Lat Am J Palliat Care 2023; 1:eLAPC20230041
DOI: https://doi.org/10.59679/LAPC2022eLAPC20230041

Brief Communication

Novel radiotherapy techniques in the management of oncologic pain

Novas técnicas de radioterapia no tratamento da dor oncológica

Antonio Cassio Assis Pellizzon[1]

ABSTRACT

Pain is an unpleasant sensory and emotional experience associated with potential or actual tissue damage. Oncologic pain (OP) generally increases with disease progression. Moderate or severe OP occurs in around 30% of cancer patients receiving treatment and in 60% to 90% of patients with advanced cancer. Radiotherapy (RT) is an effective non-pharmacological treatment of OP. The RT mechanisms of analgesia are complex and continue to evolve as it interact with cytostatic drugs and immunotherapy. Recent studies have shown that high doses of RT can increase apoptosis by cellular signaling effects and release of signaling molecules as cytokines, nitric oxide, or reactive oxygen species. Two new RT techniques are available for pain control: ablative RT for oligometastatic disease, which can also reverberate on disease control and survival through immune-modulation, and lattice RT, a technique based on 3-dimensional plans that deliver precise inhomogeneous high doses of radiation to different areas within tumor volumes. In conclusion, pain is a complex biological phenomenon. The successful treatment of OP requires careful assessment of its nature and the identification of different types and patterns. The knowledge of the different treatment options is key to selecting the most effective one. The management of OP with new radiation techniques can be effective, reducing the use of analgesics and improve quality of life.

Keywords: Pain; Analgesia; Radiotherapy Internal-External Control; Overall Survival.

RESUMO

A dor é uma experiência sensorial e emocional desagradável, associada a um dano tecidual real ou potencial. A dor oncológica (DO), em geral, aumenta com a progressão da doença. DO de intensidade moderada ou intensa ocorre em cerca de 30% dos pacientes com câncer que recebem tratamento, sendo sua prevalencia de ate 60% a 90% nos pacientes com doença avançada. A radioterapia (RT) é um método não farmacológico eficaz de tratamento da DO. Os mecanismos de ação da RT analgésica são complexos e evoluem à medida que se integram cada vez mais com medicações citostáticas e com a imunoterapia. Estudos recentes mostraram que altas doses de radiação podem induzir à apoptose por efeitos de sinalização celular e por liberação de citocinas, óxido nítrico e espécies reativas de oxigênio. Duas novas técnicas de RT estão disponíveis para controle da DO: a radioterapia ablativa, para doença oligometastática, que também pode repercutir no controle da doença e sobrevida através de imunomodulação, e a técnica Lattice, indicada para tumores volumosos, baseada em planos tridimensionais que fornecem com precisão altas doses não homogêneas de radiação para diferentes áreas dentro do volume tumoral. Em conclusão, a DO é um fenômeno biológico complexo e o sucesso do seu tratamento requer uma avaliação cuidadosa de sua natureza, bem como a compreensão dos seus diferentes tipos e padrões. O manejo específico da DO com novas técnicas de radiação é eficaz e pode proporcionar um bom controle da dor, permitindo a redução do uso de analgésicos e melhorando a qualidade de vida.

Palavras-chave: Dor; Analgesia; Radioterapia; Controle Interno-Externo; Sobrevida Global.

[1]AC Camargo Cancer Center, Divisão de Rádio Oncologia, São Paulo, São Paulo, Brazil.
Corresponding author: Antonio Cassio Assis Pellizzon; **Email:** acapellizzon@accamargo.org.br.
Conflict of interest: The author declares no conflict of interest.
Received on January 30, 2023; **Final version received on** November 5, 2023; **Accepted on** November 26, 2023; **Published on** December 29, 2023.
Editor-in-chief: João Batista Santos Garcia; **Scientific editor:** Rudval Souza da Silva.

