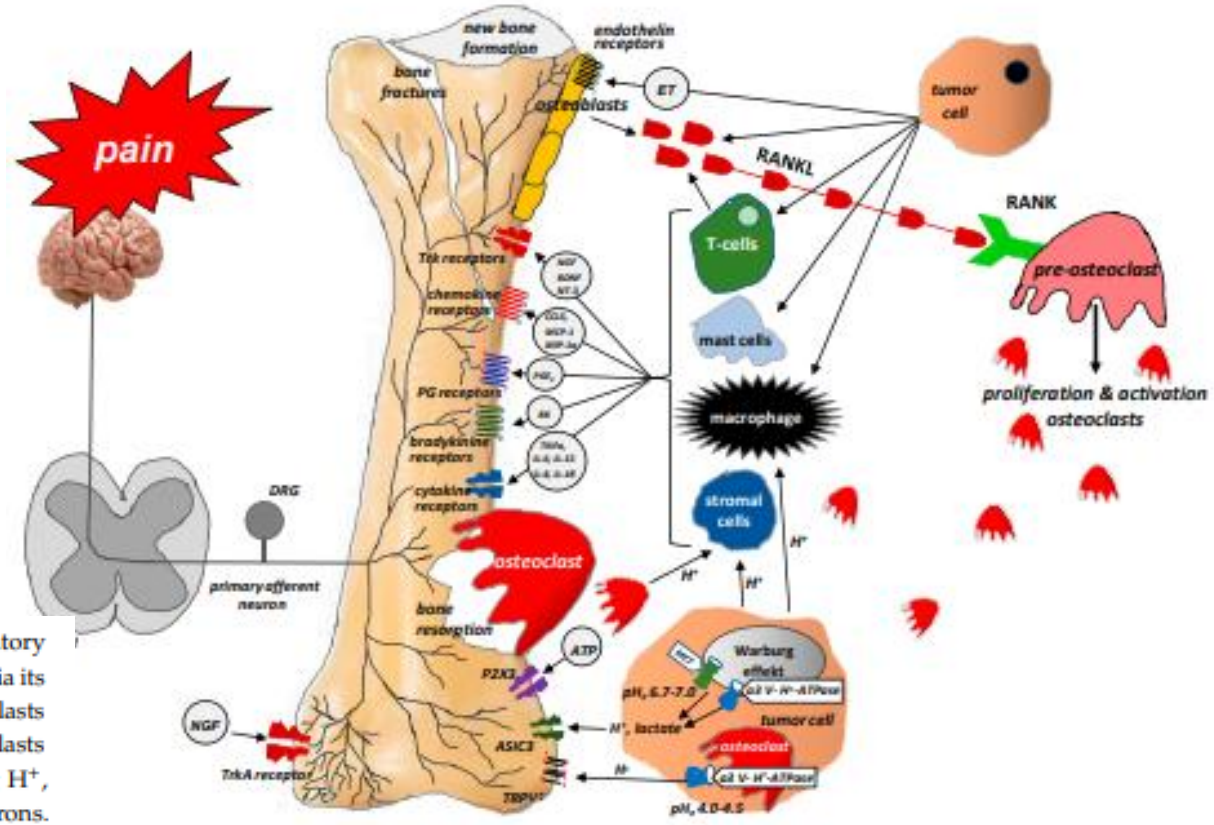


Figure 2. Interactions between tumor cells, osteoblasts, osteoclasts, stromal cells, and inflammatory cells at the site of bone metastasis (According to [12]). Tumor cells release endothelin (ET), which, via its appropriate receptors, interacts with osteoblasts to stimulate their proliferation. Activated osteoblasts release RANKL, which, in turn, provides a signal for the proliferation and maturation of osteoclasts and, hence, their destructive effect on bones. Osteoclasts produce ATP and acidosis-inducing H^+, which activate appropriate receptors (P2X, TRPV1, ASICS3) located on bone-innervating neurons. Moreover, tumor cells, stromal cells, and activated immune cells secrete several mediators (endothelin, prostaglandin, NGF, bradykinin, pro-inflammatory cytokines, chemokines, H^+, and ATP), which activate appropriate receptors (endothelin receptor, prostaglandin receptor, TrkA receptor, bradykinin receptor, cytokine receptors, chemokine receptors, TRPV1, ASIC3, P2X3) located on bone-innervating nerve fiber endings. These receptors help to detect and transmit signals about noxious stimuli to the spinal cord and then to the cerebral cortex, where perception takes place.

Bone metastases

Multifactorial etiopathogenesis

Bone pain

Chemical mediators

Increased pressure within bone

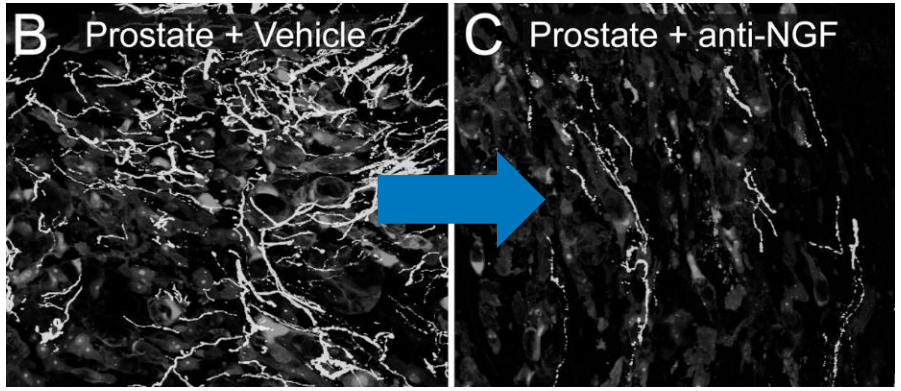
Microfractures

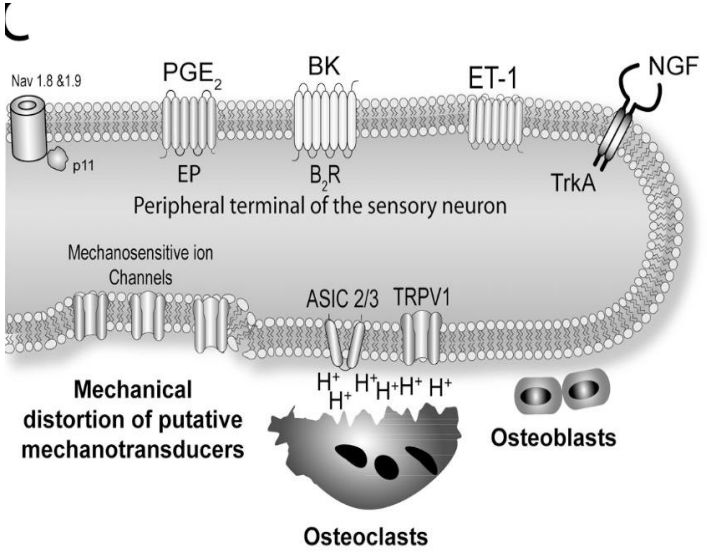
Stretching of periosteum

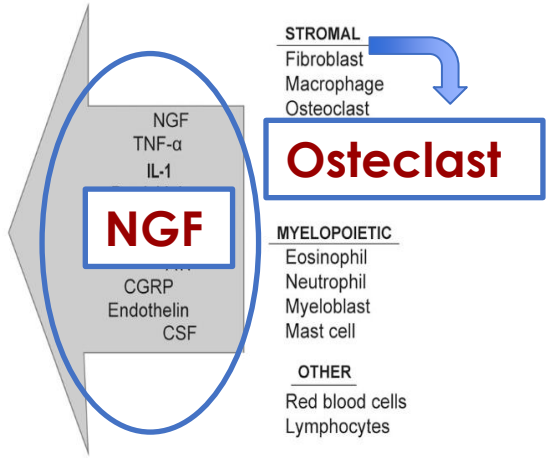
Nerve root infiltration

Nerve compression

Courtesy by L. Costa







NGF regulates
- Survival
- Development
- Function

of subsets of sensory and sympathetic neurons

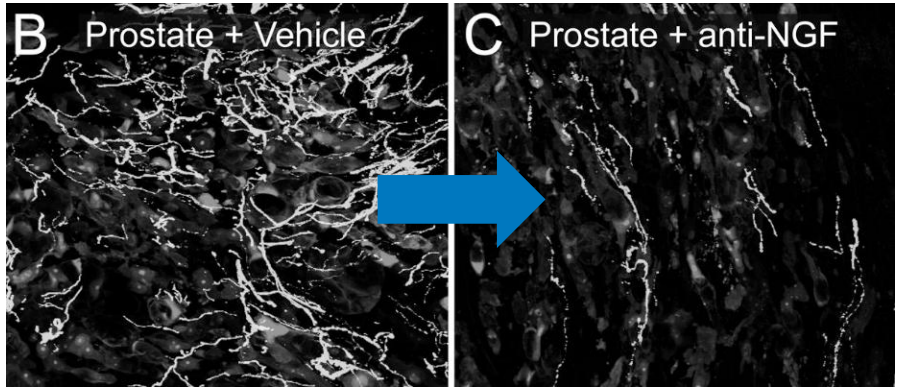
Mercadante S. et al. Pain 1997
Smeyne RJ. et al.Nature 1994
Bloom AP. et al. J Pain 2011
Jimenez-Andrade JM. et al. J Neurosci 2010

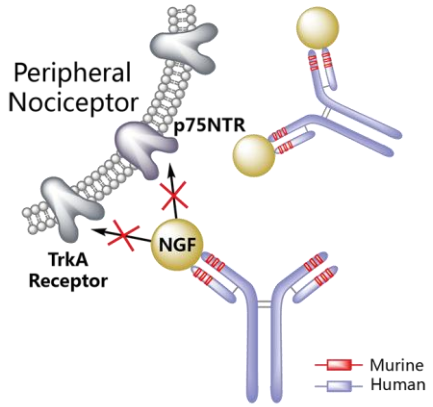
Remarkable and dramatic sprouting of nerve fibers with unique

- Morphology
- Organization
- High density

that in normal bone

NGF is required (anti-NGF blocks the neuroma-like formation and sprouting of sensory nerve fibers)





- Canine prostate cells injected into the mouse bone
- Prostate cells do not express detectable levels of m RNA coding for NGF
- Associated stromal (such as **OSTEOCLASTS**), inflammatory and immune cells (10-70% of the tumor mass)are the source of NGF
- NGF can induce a 10-70 fold increase in density of sensory nerve fibers

Mercadante S. et al. Pain 1997
Smeyne RJ. et al.Nature 1994
Bloom AP. et al. J Pain 2011
Jimenez-Andrade JM. et al. J Neurosci 2010

Skeletal Related Events (SREs)

