

PAIN MANAGEMENT OF PATIENTS WITH HEAD AND NECK CANCER IN PALLIATIVE CARE: A LITERATURE REVIEW

CONTROLE DE DOR DE PACIENTES COM CÂNCER DE CABEÇA E PESCOÇO EM CUIDADOS PALIATIVOS: UMA REVISÃO DE LITERATURA

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ABSTRACT

Patients with head and neck cancer (HNC) display limitations and functional impairments. Orofacial pain affects the majority of these patients and may be caused by various factors, both in soft and hard tissues. Patients with advanced stage HNC need to be assisted in a way that promotes quality of life for them and their relatives, as a form of palliative care, especially when the disease is no longer likely to be controlled. Pharmacological analgesia is the backbone of the treatment of cancer pain, but it can also be carried out through non-pharmacological therapies. This study aimed at reviewing the literature and seeking the different pathways to control orofacial pain in patients with HNC in palliative care. Searches in the PubMed and SciELO databases were performed with the words "(pain control) AND (palliative care) AND (head and neck cancer)," aiming to find papers published through the last ten years (2011-2021) and restricting them to clinical trials and randomized clinical trials. We found ten articles in the PubMed database and none in SciELO. After reading their titles and abstracts, we excluded five of them since they did not evaluate patients with HNC nor did they have the analgesic approach as a study objective; therefore, five papers were included in our review. Most studies have shown that analgesia in patients in palliative care affected by malignant head and neck injuries happens with opioids. In this review, we observed a few clinical trials, and further studies must be carried out to seek new ways to reduce symptoms and improve the quality of life of these patients.

KEYWORDS: Mouth Neoplasms; Cancer Pain; Pain Management; Pain Measurement; Palliative care; Analgesia

RESUMO

Pacientes com câncer de cabeça e pescoço (CCP) apresentam limitações e comprometimentos funcionais. A dor orofacial acomete grande parte desses pacientes e pode ser causada por inúmeros fatores, tanto nos tecidos moles quanto nos duros. Pacientes com CCP em estágio avançado, necessitam receber assistência que possibilite melhor qualidade de vida para ele e seus familiares, como forma de cuidado paliativo, principalmente quando a doença não tem mais chance de ser controlada. A analgesia farmacológica é o principal pilar no tratamento da dor oncológica, mas também pode ser realizada por meio de terapias não farmacológicas. Este estudo teve como objetivo revisar a literatura buscando as diferentes formas de controle da dor orofacial de pacientes com CCP em cuidados paliativos. Foram realizadas buscas nas bases de dados PubMed e SciELO com as palavras "(pain control) AND (palliative care) AND (head and neck cancer)", buscando artigos dos dez últimos anos (2011-2021) e restringindo para ensaios clínicos e ensaios clínicos randomizados. Encontramos dez artigos na base PubMed e nenhum na SciELO. Após a leitura do título e resumo, excluímos cinco por não avaliarem pacientes com CCP ou não terem a abordagem analgésica como objetivo do estudo, sendo incluídos finalmente 5 artigos em nossa revisão. A maioria dos estudos mostrou que a analgesia realizada nos pacientes em cuidados paliativos acometidos por lesões malignas de cabeça e pescoço acontece com opioides. Nesta revisão observamos poucos estudos clínicos, sendo importante a realização de trabalhos que busquem novas formas de diminuir os sintomas e melhorar a qualidade de vida desses pacientes.

PALAVRAS-CHAVE: Neoplasias bucais; Dor do câncer; Manejo da dor; Medição da dor; Cuidados paliativos; Analgesia.

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INTRODUCTION

Patients with head and neck cancer (HNC), especially after it reaches their oral cavity, display severe limitations and functional impairments. When the injury does not present forms of treatment, palliative care (PC) may be applied. In these cases, the symptoms may worsen, requiring case-by-case special attention(1). PCs seek to better the quality of life of patients and their relatives because of threatening diseases, through the prevention and relief of suffering(2). The principles of palliative care are: to promote relief of pain and other distressing symptoms; to affirm life and recognize death as a natural process; not to seek to anticipate or postpone death; to integrate psychological and spiritual aspects as part of patient care; to offer a support system to aid the patient in living as actively as possible until death; to offer a support system to the family that allows it to take care of the patient until the end(3).