According to the International Association for the Study of Pain (IASP) definition, pain is "*an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage*"[1]. Pain is a unique and personal experience and is referred to as the fifth vital sign, which draws the attention of health professionals to its evaluation, measurement and adequate treatment.

Pain also limits lifestyle, particularly mobility, patience, resignation, and can be interpreted as an indicator of disease resolution or progression[2].

It is known that in some cases the severity of pain is not directly proportional to the level of injured tissue, as many factors can influence pain perception, such as fatigue, depression, anger, fear, anxiety, feelings of hopelessness and lack of support[3].

In oncology, the prevalence of oncologic pain (OP) generally increases with disease progression. OP results from complex pathological mechanisms, including cellular, tissue, and systemic changes caused by tumor growth[4].

OP has three main sources: 1- Somatic pain, i.e. pain transmitted by nerves that signals damage to a body part, including infiltration of soft tissues, serous membranes, and occlusion of blood and/or lymphatic vessels. 2- Visceral pain caused by, among other things, stretching of the sensory innervated capsule of an organ and tissue ischemia due to cancer infiltration into supplying blood vessels or compression of ligaments, blood, or lymphatic vessels by tumor tissue. 3- Neuropathic pain caused by damage to the nervous system[5]. The pathophysiology of neuropathic pain involves damage by direct compression and/or nerve infiltration by the tumor mass, toxic effects of cytostatic and or molecular therapies and radiotherapy, or toxins released by the tumor[6].

About 60% of patients experience significant pain at some stage of oncologic treatment. Moderate or severe OP occurs in around 30% of cancer patients receiving treatment and in 60% to 90% of patients with advanced cancer[7]. Seventy-five to 80% of OP is caused by tumor infiltration of soft tissues, serous membranes, and occlusion of blood and or lymphatic vessels[8].

OP impairs the patient's cognitive functions, sleep, and social life and, in general, the presence and intensity of pain varies according to the stage of the disease and its location[3].

Radiotherapy (RT) is an effective non-pharmacological method of treatment of OP. Common indications for analgesic RT include pain caused by solid tumors per se or by pressure on nerve structures, bone metastasis and pain due to increased intracranial pressure. The mechanisms of action of analgesic RT are complex and evolve as they interact with cytostatic drugs and immunotherapy. The cytotoxic effect of radiation leads to a decrease in tumor volume and pressure on surrounding tissues, resulting in pain relief. RT also changes the cell environment by modulating chemical mediators of pain and inflammatory cytokines such as tumor necrosis factor alpha (TNF-α), which can activate ion channels receptors on sensory neurons[9].

The duration of the analgesic effect of radiation is on average 3–4 months, and in about half of the patients the pain at the irradiated site progresses after this time. In these cases, repeated radiotherapy can be effective in 50–60% of patients, and 16–28% of patients can experience complete pain relief[10].

Developments in early diagnosis and treatment have increased survival for almost all cancer types, and the detection of oligometastatic lesions is growing[11]. Recent studies have found that local treatment of all metastatic sites shows promising results, with increased overall survival in various cancers sites and types[12]. Hellman and Weichselbaum proposed in 1995 that radical treatment of oligometastatic disease with metastasis-directed therapy (MDT) can prevent additional metastatic spread and improve survival[13].

Recent studies have shown that high doses of radiation can increase apoptosis by cellular signaling effects and the release of signaling molecules such as cytokines, nitric oxide, or reactive oxygen species[14]. Supporting data from randomized phase II studies confirmed positive results of ablative therapies on overall survival (OS)[15,16]. The SABR (stereotactic ablative radiotherapy) COMET randomized study, in which 21% of the patients had oligometastatic disease and underwent local SABR, achieved a recurrence-free survival of more than 5 years, concluding that the use of SABR for pain control in oligometastatic disease can also reverberate on disease control and survival[17].