- hypercalcaemia: further complication

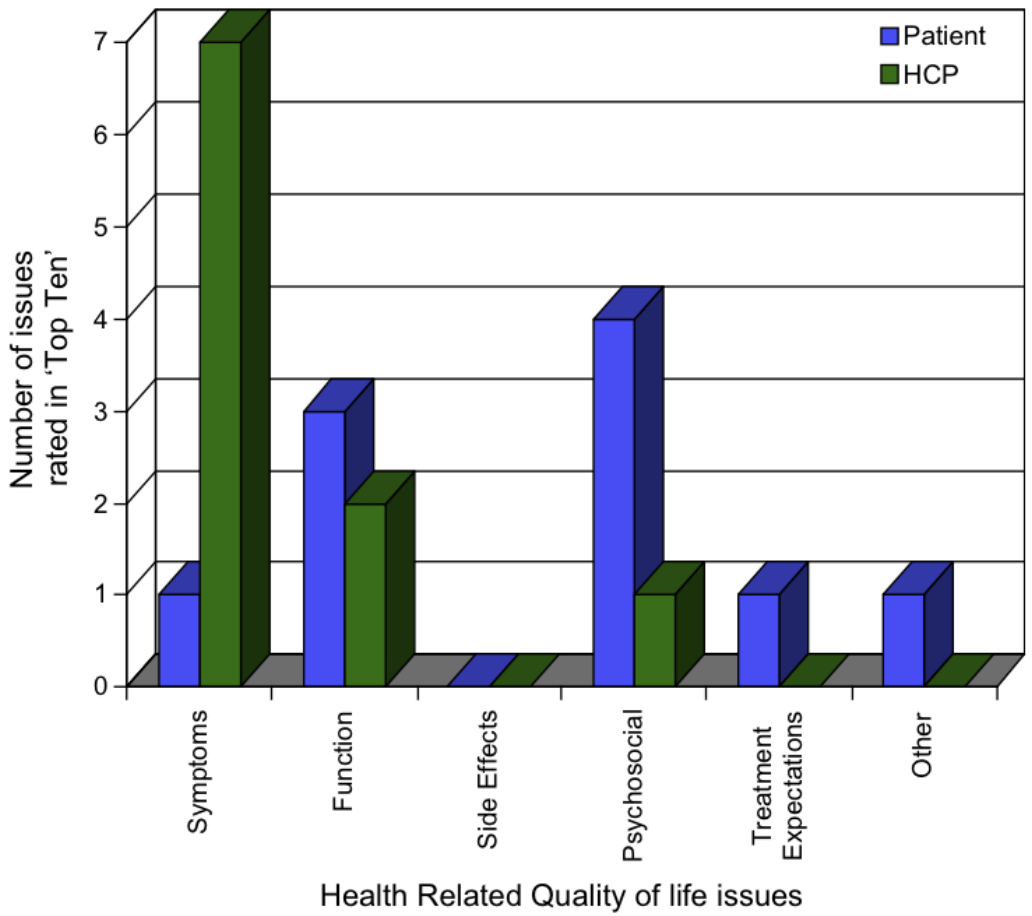
- The prevention of SREs and pain control at rest and on movement have a significant impact on patients' daily life activity, mobility and QoL.

Saad F, et al. J Natl Cancer Inst 2004
Sartor O, et al. Lancet Oncol 2014

‘Top 10’ ranked HRQoL issues for cancer patients with bone metastases

1. • Long-term
2. • Difficulty ca
3. • Worry abou
4. • Worry abou
5. • Worry abou
6. • Ability to p
7. • Difficulty in
8. • Ability to p
9. • Financial bu
10. • Hope treatr

omplications



Harris K, et al. Eur J Cancer 2009;45:2510–8.

Courtesy by L. Costa

Analgesics and bone pain

clinical practice guidelines

Annals of Oncology 23 (Supplement 7): vii139–vii154, 2012
doi:10.1093/annonc/mds233

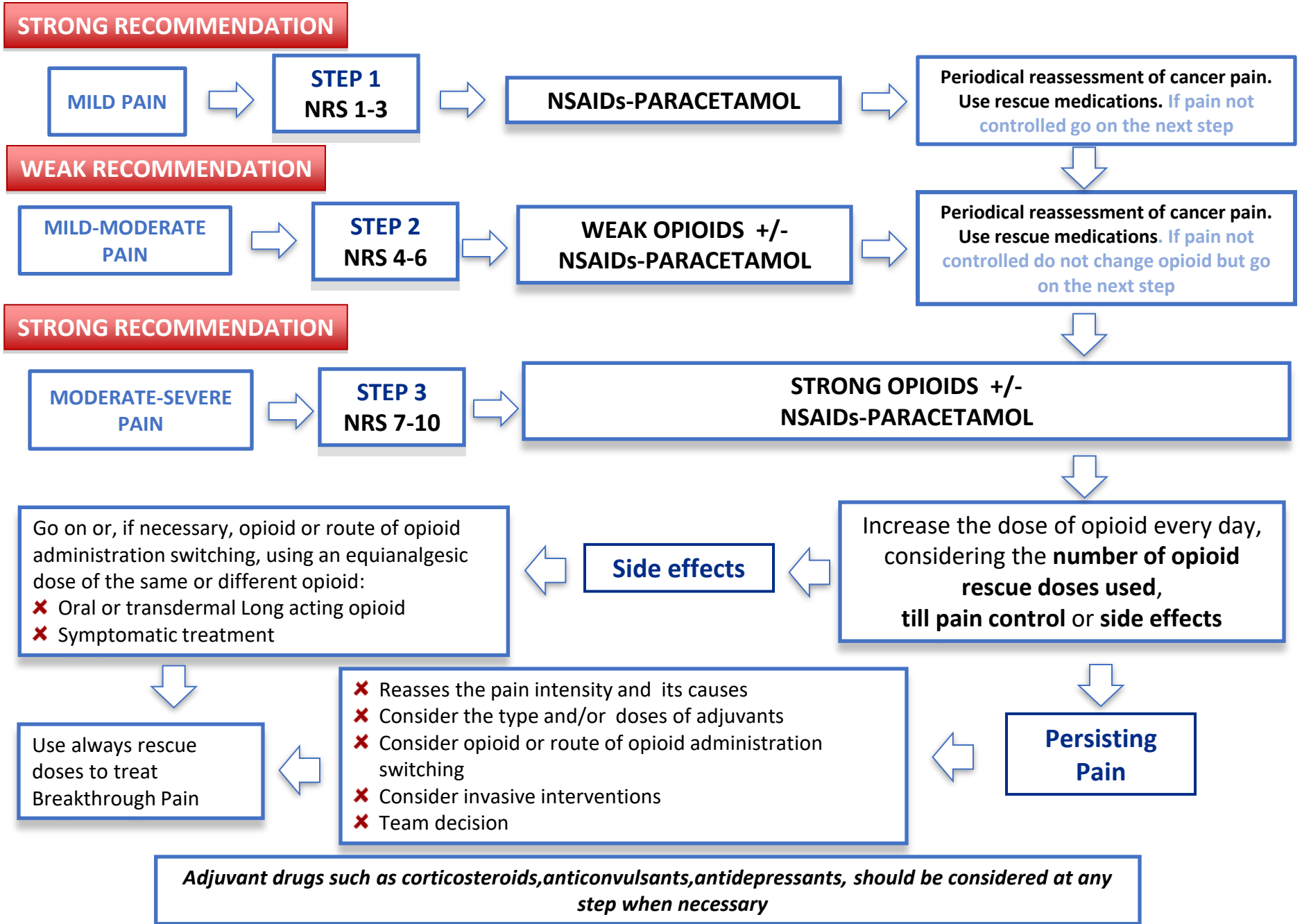
Management of cancer pain: ESMO Clinical Practice Guidelines†

C. I. Ripamonti[1], D. Santini[2], E. Maranzano[3], M. Berti[4] & F. Roila[5], on behalf of the ESMO Guidelines Working Group*

[1]Supportive Care in Cancer Unit, Fondazione IRCCS, Istituto Nazionale Tumori, Milan, Italy; [2]Oncologia Medica, Università Campus Bio-Medico, Rome, Italy; [3]Department of Oncology, Radiation Oncology Centre, S. Maria Hospital, Terni, Italy; [4]Anaesthesiology Intensive Care and Pain Therapy, University Hospital Parma, Parma, Italy; [5]Department of Medical Oncology, S. Maria Hospital, Terni, Italy

European Society for Medical Oncology

Treatment of cancer bone pain: analgesics (ESMO GLs)



Can we overlap the second step in bone related moderate pain? **Yes, we can**

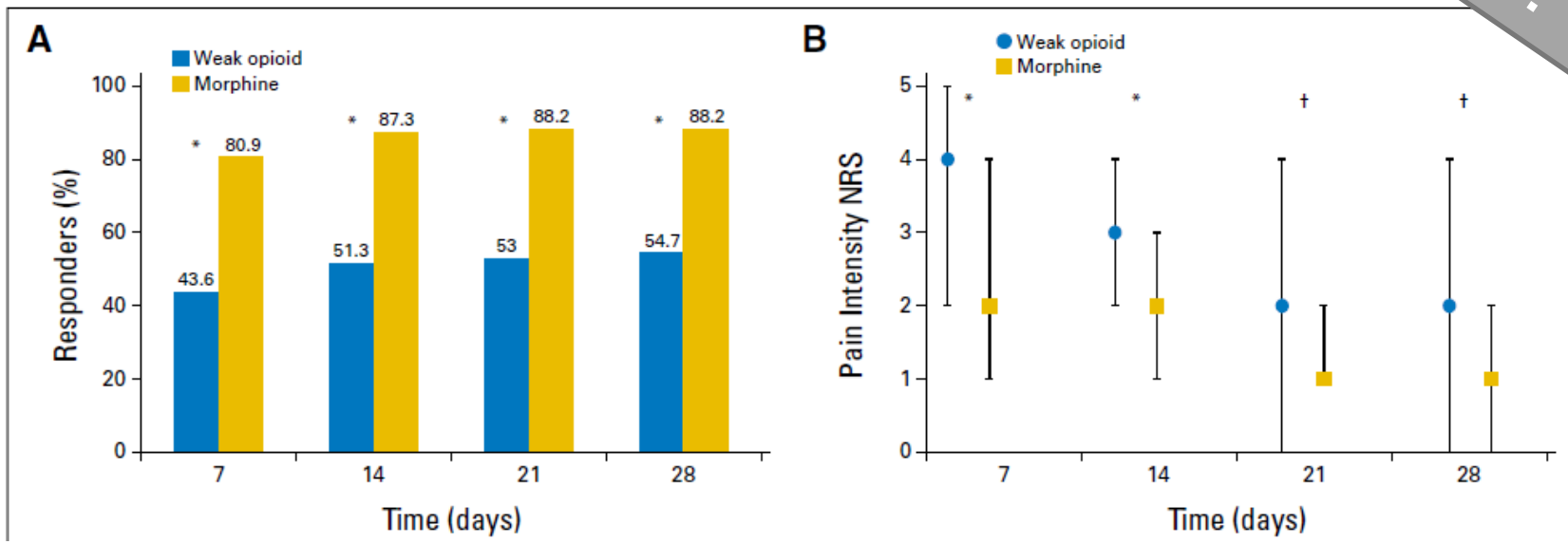
Oppiodi forti prima scelta???