Orofacial pain may be caused by various diseases or abnormalities in the soft and mineralized tissues of the oral cavity and face. These include temporomandibular dysfunction, trigeminal neuralgia, burning mouth syndrome, oral-dental infections, and cancer(4). Pain is a symptom that 80% of patients with cancer experience in the last year of their lives, and a quarter of them experience severe pain(5,6). Patients with HNC in PC display severe functional restrictions. In such a condition, symptoms may worsen and are not always curable, requiring special attention and care(7). The more frequent oral symptoms are pain, dysphagia, bleeding, trismus, tumor wounds, opportunistic infections, drooling, xerostomia, malnutrition, dehydration, anorexia, and disfigurement(1). In cases of advanced oral cancer, pain, ulceration, bleeding, and trismus are the most relevant symptoms(8).

When pain is caused by a malignant injury, it occurs as the disordered growth of tumor cells may lead to harmful, neurological, inflammatory, and ischemic components that cause cancer pain. Peripheral phenomena are the result of the sensitization of inflammatory mediators of primary afferent neurons. Additionally, there are a few central mechanisms (spine and supraspinatus) that can affect pain. Pain can be caused by the direct action of the tumor (related to tumor invasion) or by treatment (mucositis caused by chemotherapy and radiotherapy) and is an unpleasant, emotional, and sensitive experience, unique, associated with actual or subjective tissue damage(9). It means, thus, that pain is an individual and unique experience, altered by previous knowledge about the damage that the patient may have experienced or imagined - any situation that the patient refers to

and describes. Therefore, for correct treatment, a complete evaluation is crucial(10).

In such a way, to promote relief of pain and other symptoms, it is necessary to have specific knowledge of the patient's condition for prescribing drugs, adopting non-pharmacological measures, and addressing the spiritual and psychological aspects that characterize the "total symptom." Thus, the concept of "total pain" created by Dame Cicely Saunders is taken into account, in which all of these factors may contribute to the exacerbation or attenuation of symptoms, and care must be focused on its multifactorial form and taken into consideration in the approach towards the patient in PC with HNC (11,12).

The World Health Organization (WHO) created, in 1986, the first protocol for the management of cancer pain considering the "analgesic ladder." The tactic was to assess and adapt the drug management according to the need of the patient, moment by moment, sequentially, and progressively. The aid in the reduction of symptoms can be around 70 to 90% of cases with the proposed method(13,14). Pharmacological analgesia is the backbone of the treatment of cancer pain. The basic principles of the analgesic ladder are points by mouth and by clock (concerning administration intervals), a treatment that must be personalized for each patient, with continuous evaluation throughout it and frequent reassessments that may allow dose readjustments more efficiently, as well as more accurate diagnoses concerning pain(15).

In addition to the possibility of controlling pain with pharmacological analgesics, there is the use of non-pharmacological therapies, including relaxation, distraction, directed imagination techniques, acupuncture, massage therapy, etc (10,16). This study aimed at reviewing the literature and seeking the different pathways to control orofacial pain in patients with HNC in PC.

LITERATURE REVIEW

A search was carried out in the PubMed and SciELO databases with the words "(pain control) AND (palliative care) AND (oral cancer)" and "(pain control) AND (palliative care) AND (head and neck cancer)." The search was limited to the period of the last ten years (2011-2021) and restricted to clinical trials and randomized clinical trials.

The variables of the articles were analyzed, such as study type, the number of patients evaluated, forms of analgesia, forms of pain measurement, possible side effects, and results found. In the search for "(pain control) AND (palliative care) AND (oral cancer)," we found 39 papers in PubMed and five in SciELO, but none of them met the inclusion criteria of our review. As for the words "(pain

control) AND (palliative care) AND (head and neck cancer),” we found ten articles in PubMed and none in SciELO (Figure 1). After reading their titles and abstracts, we excluded five of them since they did not evaluate patients with HNC nor did they have the analgesic approach as a study objective.