Conversely to the treatment of oligometastatic disease, approaches for voluminous tumors are, in general, limited and offer few options. When surgical resection is not feasible, there is no effective treatment for tumor reduction or pain control, which is a challenge in oncology. Large tumors can cause somatic and/or visceral pain. As these large lesions usually have a poor blood supply, they tend to produce factors such as hypoxia-inducible factor 2 alpha (HIF-2α), thus reducing apoptosis, which allows tumor growth, leading to compression and pain[18].

Analgesic conventional fractionated RT, with or without associated chemotherapy, can be indicated for the control of large tumors, but is of limited efficacy for pain control in these situations, making lattice RT a reasonable option. According to Pellizzon. "*lattice radiotherapy (LTR) is a technique based on 3-dimensional plans that may provide equivalent or superior clinical response in the management of large tumors while limiting toxicity to adjacent normal tissues as*

it precisely deliver inhomogeneous high doses of radiation to different areas within the tumor volumes"[19].

LTR has been indicated for primary or secondary tumors with more than 45cc in volume, lesions that are not be tractable by conventional radiation or that have proven refractory to chemoradiation[20].

Base on the above, OP is a complex biological phenomenon. It is still not well understood or classified, and no specific or widely acceptable taxonomy exists for OP to date[21].

The common pathways, signaling molecules and cell types involved in the pathological processes, results both in tumor growth and metastasis, which cause OP[22].

In conclusion, the successful treatment of OP requires careful assessment of its nature. The understanding of different types and patterns of OP is key in selecting the best treatment option. The management of OP with new radiation techniques can be effective and provide good pain control, making it possible to reduce the use of analgesics even before considering the use of strong opioids and, consequently improving the quality of life.