Randomized Trial of Low-Dose Morphine … Opioids in Moderate Cancer Pain

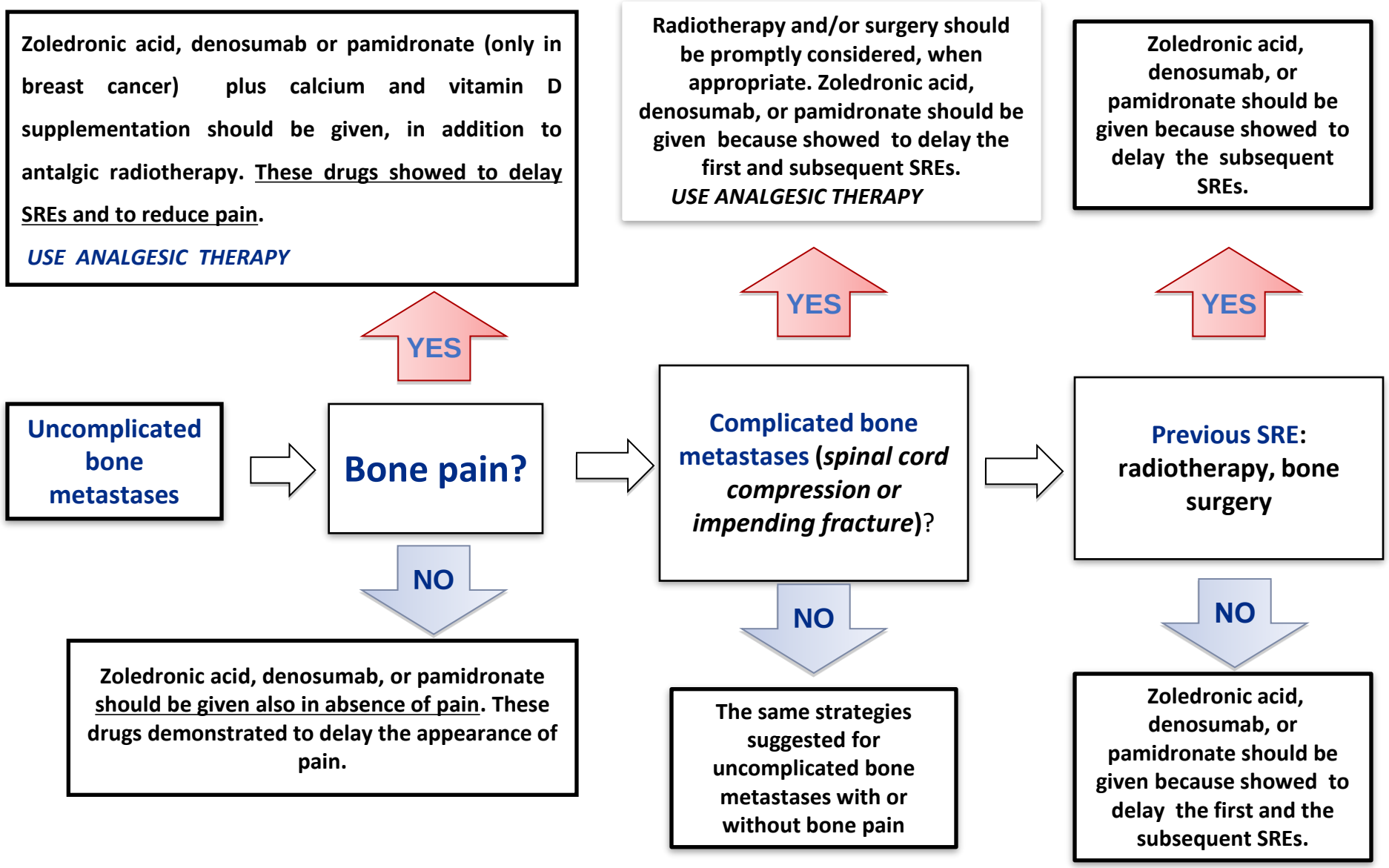
Elena Bandieri, Marilena Romero, Carla Ida Ripamonti, Fabrizio Artioli, Daniela Si… Daniele Santini, Luigi Cavanna, Barbara Melotti, Pier Franco Conte, Fausto Roila, Stefa… Eduardo Bruera, Gianni Tognoni, and Mario Luppi

JOURNAL OF CLINICAL ONCOLOGY

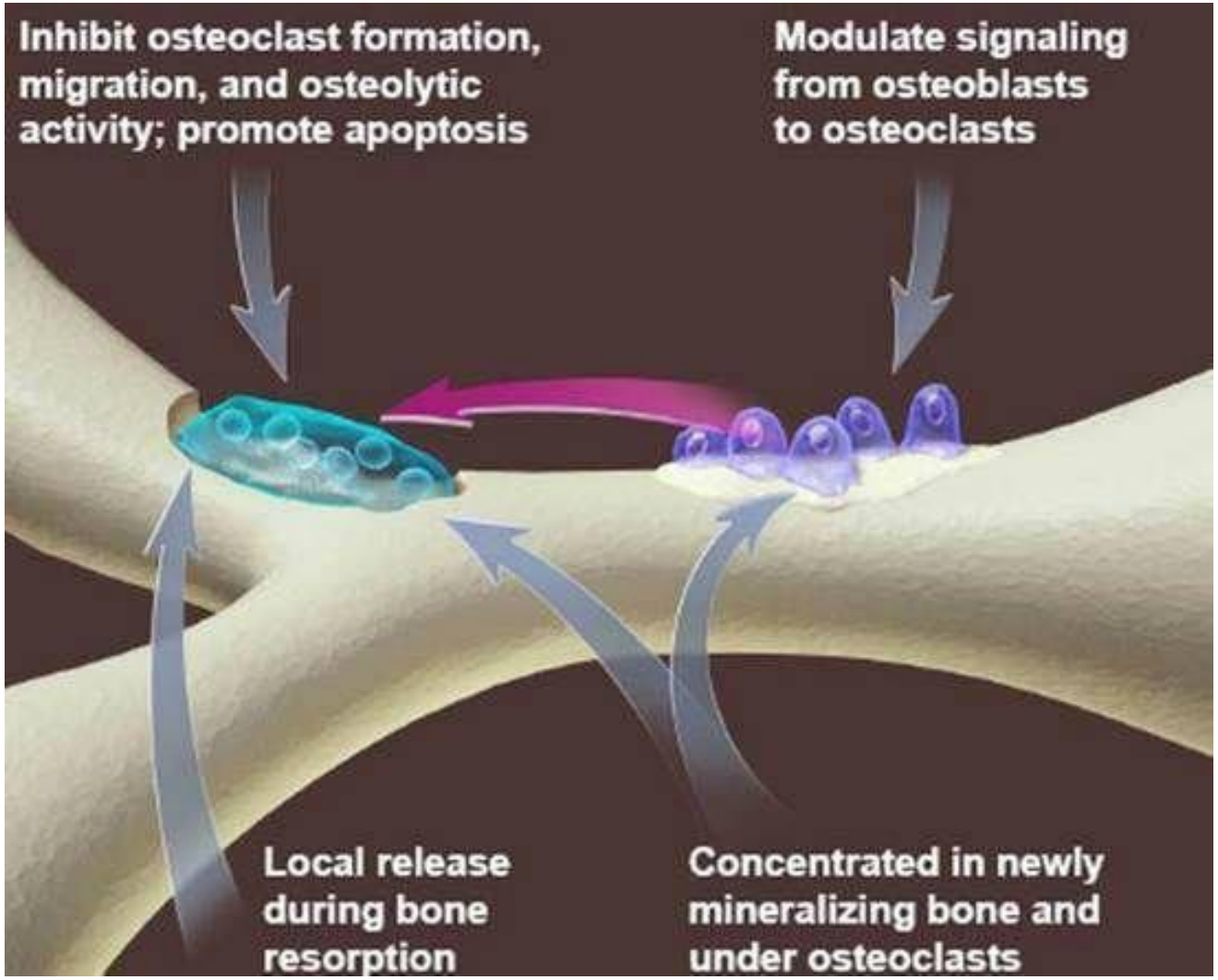
J Clin Oncol 3…



Treatment of pain due to bone metastases: *bone targeted therapies* (ESMO GLs)



ZA (Zoledronic Acid)



International Journal of Molecular Sciences

MDPI

Review

Bone Pain in Cancer Patients: Mechanisms and Current Treatment

Renata Zajączkowska [1,*], Magdalena Kocot-Kępska [2,*], Wojciech Leppert [3] and Jerzy Wordliczek [1]

Bisphosphonates have a direct apoptotic effect on osteoclasts. They inhibit their differentiation and maturation and reduce bone pain and the use of analgesics.