Among the papers that were selected, we extracted information on the study site, study design, the number of patients studied, the form of analgesia tested, how symptoms were measured, possible side effects, and results obtained by the study (Table 1). The year of the studies ranged from 2015 to 2020, two of them from 2018. The studies’ sites included India, Italy, and London, and two of them were from the Netherlands.

Four out of the five papers analyzed were controlled, randomized clinical trials and only one was a clinical trial. How patients’ pain was measured varied in all studies of the different research groups, namely: Numerical Rating Scale (NRS-11)(17), Brief Pain Inventory (BPI), which is a numerical rating scale filled by the patient (18,19). Leeds assessment of neuropathic symptoms and signs (S-LANSS fillable by the patient) (20), and the Visual Analogue Scale (VAS) for self-assessment(21). The only study that reported side effects was the one that tested Fentanyl *versus* Methadone in 82 patients(19), finding out that 72% of those evaluated reported dry mouth. All of the other studies did not report the presence of adverse effects.

In the study of Kashyap *et al.*, 2020, 80 patients were included, sectored into two different groups

of 40 each. The control group received the usual treatment with oral opioids (morphine and tramadol), while the experimental group, in addition to opioids, received Scrambler therapy (ST)(17). As a result, a decrease in pain was found in both groups, but the control group experienced a higher intensity of pain. In the studies by Haumann *et al.*, 2016 (12) and Haumann *et al.*, 2018 (13), the results of Fentanyl and Methadone treatments were assessed. In the 2016 paper, 52 patients were included, 26 in each group, and the results were significantly better for the Methadone group compared with the use of Fentanyl in cases of neuropathic pain treatment. As for the 2018 paper, 82 subjects were included—40 in the Fentanyl group and 42 in the Methadone one. It was found that Methadone is not inferior to Fentanyl in the treatment of nociceptive pain.

Regarding the study conducted by Williams *et al.*, (2015) (14), 156 patients were included—75 in the experimental group and 74 in the control group. The study’s objective was to provide the experimental group with a pain treatment protocol, with a weekly adaptation of medications, regular visits, association with an educational program, and guidance on pain, whereas individuals in the control group were kept with the usual care. When comparing the results between the groups, no difference was found in the pain severity index. However, the experimental group presented better comfort, greater adherence, and fewer complaints.