REFERENCES

1. Raja SN, Carr DB, Cohen M, Finnerup NB, Flor H, Gibson S, Keefe FJ, Mogil JS, Ringkamp M, Sluka KA, Song XJ, Stevens B, Sullivan MD, Tutelman PR, Ushida T, Vader K. The revised International Association for the Study of Pain definition of pain: concepts, challenges, and compromises. Pain. 2020 Sep 1;161(9):1976-1982.
2. Hickey M, Barry D, Redito J, Anand N, Bianchi N, Reneman M, Escorpizo R. Content validity of patient-reported outcome measures for patients with chronic pain: considering the patient's perspective. Pain. 2023 Feb 1;164(2):252-257.
3. Fillingim RB. Individual Differences in Pain: Understanding the Mosaic that Makes Pain Personal Pain. 2017 Apr; 158(Suppl 1): S11–S18.
4. Chwistek M. Recent advances in understanding and managing cancer pain. F1000 Res. 2017 Jun 20;6:945.
5. Kumar SP. Cancer Pain: A Critical Review of Mechanism-based Classification and Physical Therapy Management in Palliative Care. Indian J Palliat Care. 2011 May;17(2):116-26.
6. Zajączkowska R, Leppert W. Treatment of neuropathic pain in cancer patients. Palliat Med Pract 2016; 10: 14-21.
7. van den Beuken-van Everdingen MH, Hochstenbach LM, Joosten EA, Tjan-Heijnen VC, Janssen DJ. Update on Prevalence of Pain in Patients With Cancer: Systematic Review and Meta-Analysis. J Pain Symptom Manage. 2016 Jun;51(6):1070-1090.e9.
8. Leppert W, Zajaczkowska R, Wordliczek J, Dobrogowski J, Woroń J, Krzakowski M. Pathophysiology and clinical characteristics of pain in most common locations in cancer patients. J Physiol Pharmacol 2016; 67: 787-799.
9. Hendrickx TC, Barbeau LMO, Giuranno L, Dams G, Ient J, Olivo Pimentel V, van Gisbergen MW, Dubois LJ, Vooijs MA. HIF-1α and HIF-2α Differently Regulate the Radiation Sensitivity of NSCLC Cells. Cells. 2019 Jan 12;8(1):45.
10. Iezzi R, Kovács G, Dimov V, Contegiacomo A, Posa A, Efthymiou E, Lancellotta V, Rodolfino E, Punzi E, Trajkovski ZB, Valentini V, Manfredi R, Filippiadis D. Multimodal locoregional procedures for cancer pain management: a literature review. Br J Radiol. 2022 Nov 25:20220236.
11. Pacifico P, Colciago RR, De Felice F, Boldrini L, Salvestrini V, Nardone V, Desideri I, Greco C, Arcangeli S. A critical review on oligometastatic disease: a radiation oncologist's perspective. Med Oncol. 2022 Sep 7;39(12):181.
12. Palacios-Eito A, García-Cabezas S. Oligometastatic disease, the curative challenge in radiation oncology. World J Clin Oncol. 2015 Aug 10;6(4):30-4.
13. Hellman S, Weichselbaum RR. Radiation oncology and the new biology. Cancer J Sci Am. 1995 Sep-Oct;1(3):174-9.
14. Sia J, Szmyd R, Hau E, Gee HE. Molecular Mechanisms of Radiation-Induced Cancer Cell Death: A Primer. Front Cell Dev Biol. 2020 Feb 13;8:41.
15. Sun B, Brooks ED, Komaki R, Liao Z, Jeter M, McAleer M, Balter PA, Welsh JD, O'Reilly M, Gomez D, Hahn SM, Sepesi B, Rice DC, Heymach JV, Chang JY. Long-Term Outcomes of Salvage Stereotactic Ablative Radiotherapy for Isolated Lung Recurrence of Non-Small Cell Lung Cancer: A Phase II Clinical Trial. J Thorac Oncol. 2017 Jun;12(6):983-992.
16. Arcidiacono F, Anselmo P, Casale M, Zannori C, Ragusa M, Mancioli F, Marchetti G, Loreti F, Italiani M, Bracarda S, Maranzano E, Trippa F. STereotactic Ablative RadioTherapy in NEWly Diagnosed and Recurrent Locally Advanced Non-Small Cell Lung Cancer Patients Unfit for ConcurrEnt RAdio-Chemotherapy: Early Analysis of the START-NEW-ERA Non-Randomised Phase II Trial. Int J Radiat Oncol Biol Phys. 2022 Oct 24:S0360-3016(22)03459-9.
17. Harrow S, Palma DA, Olson R, et al. Stereotactic Radiation for the Comprehensive Treatment of Oligometastases (SABR-COMET)—extended long-term outcomes. Int J Radiat Oncol Biol Phys. 2022;S0360–3016(22):00412–416.
18. Moreno Roig E, Groot AJ, Yaromina A, Hendrickx TC, Barbeau LMO, Giuranno L, Dams G, Ient J, Olivo Pimentel V, van Gisbergen MW, Dubois LJ, Vooijs MA. HIF-1α and HIF-2α Differently Regulate the Radiation Sensitivity of NSCLC Cells. Cells. 2019 Jan 12;8(1):45.
19. Pellizzon ACA. Lattice radiation therapy - its concept and impact in the immunomodulation cancer treatment era. Rev Assoc Med Bras (1992). 2020 Jun;66(6):728-731.
20. Amendola BE, Perez NC, Wu X, Amendola MA, Qureshi IZ. Safety and Efficacy of Lattice Radiotherapy in Voluminous Non-small Cell Lung Cancer. Cureus. 2019 Mar 18;11(3):e4263.
21. Paice JA, Mulvey M, Bennett M, Dougherty PM, Farrar JT, Mantyh PW, Miaskowski C, Schmidt B, Smith TJ. AAPT Diagnostic Criteria for Chronic Cancer Pain Conditions. J Pain. 2017 Mar;18(3):233-246.
22. Brown MR, Ramirez JD: Neuroimmune mechanisms in cancer pain. Curr Opin Support Palliat Care. 2015;9(2):103–11.