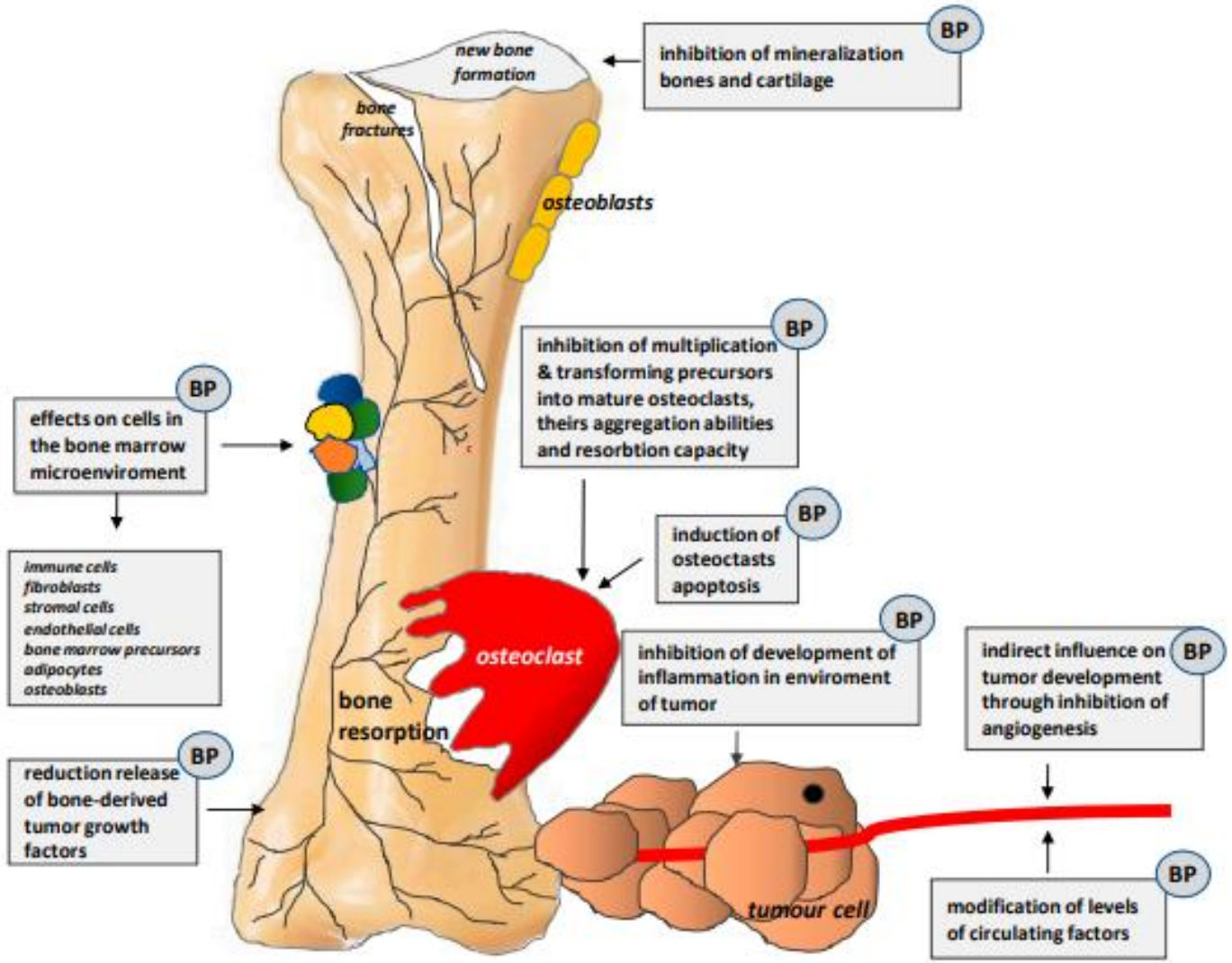


Figure 6. Mechanisms of action of bisphosphonates (BPs) (According to [13]).

Modif. da: Figura, N. et al.Mechanisms of, and Adjuvants for, Bone Pain. Hematol. Oncol. Clin. N. Am. 2018, 32, 447–458

Tanezumab e l'NGF

International Journal of *Molecular Sciences*

MDPI

Review

Bone Pain in Cancer Patients: Mechanisms and Current Treatment

Renata Zajączkowska [1,*], Magdalena Kocot-Kępska [2,*], Wojciech Leppert [3] and Jerzy Wordliczek [1]

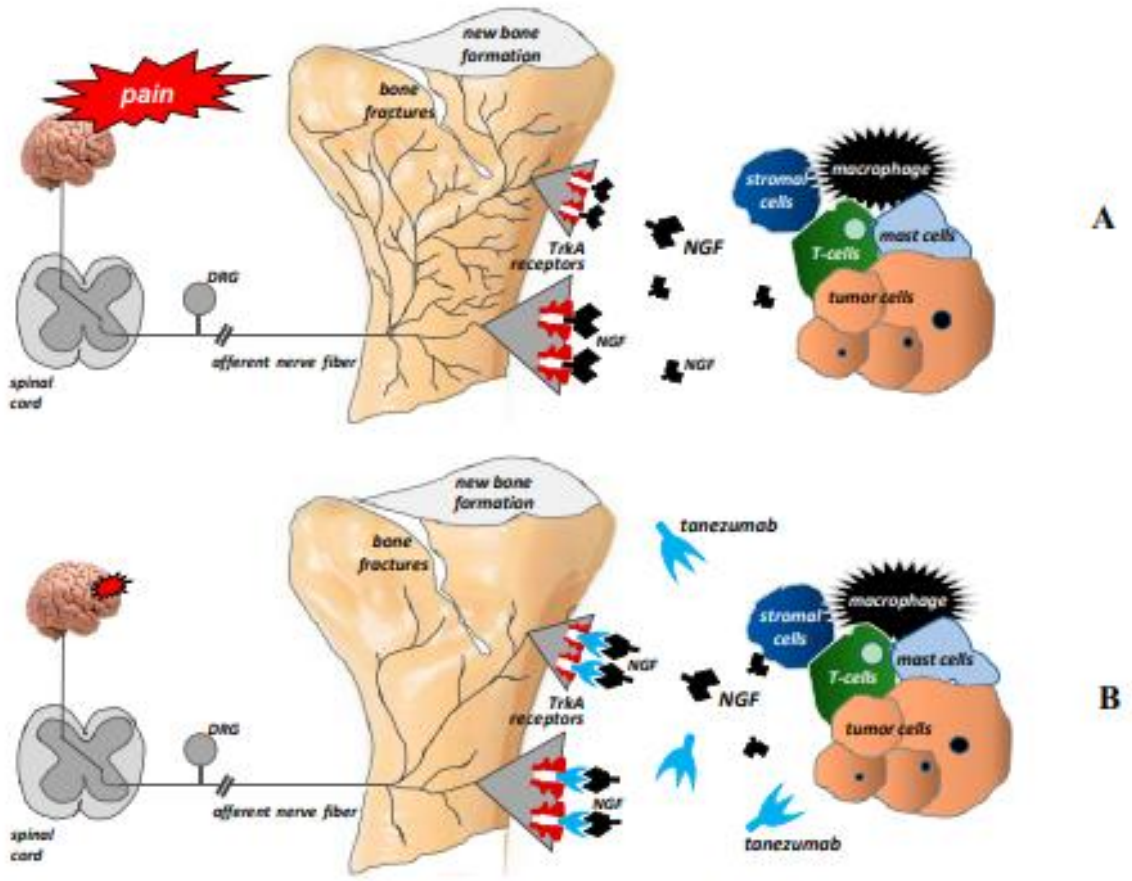


Figure 4. Pathological nerve sprouting in bone metastases and the mechanisms of action of tanezumab (according to [42]). After binding to the TrkA receptor, nerve growth factor (NGF) activates the pathological formation and growth of a network of new nerve fibers characterized by a unique morphology, organization, and density, which exceeds the density of nerve fibers in normal bone by up to 10–70 times. These new pathological nerve fibers are formed within the periosteum, mineralized bone tissue, and bone marrow (**A**). Tanezumab, a humanized anti-NGF monoclonal antibody, prevents NGF from binding to the TrkA receptor and consequently inhibits the pathological sprouting and formation of new pathological nerve fiber networks (**B**).

International Journal of Molecular Sciences

MDPI

Denosumab e l'asse RANKL/RANK

Review

Bone Pain in Cancer Patients: Mechanisms and Current Treatment

Renata Zajączkowska [1,*], Magdalena Kocot-Kępska [2,*], Wojciech Leppert [3] and Jerzy Wordliczek [1]

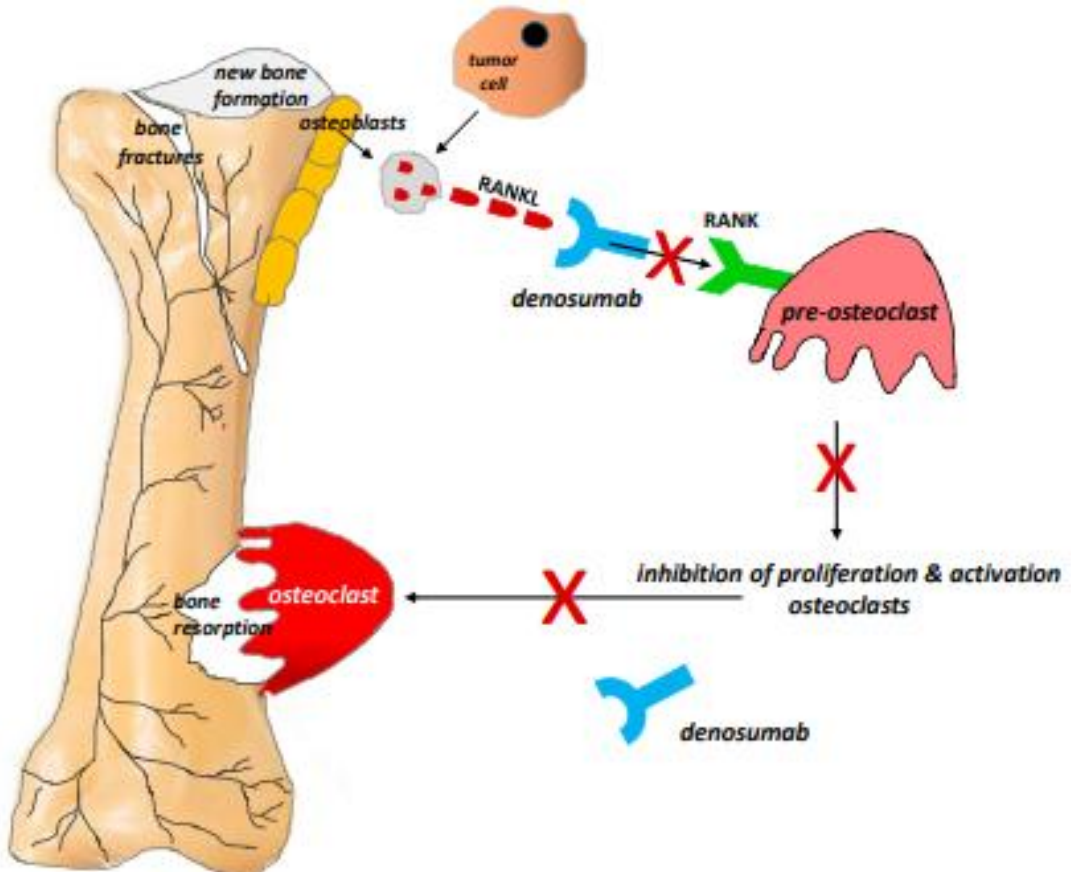
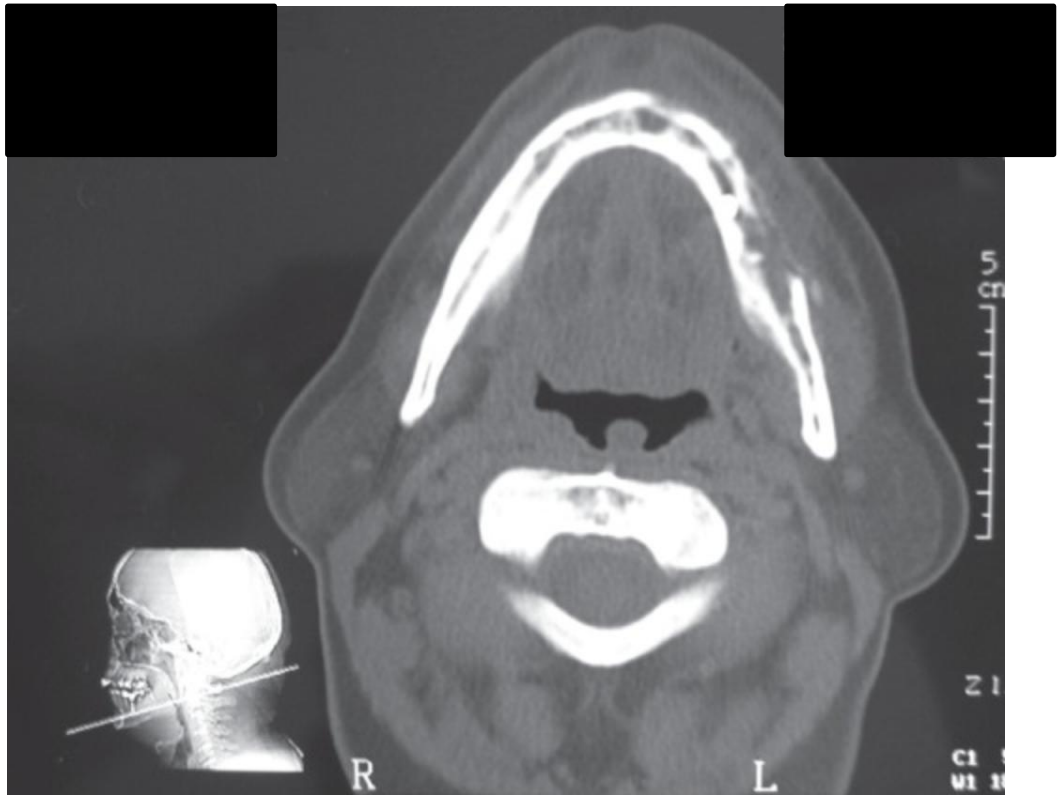