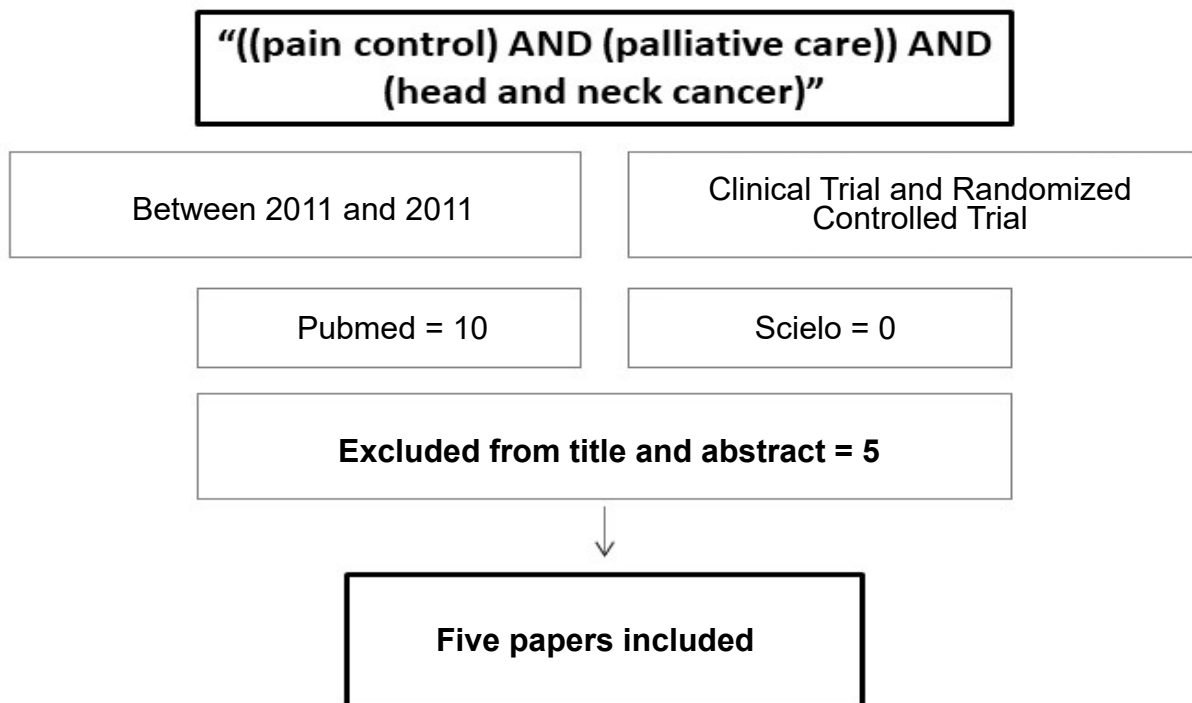


Figure1. Flowchart of articles included in the review.

TABLE 1. SELECTED ARTICLES

Author, year	Study site	Study design	Number of patients	CG	Type of analgesia	Pain measurement	Side effects	Results:
Kashyap <i>et al.</i> , 2020 (17)	New Delhi (India)	RCT	80 patients - 40 in the EG and 40 in the CG	Yes	EG = oral opioids (morphine and tramadol) + Scrambler therapy CG = oral opioids (morphine and tramadol)	Numerical Rating Scale (NRS-11)	Not reported	Overall, pain decreased in both groups. However, from the second day of treatment, there was a difference in mean pain scores, with patients in the control arm experiencing slightly more pain than patients in the intervention arm. The difference in mean pain increased over the treatment and follow-up period.
Haumann <i>et al.</i> , 2016 (18)	Maastricht (the Netherlands)	RCT	52 patients - 26 in the Fentanyl group and 26 in the Methadone group	No	Fentanyl and Methadone	Brief Pain Inventory (BPI)	No serious adverse effects were observed in the study	Methadone is significantly better than Fentanyl in neuropathic pain treatment in patients with head and neck cancer, in terms of pain relief and time to obtain pain relief in cancer patients.
Haumann <i>et al.</i> , 2018 (19)	Maastricht (the Netherlands)	RCT	82 patients - 40 in the Fentanyl group and 42 in the Methadone group	No	Fentanyl and methadone	Brief Pain Inventory (BPI)	The most common side effect was dry mouth, reported by 72% of patients during the study	Methadone is not inferior to Fentanyl in the treatment of radiation-induced nociceptive pain in patients with head and neck cancer, between one and three weeks of pharmaceutical pain treatment.
Williams <i>et al.</i> , 2015 (20)	Royal Marsden Hospital (London)	RCT	156 patients - 75 in the EG and 74 in the CG	Yes	EG = pain treatment protocol and an educational program. CG = usual care.	Leeds assessment of neuropathic symptoms and signs (S-LANSS self-assessment)	Not reported	There was no difference in the Pain Severity Index between the two groups.
Farina <i>et al.</i> , 2018 (21)	Campobasso (Italy)	Clinical trial	48 patients	No	To assess the reduction of symptoms produced by accelerated radiotherapy, administered in four total fractions, twice a day.	Visual Analogue Scale (VAS)	Not reported	Short-term accelerated radiotherapy in locally advanced or metastatic cancers is effective in terms of symptom relief and well tolerated even in older patients.

RCT = Randomized Controlled Trial; EG = Experimental Group; CG = Control Group.

With the clinical trial model of Farina et. al., 2018 (15), 48 subjects were assessed for symptom reduction after the application of short-term accelerated radiotherapy. They were treated with a radiotherapy regimen based on four fractions, twice a day, for two consecutive days. The total dose ranged from 14 and 20 Gray (Gy) (median: 20 Gy), and the dose per fraction ranged from 3.5 to 5 Gy (median: 5 Gy). In cases of locally advanced or metastatic cancer, it was effective in relieving symptoms.

DISCUSSION

The forms of analgesia used in cases of patients in palliative care are still basically based on medications. In this review, four out of the five papers included assessed the results of medication treatment and only one assessed another form of analgesia. In order to understand treatment forms, the causes of pain and from where they originated need to be clarified. In the majority of cases, the causes of pain are varied and increasing, and they may or may not be directly related to the disease. Aspects that can affect the cause of pain are tumor type and origin, location, stage, and treatment(4,22).

The neurophysiological classification of pain is based on the trigger mechanism and is sectorized into nociceptive, neuropathic, and complex or mixed. Nociceptive pain is caused by the activation of nociceptors (δ and C fibers) and may be somatic or visceral. Somatic pain is triggered or aggravated by exercise and is relieved by rest. Visceral pain is caused by swelling of the hollow organs and characterized by compression, contraction, or colic. It is difficult to position and may be accompanied by nausea, vomiting, and sweating. On the other hand, neuropathic pain is related to persistent or occasional, acute or chronic dysfunction of the central or peripheral nervous system, and may not be related to any detectable damage. It is described as a sensation of burning, tingling, and shock, and may or may not be accompanied by paresthesia and allodynia (a stimulus that does not produce pain but is considered to be painful). Complex or mixed pain is much more common in patients with cancer and its increase leads to inflammation and compression of adjacent structures. It includes the association between nociceptive pain and neuropathic pain, making diagnosis and treatment more complicated(4,23).

Considering the ways of treating patients, the WHO, in 1986, launched the "analgesic ladder" as their first protocol for the management of cancer pain. The strategy was to assess and adapt the drug management according to the need of the patient, moment by moment, sequentially, and progressively. The symptoms' relief along with this protocol may be around 70 to 90%(13,24,25). Nonetheless, even with the efforts of the WHO, this protocol is inadequate in 40 to 50% of the cases (26,27). Thus, we were able to

find many reports on inadequate pain management in cancer patients (6,28).

Taking into consideration the opioid analgesics, which are derived from Opium, whether natural or synthetic, weak or strong, this class of drugs should be administered with caution, starting with low doses and increasing them if necessary. They cannot be discontinued abruptly, as they would generate abstinence in the patient(23). In the studies included in this review, Tramadol was used in association with Morphine(17), and Fentanyl was compared to Methadone(18,19). Tramadol is considered a weak opioid, is synthetic, and is metabolized by the liver, and its oral administration is twice as bioavailable as parenteral administration. Morphine is considered a strong opioid, and it is administered for the treatment of moderate to severe pain. In the study by Kashyap *et al.*, 2020(17), the results presented that, with the decrease in patients' pain, Morphine is reduced first, and only then Tramadol is reduced. Hence, it is expected Tramadol to be reduced less significantly than Morphine.

Fentanyl and Methadone, investigated in the above mentioned works by Haumann *et al.*(18,19), are considered strong opioids. Fentanyl for transdermal use is a synthetic opioid similar to morphine and is administered over 72 hours. As for Methadone, which is also synthetic, its administration is aimed at reducing cases of neuropathic pain and intense pain, and, in addition to an effect mediated by the opioid receptor, it has an additional effect on the N-methyl-D-aspartate receptor (NMDA). This receptor is known for being important in central sensitization(29). With this double mechanism of action of Methadone, authors found positive results: it is superior to Fentanyl in the relief of pain in patients with cancer pain with a component of neuropathic pain(18).

According to the results found in the existing literature, we observed that cancer pain treatment is still conducted, basically, with opioids. Notwithstanding, it must be taken into account their wide use *versus* their toxicity and side effects. Opioids may be natural, semi-synthetic, and synthetic, and operate on receptors present in the central nervous system and peripheral nervous system(10). Some points worth highlighting are as follows: the probability of tolerance, caused by desensitization of receptors and consequent gradual loss of their function, leads initially to side effects (except constipation) and then to analgesic effects which can be reversed with the increasing of the dose or drugs rotation. As for side effects, the most common ones are nausea, vomiting, sleepiness, and itching, and they occur more frequently at the beginning of drug administration and when the dose is increased. In HNC, the aim of providing comfort prevails in the choice of the best drugs for each patient and is also in the route of administration of each one(16).