Figure 3. Role of the RANKL/RANK system and the mechanism of action of denosumab in bone pain due to cancer (According to [12]). RANKL is a protein secreted by tumor cells and the osteoblastic cell line (i.e., by mature osteoblasts and their precursors). RANKL binds to RANK receptors located on the osteoclast surface, which triggers the proliferation and maturation of osteoclasts, thereby initiating their damaging effect on bones. Denosumab is characterized by a high affinity and specificity for RANKL. It prevents the activation of RANK receptors on the surface of osteoclasts and their precursors, thereby inhibiting the formation, proliferation, and survival of osteoclasts, which reduces osteoclastic bone resorption. **X** = stop.

Il rischio ONJ è dietro l'angolo. Effettuare SEMPRE videat odontoiatrico ed eventuale bonifica del cavo orale!!

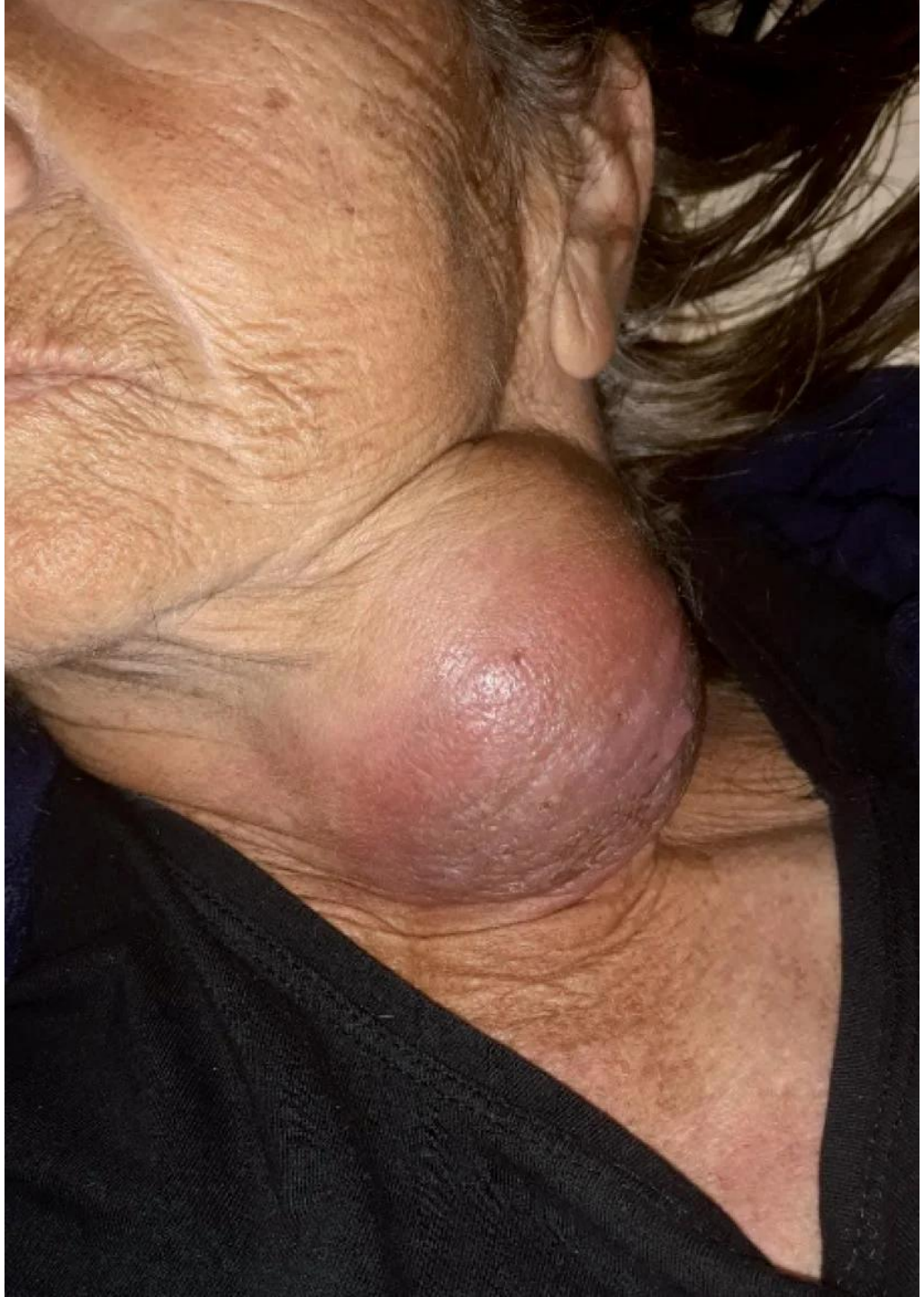


Fusco V. Expert Opin Drug Saf. 2016

Chronic pain syndromes directly related to cancer

Neuropathic pain syndromes

Leptomeningeal metastases
Malignant painful radiculopathy
Painful cranial neuralgias
Radiculopathies
Plexopathies
Painful peripheral mononeuropathies
Paraneoplastic sensory neuropathy



DOLORE NEUROPATICO IATROGENO

- Derivati della vinca
- Platino e derivati
- Taxani
- Bortezomib
- Talidomide

- Flogosi, fibrosi, necrosi post-attiniche

- Post-toracotomia
- Post-mastectomia
- Post-amputazioni

Caraceni A, Portenoy RK; Working Group of the IASP Task Force on Cancer Pain. Pain 1999
Urch CE, Dickenson AH. Neuropathic pain in cancer. Eur J Cancer. 2008;44:1091–6.

Chronic pain syndromes associated with cancer treatment

Chemotherapy-related pain syndromes / *Immunotherapy ?*
Hormonal therapy-related pain syndromes
Radiation-related pain syndromes
Surgical pain syndromes

Chemotherapy-induced peripheral neuropathy CIPN

Type of Drug	Target / Mechanisms / Drug effects	Neuropathy type
Vinca Alkaloids • Vincristine • Vinblastine • Vinorelbine • Vinflunine • Vindesine	• Microtubule disrupting agents • Interfere with mitotic spindle formation/function leading to mitotic arrest • Interfere with formation of cytoskeleton and axoplasmic flow leading to impaired axonal transport (axonopathy) with "dying back" • Dorsal root ganglion toxicity with necrosis of neurons	• Sensory • Motor • Autonomic
Platinum agents • Cisplatin • Carboplatin • Oxaliplatin • Nedaplatin • Lobaplatin • Heptaplatin	• Platinum-containing compounds can covalently couple to methionine- cysteine- and histidine- containing peptides or proteins including α- and β-tubulin interfering with their polymerization and function • Some have suggested cisplatin can block tubulin assembly via a two-step binding to GTP in the GTP center of tubulin • Cross link DNA and interfere with its repair and replication • Platinum compounds accumulate in and lead to apoptosis of neurons in dorsal root ganglia • Platinum compounds can lead to mitochondrial dysfunction by oxidative stress	• Sensory, large fiber • Sensory, small fiber
Taxanes • Paclitaxel • Docetaxel • Cabazitaxel • Nab-paclitaxel (nanoparticle albumin bound paclitaxel)	• Microtubule stabilizing agents • Interfere with cell division by disrupting mitotic spindle • Interfere with cellular transport, by stabilizing microtubules, preventing depolymerization leading to distal sensory axonal degeneration	• Sensory, large fiber •Sensory, small fiber • Motor involvement typically minimal unless at an unusual high dose

Prevalence of CIPN [1]

Number of months after chemotherapy	Number of studies included	Number of patients included	Prevalence of CIPN(95% CI)
≤1	22	2,085	68.1% (57.7 – 78.4)
3	5	234	68.1% (57.7 – 78.4)
≥6	4	1,860	30.0% (6.4 – 53.5)

The prevalence of CIPN is dependent on the type of malignancy, drug regimen, cumulative doses, duration, synergistic neurotoxicity from prior chemotherapy, comorbidities, and other risk factors

S. Zhang/Seminars in Oncology 48 (2021)

Immunotherapy-induced pain

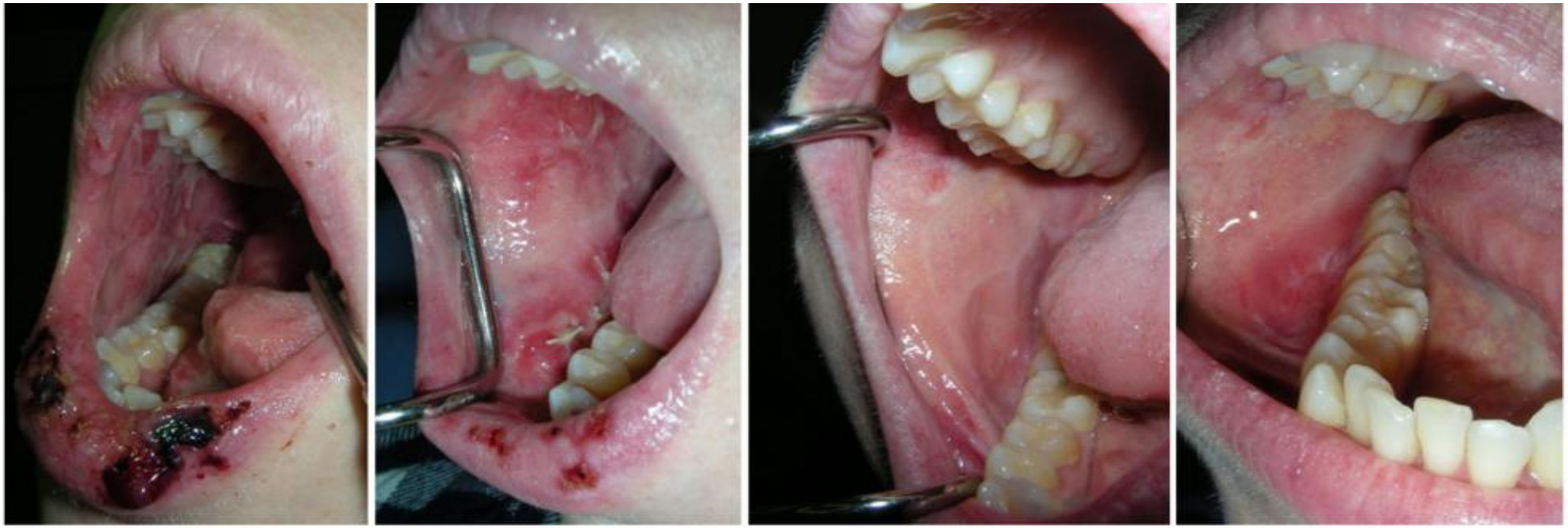


Figure 2. Lichenoid lesions and lip crusts in a patient treated for melanoma with a single dose of Nivolumab + Ipilimumab, and then with another 4 doses of Nivolumab (A3). There was prompt, complete resolution of the oral lesions with systemic and topical steroids. The lesion recurred 2 months following discontinuation of the immunotherapy.