Amongst the studies for non-medicated pain control, the use of Scrambler therapy was assessed, which is similar to transcutaneous electrical nerve stimulation (TENS). They are the most used neuromodulatory techniques(30). Scrambler therapy is a new method, introduced in the early 2000s, which uses a device that produces 16 different electrical current signals. These signs simulate the normal action potential of the nerve, and the electrodes around the area of pain usually lead to immediate relief. Each session of ST lasts 30 to 45 minutes. The majority of patients report pain relief as early as the first sessions, which continues after that(31,32). It has been used to treat pain, including cancer pain. Pain relief associated with this therapy was considered significant and lasting among numerous patient groups(33). In the study, results improved over time. Thus, it may be a good choice for patients for whom pharmacological pain management has not brought sufficient relief(17).

Another therapy assessed is palliative radiotherapy, which may have relevant importance in this population(34). Since it is a sort of therapy that does not interfere with others, it could simply be integrated into the treatment plan without causing the interruption of other treatments. The study conducted by Farina *et al.*, 2018, treated patients with a radiotherapy regimen based on four fractions, twice a day, for two consecutive days. The total dose ranged from 14 and 20 Gray (Gy) and the dose per fraction ranged from 3.5 to 5 Gy (median: 5 Gy). The pain relief response rate was 89.7% after radiotherapy. Therefore, we found in the literature other reports that assess this therapy and address its benefits. Taking into account older patients, radiation treatment plays a vital role in curative and palliative cancer therapy(35). Hence, palliative treatment with radiotherapy could be part of the therapeutic arsenal in this scenario(21).

The problem of pain in patients with cancer has already been considered, and copious recommendations have been made by national and international bodies(36,37). These include pain screening and the use of analgesic treatment pathways integrated into routine cancer treatment(38). A study with patients with HNC presented a prevalence of “moderate to severe” pain in 34% of patients treated with usual care guidelines(39). Accordingly, the objective of the study by Williams *et al.*, 2015, was to determine whether it would be possible to improve pain reduction scores through the introduction of a combined screening, treatment, and educational approach (intervention group) in these patients. The results did not show any additional benefit since both groups experienced substantial improvements in pain scores. Patients in the intervention group

had some improvements, but with a substantially increased cost, not adequate in cost-benefit(20). In such a way, the pain screening model is easy to implement and can be combined with existing therapies. It is an effective and economical treatment strategy for patients with cancer pain.

CONCLUSION

Most of the analgesia performed in patients affected by malignant head and neck injuries happens with opioids. Our review of the literature found a small number of clinical trials with this population. Thus, we believe it is of paramount importance that more studies that seek new ways to reduce symptoms and bring relief from suffering should be carried out.

The authors declare that there is no conflict of interest.

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REFERENCES

1. Jales SM da CP. Avaliação da efetividade de um protocolo de cuidados odontológicos no alívio da dor, sintomas bucais e melhora da qualidade de vida em pacientes com câncer de cabeça e pescoço em cuidados paliativos: ensaio clínico não-controlado [Internet] [Doutorado em Neurologia]. [São Paulo]: Universidade de São Paulo; 2011 [citado 7 de julho de 2021]. Available at: <http://www.teses.usp.br/teses/disponiveis/5/5138/tde-08122011-161547/>
2. Cuidados paliativos | INCA – Instituto Nacional de Câncer [Internet]. [citado 8 de julho de 2021]. Available at: <https://www.inca.gov.br/controlado-do-cancer-do-colo-do-utero/acoes-de-controlado/cuidados-paliativos>
3. Pimenta CA de M, Mota DDC de F, Cruz D de ALM da. Dor e cuidados paliativos: enfermagem, medicina e psicologia. 2006 [citado 24 de julho de 2021]; Available at: <https://repositorio.usp.br/item/001482203>
4. Guimarães AN, Dias MF, Miranda RM de C, Aguiar T de M, Arantes DCB, Pedras RB de N. Diagnóstico e manejo da dor orofacial oncológica: relato de três casos clínicos. Arq Em Odontol [Internet]. 2015 [citado 7 de julho de 2021];51(4). Available at: <https://periodicos.ufmg.br/index.php/arquivoemodontologia/article/view/3693>
5. Pidgeon T, Johnson CE, Currow D, Yates P, Banfield M, Lester L, *et al.* A survey of patients' experience of pain and other symptoms while receiving care from palliative care services. *BMJ Support Palliat Care*. setembro de 2016;6(3):315–22.
6. Sampaio SG dos SM, Motta LB da, Caldas CP. Medicamentos e Controle de dor: Experiência de um Centro de Referência em Cuidados Paliativos no Brasil. *Rev Bras Cancerol*. 24 de outubro de 2019;65(2):e-13365.

7. Jales SMCP, Siqueira JTT. Papel do dentista em Cuidado Paliativo. Em: Manual de Cuidados Paliativos. Rio de Janeiro: Diagraphic; 2009.
8. Narayanan RS, Nair MK, Padmanabhan TK. Palliation of pain in advanced oral cancer. *Headache*. maio de 1988;28(4):258–9.
9. Merskey, H, Bogduk, N. Task forces of taxonomy: classification of chronic pain. 2nd Edition. IASP Press; 1994.
10. Medeiros e Silva S. MANEJO DA DOR NO PACIENTE ONCOLÓGICO. Em: Diretrizes Oncológicas 2. 2o ed São Paulo: Doctor Press Ed. Científica; 2019. p. 15–23.
11. Dalva Yukie Matsumoto. Cuidados Paliativos: conceito, fundamentos e princípios. Em: Manual de Cuidados Paliativos da ANCP. 1a ed. Rio de Janeiro: Diagraphic; 2009.
12. Leticia Meda Vendrusculo-Fangel. CUIDADOS PALIATIVOS: CONCEITOS, FUNDAMENTOS E PRINCÍPIOS. Em: Diretrizes Oncológicas 2. São Paulo: Doctorpress; 2019.
13. Vargas-Schaffer G. Is the WHO analgesic ladder still valid? Twenty-four years of experience. *Can Fam Physician Med Fam Can*. junho de 2010;56(6):514–7, e202-205.
14. WHO | National cancer control programmes: [Internet]. WHO. World Health Organization; [citado 7 de julho de 2021]. Available at: <https://www.who.int/reproductivehealth/publications/cancers/9241545577/en/>
15. Rangel O, Telles C. Tratamento da dor oncológica em cuidados paliativos. *Rev Hosp Univ Pedro Ernesto* [Internet]. 2012;11(2). <https://www.e-publicacoes.uerj.br/index.php/revistahupe/article/view/8928>
16. Cardoso MG de M. Controle da Dor. Em: Manual de cuidados paliativos. Rio de Janeiro: Diagraphic; 2009.
17. Kashyap K, Singh V, Mishra S, Dwivedi SN, Bhatnagar S. The Efficacy of Scrambler Therapy for the Management of Head, Neck and Thoracic Cancer Pain: A Randomized Controlled Trial. *Pain Physician*. setembro de 2020;23(5):495–506.
18. Haumann J, Geurts JW, van Kuijk SMJ, Kremer B, Joosten EA, van den Beuken-van Everdingen MHJ. Methadone is superior to fentanyl in treating neuropathic pain in patients with head-and-neck cancer. *Eur J Cancer Oxf Engl* 1990. setembro de 2016;65:121–9.
19. Haumann J, van Kuijk SMJ, Geurts JW, Hoebbers FJP, Kremer B, Joosten EA, *et al*. Methadone versus Fentanyl in Patients with Radiation-Induced Nociceptive Pain with Head and Neck Cancer: A Randomized Controlled Noninferiority Trial. *Pain Pract Off J World Inst Pain*. março de 2018;18(3):331–40.
20. Williams JE, Peacock J, Gubbay AN, Kuo PY, Ellard R, Gupta R, *et al*. Routine screening for pain combined with a pain treatment protocol in head and neck cancer: a randomised controlled trial. *Br J Anaesth*. outubro de 2015;115(4):621–8.
21. Farina E, Capuccini J, Macchia G, Caravatta L, Nguyen NP, Cammelli S, *et al*. Short course accelerated radiation therapy (SHARON) in palliative treatment of advanced solid cancer in older patients: A pooled analysis. *J Geriatr Oncol*. julho de 2018;9(4):359–61.
22. Siqueira JTT, Jales S, Vilarim RCB. Dor orofacial e cuidados paliativos orais em pacientes com câncer. *Revista Onco*. junho de 2013;Ano 3(n° 17):25–8.
23. Adriana Thomaz. Dor oncológica: conceitualização e tratamento farmacológico. *Revista Onco*. setembro de 2010;Ano 1(n° 1):24–9.