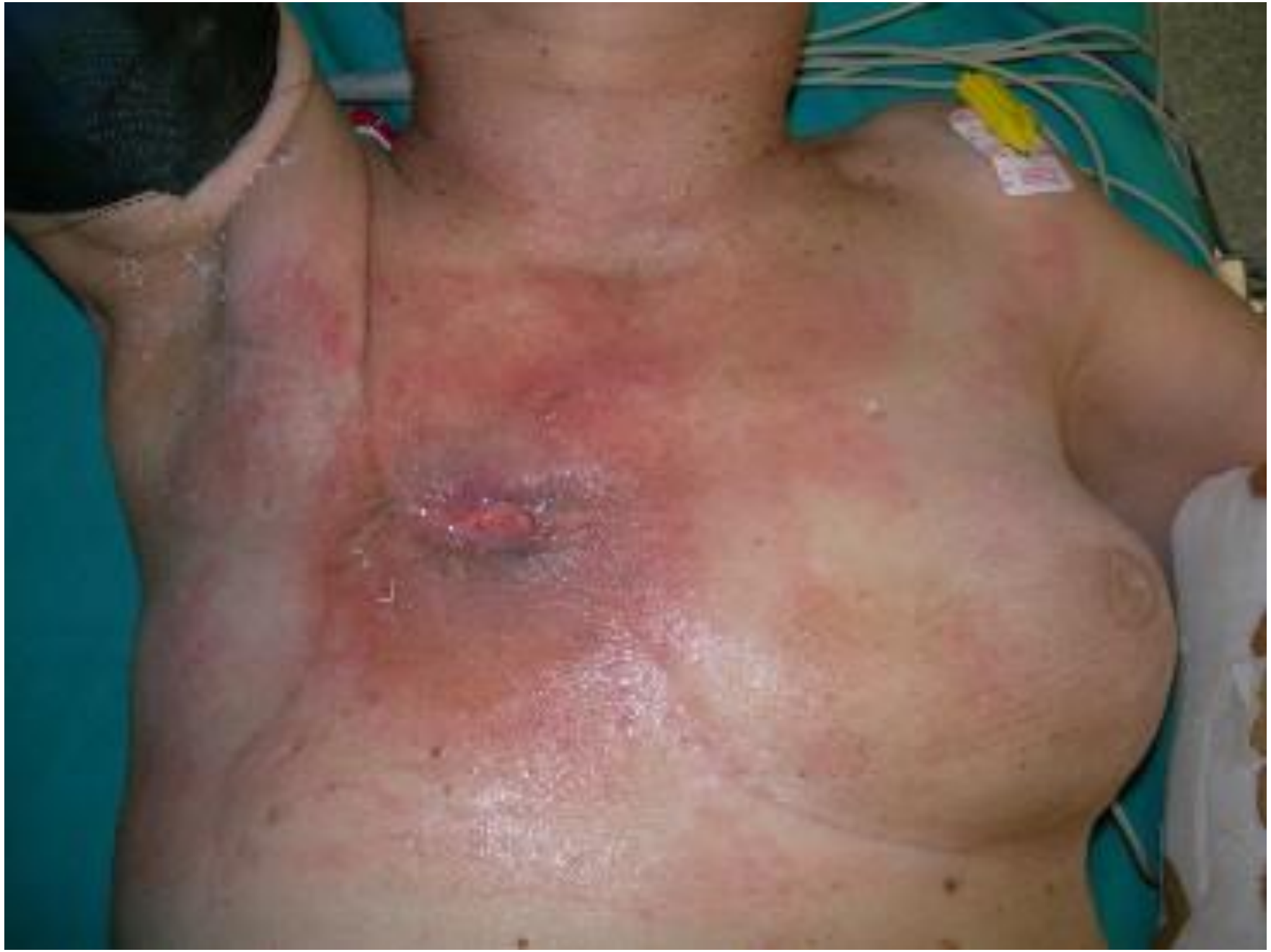
Elad S, et al. Immunotherapy-Related Oral Adverse Effects: Immediate Sequelae, Chronicity and Secondary Cancer. Cancers (Basel). 2023 Sep 28;15(19):4781. doi: 10.3390/cancers15194781. PMID: 37835475; PMCID: PMC10571987.

«*Dolore procedurale*»
DA TERAPIE

Dolore da radioterapia

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

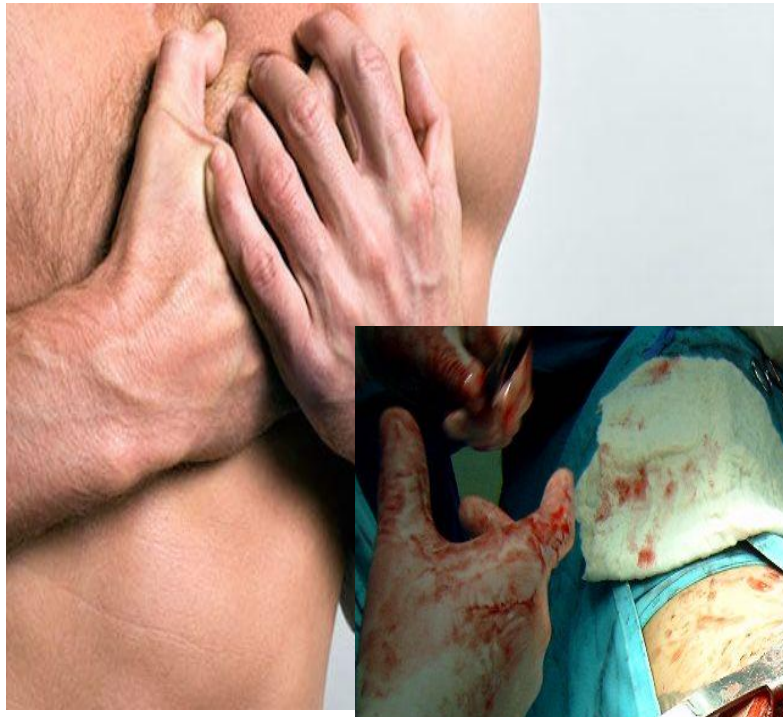
Radiation therapy-related pain	
Acute phase	Acute mucosal inflammation: stomatitis, pharingitis, oesophagitis, enteritis, proctitis, etc.
	Radiation dermatitis
	Pain flare effect
	Procedural pain: brachytherapy; implantation of 'fiducial markers' in an organ for image-guided radiotherapy; passive mobilization of bone metastatic patient during simulation and treatment
Late phase	Radiation fibrosis syndrome
	Osteoradionecrosis of the jaw
	Chest wall pain
	Oesophageal stricture
	Abdominal pain due to bowel spasms
	Urethral pain
	Dyspareunia
	Anal stricture