24. Ventafridda V, Tamburini M, Caraceni A, De Conno F, Naldi F. A validation study of the WHO method for cancer pain relief. *Cancer*. 15 de fevereiro de 1987;59(4):850–6.
25. Mercadante S, Fulfaro F. World Health Organization guidelines for cancer pain: a reappraisal. *Ann Oncol Off J Eur Soc Med Oncol*. maio de 2005;16 Suppl 4:iv132-135.
26. Deandrea S, Montanari M, Moja L, Apolone G. Prevalence of undertreatment in cancer pain. A review of published literature. *Ann Oncol Off J Eur Soc Med Oncol*. dezembro de 2008;19(12):1985–91.
27. Cipta AM, Pietras CJ, Weiss TE, Strouse TB. Cancer-related pain management in clinical oncology. *J Community Support Oncol*. outubro de 2015;13(10):347–55.
28. Haozous EA, Knobf MT. “All my tears were gone”: suffering and cancer pain in Southwest American Indians. *J Pain Symptom Manage*. junho de 2013;45(6):1050–60.
29. Ebert B, Andersen S, Krosggaard-Larsen P. Ketobemidone, methadone and pethidine are non-competitive N-methyl-d-aspartate (NMDA) antagonists in the rat cortex and spinal cord. *Neurosci Lett*. 10 de março de 1995;187(3):165–8.
30. Coyne PJ, Wan W, Dodson P, Swainey C, Smith TJ. A trial of Scrambler therapy in the treatment of cancer pain syndromes and chronic chemotherapy-induced peripheral neuropathy. *J Pain Palliat Care Pharmacother*. dezembro de 2013;27(4):359–64.
31. Marineo G. Inside the Scrambler Therapy, a Noninvasive Treatment of Chronic Neuropathic and Cancer Pain: From the Gate Control Theory to the Active Principle of Information. *Integr Cancer Ther*. dezembro de 2019;18:1534735419845143.
32. Marineo G, Iorno V, Gandini C, Moschini V, Smith TJ. Scrambler therapy may relieve chronic neuropathic pain more effectively than guideline-based drug management: results of a pilot, randomized, controlled trial. *J Pain Symptom Manage*. janeiro de 2012;43(1):87–95.
33. Chwistek M. Recent advances in understanding and managing cancer pain. *F1000Research*. 20 de junho de 2017;6:945.
34. Gillison TL, Chatta GS. Cancer chemotherapy in the elderly patient. *Oncol Williston Park N*. janeiro de 2010;24(1):76–85.
35. Smith GL, Smith BD. Radiation treatment in older patients: a framework for clinical decision making. *J Clin Oncol Off J Am Soc Clin Oncol*. 20 de agosto de 2014;32(24):2669–78.
36. Gordon DB, Dahl JL, Miaskowski C, McCarberg B, Todd KH, Paice JA, *et al*. American pain society recommendations for improving the quality of acute and cancer pain management: American Pain Society Quality of Care Task Force. *Arch Intern Med*. 25 de julho de 2005;165(14):1574–80.
37. Miaskowski C. The next step to improving cancer pain management. *Pain Manag Nurs Off J Am Soc Pain Manag Nurses*. março de 2005;6(1):1–2.
38. Oldenmenger WH, Sillevius Smitt PAE, van Montfort CAGM, de Raaf PJ, van der Rijt CCD. A combined pain consultation and pain education program decreases average and current pain and decreases interference in daily life by pain in oncology outpatients: a randomized controlled trial. *Pain*. novembro de 2011;152(11):2632–9.
39. Williams JE, Yen JTC, Parker G, Chapman S, Kandikattu S, Barbachano Y. Prevalence of pain in head and neck cancer out-patients. *J Laryngol Otol*. julho de 2010;124(7):767–73.