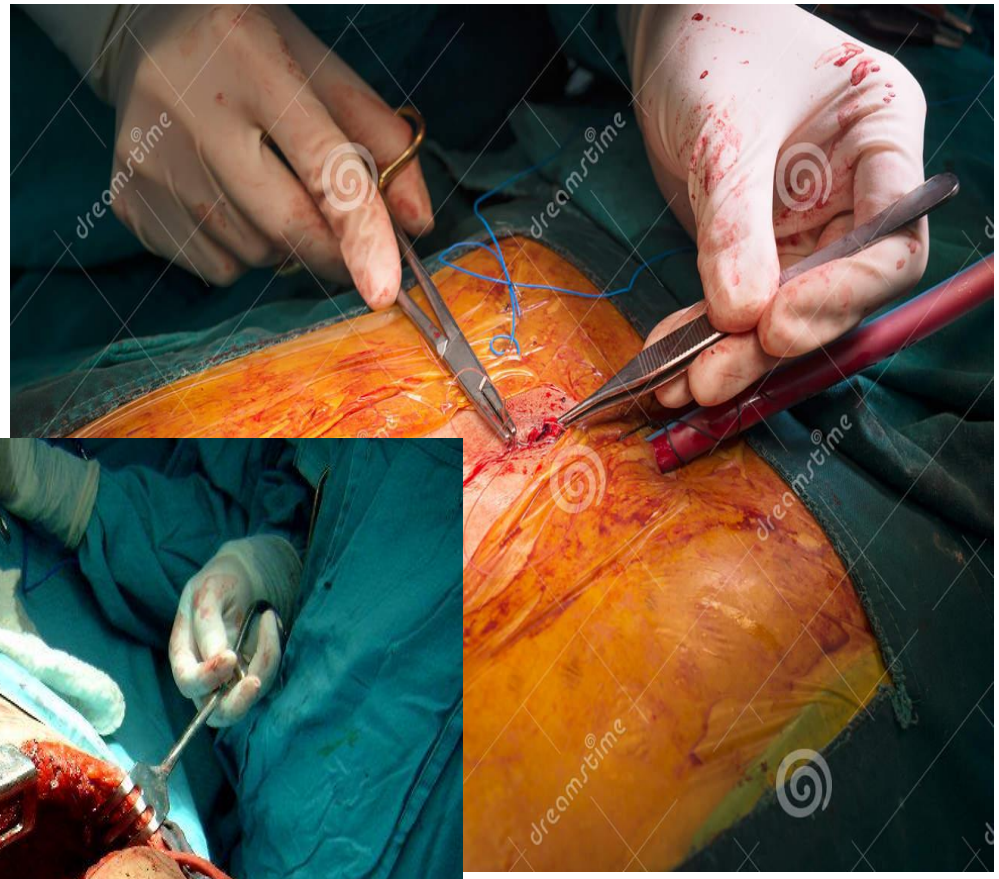


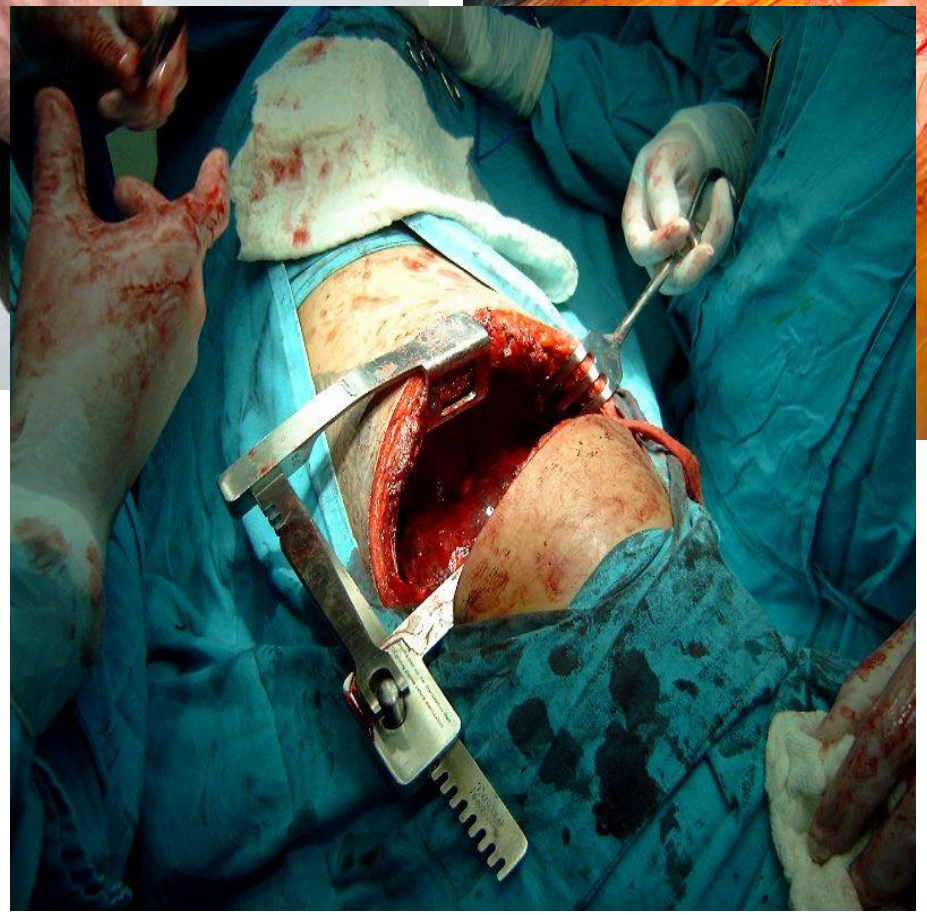
«Dolore procedurale»
DA TERAPIE
Dolore post chirurgia

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

Type of post-surgical pain	Main associations
Breast surgery pain syndromes	Either from wide local excision, breast-conserving surgery, or radical mastectomy. Particularly common with axillary dissection
Post-radical neck dissection	Poor predictive factors
Post-thoracotomy	Poor predictive factors
Post-operative frozen shoulder	Post-thoracotomy and post-mastectomy at particular risk
Phantom pain syndromes	After limb amputation
Post-surgical pelvic floor myalgia	Poor predictive factors







Dolore post chirurgia: Epidemiologia

Incidenza di dolore neuropatico post-operatorio:

- Amputazioni 30-50 %
- **Toracotomie 30-40 %**
- **Mastectomie 20-30 %**
- Ernia inguinale 10 %
- Colecistoctomie 27 %
- Failed back surgery syndrome 40 %
- Safenectomie 27 %

In riduzione con tecniche di anestesia LR?

Kehlet H, Jensen TS, Woolf CJ. Persistent postsurgical pain: factor and prevention. Lancet 2006; 367: 1618-25.

Shipton E. Post-surgical neuropathic pain. ANZ J Surg 2008; 78: 548-55. Perkins FE, Kehlet H. Chronic pain as an outcome of surgery. Anesthesiology 2000; 93: 1123-33.

Dolore post chirurgia: Epidemiologia

Dolore nell'area dell'intervento chirurgico che persiste per molti **mesi o anni** oltre il consueto corso di guarigione naturale di un dolore acuto. E' diverso dal dolore pre-operatorio.

Caratteristiche prevalentemente **neuropatiche**, spesso associato a parestesia, iperalgesia e allodinia

Meccanismi etiopatogenetici:

- Lesioni traumatiche di nervi (sezione, ischemia, intrappolamenti)
- Trazione strutture anatomiche
- Intolleranza di impianto protesico
- Sindromi aderenziali addominali
- Sacrificio di strutture anatomiche non necessariamente interessate da malattia.

Dobrogowski J, Przeklasa-Muzy□ska A, Wordliczek J. Persistent post-operative pain. Folia Med Cracov 2008; 49: 27-37.

Finnerup NB, Sindrup SH, Jensen TS. Chronic neuropathic pain: mechanisms, drug targets and measurement. Fundam Clin Pharmacol 2007; 21: 129-36.

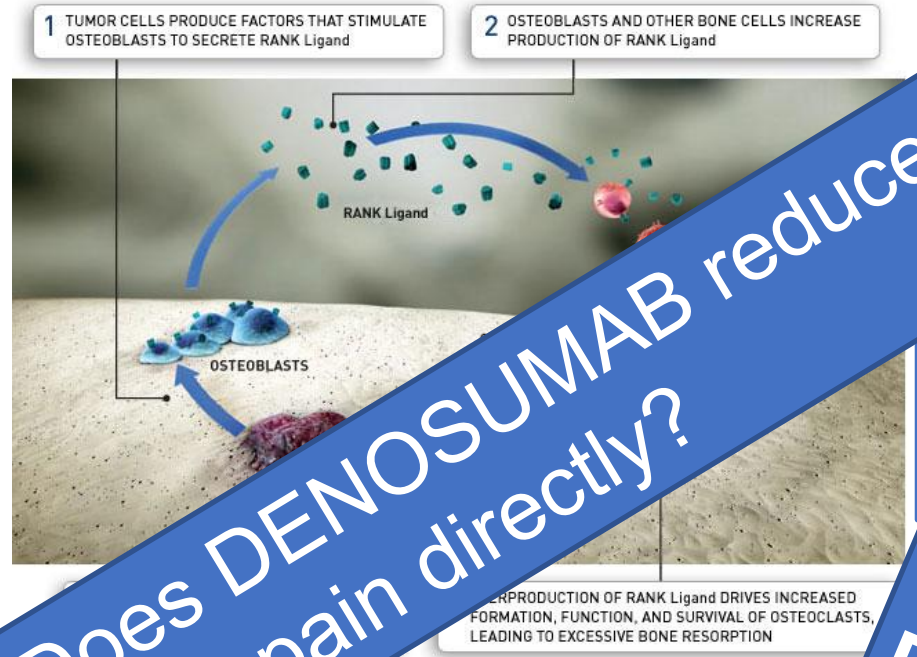
Elon E. Post-surgical neuralgia. Pain 2004; 111: 3-7.

The dark side of the moon…

«Dottore, mi creda, avrei preferito tenere il tumore, piuttosto di avere tutto questo dolore»

Enzo F., 51 anni, 2015; Enrico D., 54 anni, 2016…

Hypotheses, novelties and future perspectives



OUS CYCLE
NE
UCTION

- ble pain
-

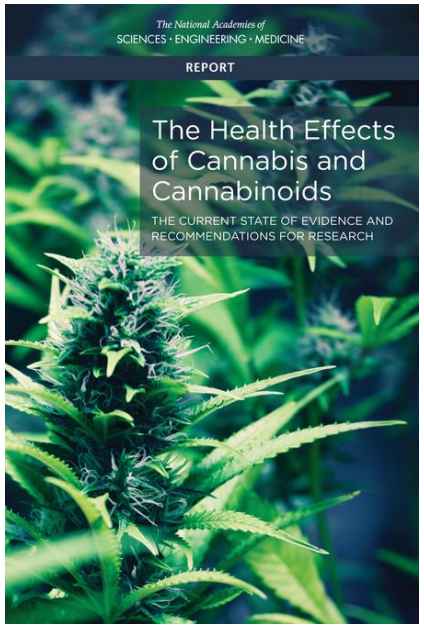
- osteclast
- Denosumab interferes with RANK/RANKL pathway
- Den reduces SREs that are pain producers

Does DENOSUMAB reduce bone pain directly?

Could the promotion of osteoclasts (**NGF Producers**) dysfunction and apoptosis lead to a lowering of NGF levels?

Clohisy DR. et al. Orthop Relat Res 2000
Clezardin P. et al. Cancer Res 2005
Lipton A. et al. Curr Opin Support Palliat Care 2008

Role of cannabinoids in the treatment of bone pain

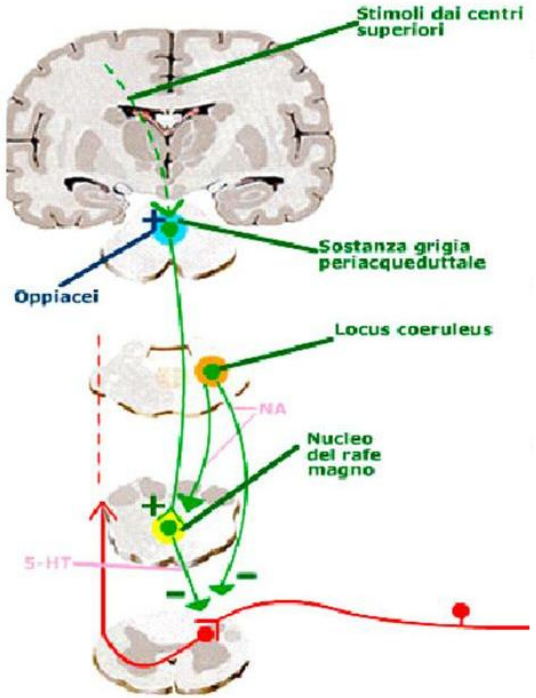


In 2017, The National Academies of Sciences, Engineering, and Medicine published a statement that

- the use of cannabis for the treatment of pain is supported by well-controlled clinical trials
- there is substantial evidence that cannabis is an effective treatment for chronic pain in adults.

Committee of the Health Effects of Marijuana . An evidence review and research agenda. The health effects of cannabis and cannabinoids. The current state of evidence and recommendations for research. Washington, DC: The National Academies Press; 2017.

Phytocannabinoids and pain



In pain, cannabinoids act at different levels of the sensitive pathways:

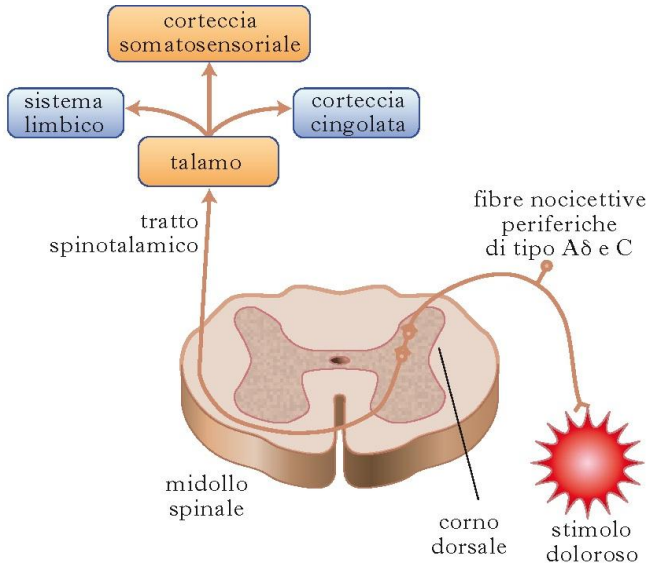
at the spinal level with activation of K receptors for opioids;

at the level of the periaqueductal gray matter (mesencephalic area particularly rich in opiate receptors, fundamental station of the descending inhibitory pathways) with the inhibition of GABA and glutamate, the effect of dopamine D2 receptors

Cichewicz DL, Martin ZL, Smith FL et al. J Pharmacol Exp Ther 1999.

Enhancement mu opioid antinociception by oral delta9-tetrahydrocannabinol: dose-response analysis and receptor identification.

Cichewicz DL, Martin ZL, Smith FL et al. J Pharmacol Exp Ther 1999.



Aδ: CBD1 receptors

C: Mu (opioids) receptors

Cannabinoids have been shown to be more effective in the treatment of neuropathic pain: it is hypothesized that the Aδ fibers, which are myelinated, of small caliber, are more closely related to the mechanoreceptors that detect the tactile sensation to the pressure and are present only in the skin. On these fibers there is a prevalence of cannabinoid receptors

compared to those for opioids that are higher in C fibers.

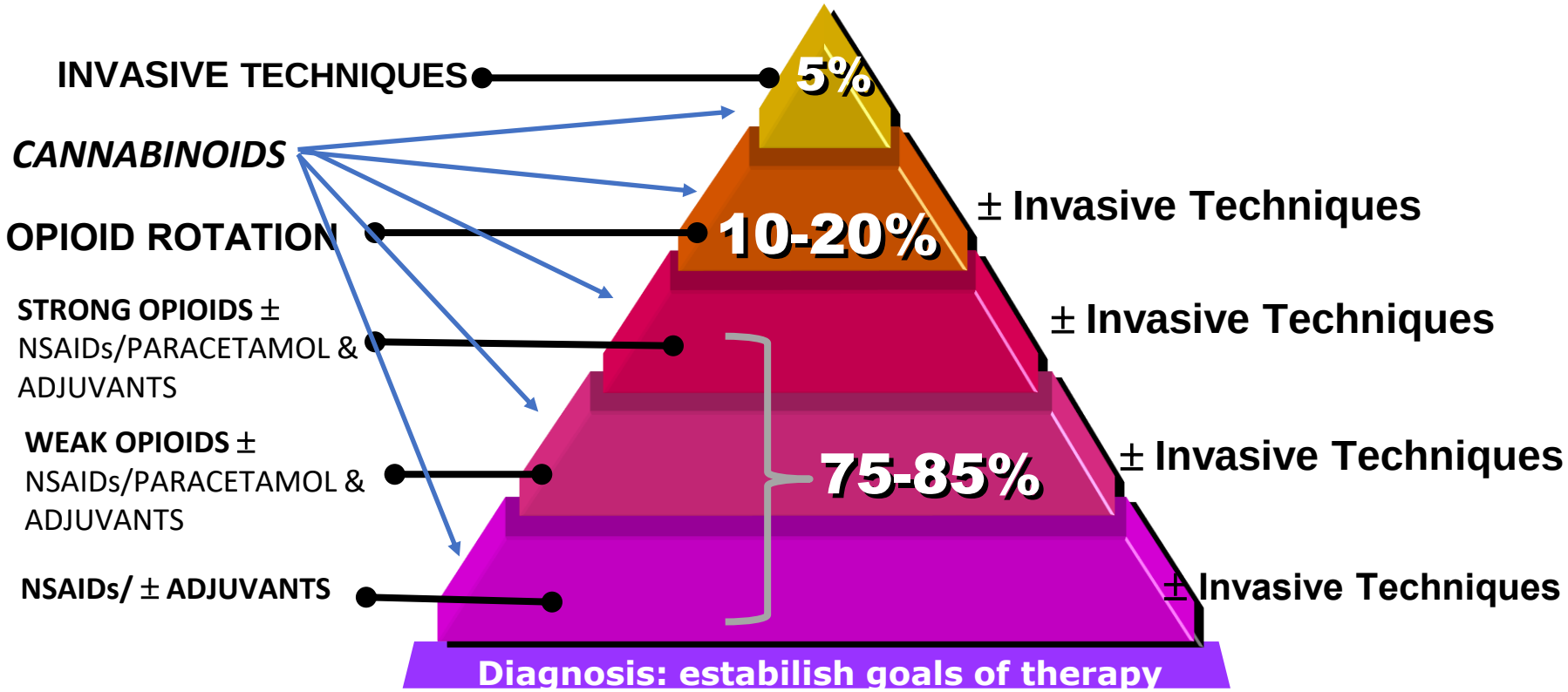
Cichewicz DL, Martin ZL, Smith FL et al. J Pharmacol Exp Ther 1999.

Medical cannabis treatment for breakthrough pain

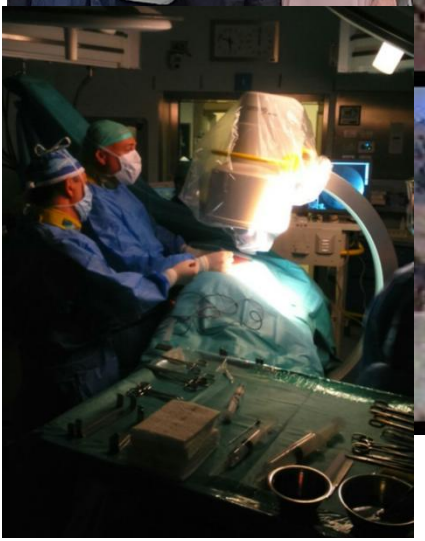
- BTcP: consider inhaled medical cannabis
- Dried flower vaporization is the referred mode of administration
- Smoking cannabis is associated with inflammation of the airways bronchitis, respiratory infections.
- When using medical cannabis to manage breakthrough pain, a balanced THC:CBD or THCpredominant product may be used as needed

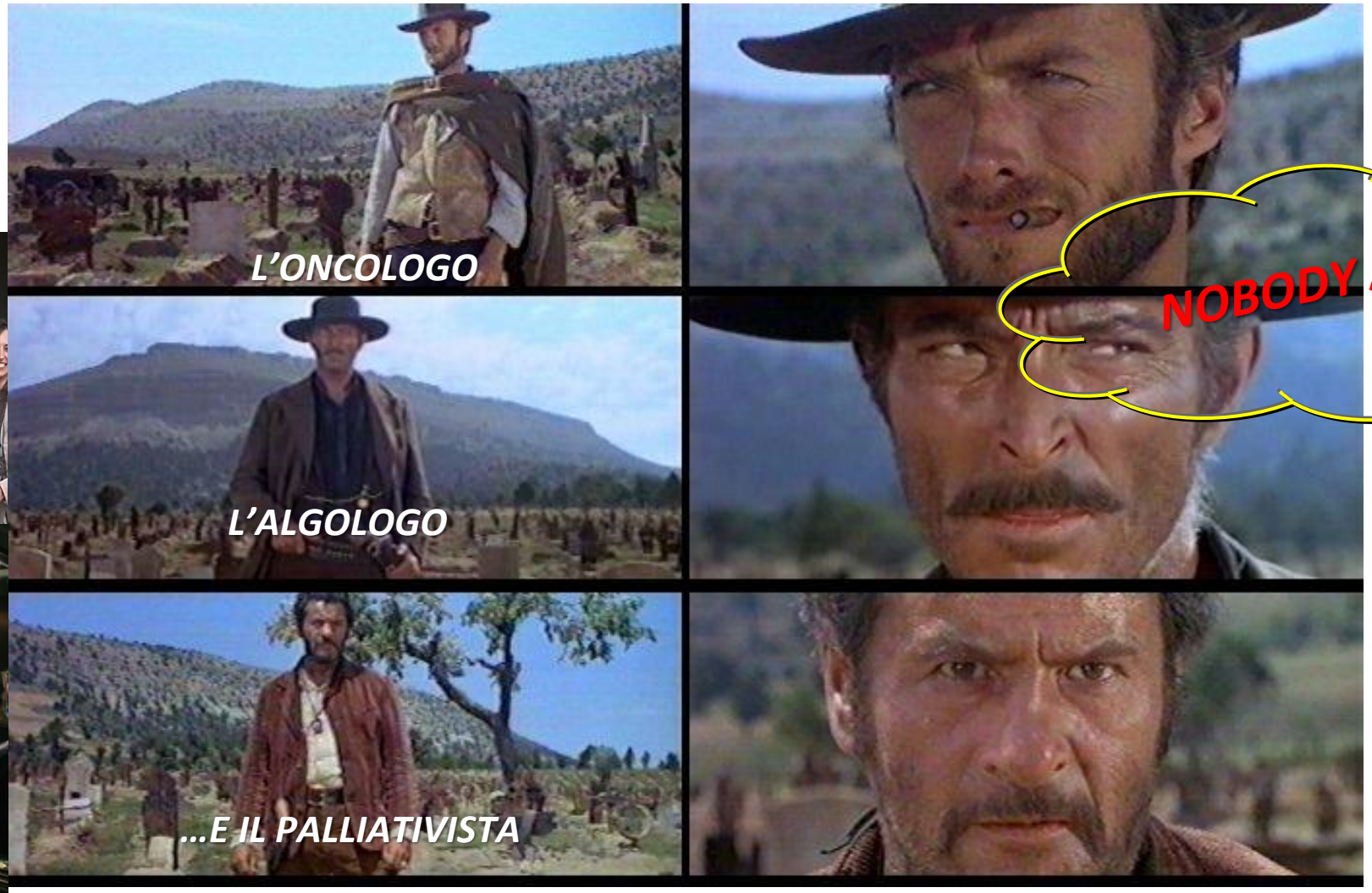
LA SCALA ANALGESICA W.H.O. NEL 21° SECOLO

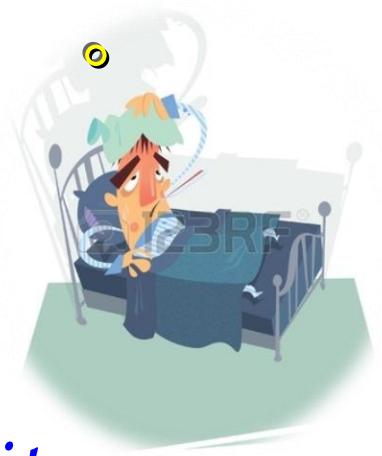
World Health Organization



Modif. from: Study group of Italian Society of Anaesthesiology, 2002;
http://www.who.int/cancer/palliative/painladder/en/index.html







vittorio.guardamagna@ieo.it