

Novel radiotherapy techniques in the management of oncologic pain

Novas técnicas de radioterapia no tratamento da dor oncológica

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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 prevalência de até 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.

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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*”. 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 progression².

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 support³.

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 growth⁴.

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 system⁵. 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 tumor⁶.

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 cancer⁷. Seventy-five to 80% of OP is caused by tumor infiltration of soft tissues, serous membranes, and occlusion of blood and or lymphatic vessels⁸.

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 location³.

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 neurons⁹.

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 relief¹⁰.

Developments in early diagnosis and treatment have increased survival for almost all cancer types, and the detection of oligometastatic lesions is growing¹¹. Recent studies have found that local treatment of all metastatic sites shows promising results, with increased overall survival in various cancers sites and types¹². Hellman and Weichselbaum proposed in 1995 that radical treatment of oligometastatic disease with metastasis-directed therapy (MDT) can prevent additional metastatic spread and improve survival¹³.

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 species¹⁴. 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 survival¹⁷.

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-2 α), thus reducing apoptosis, which allows tumor growth, leading to compression and pain¹⁸.

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 chemoradiation²⁰.

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 date²¹.

The common pathways, signaling molecules and cell types involved in the pathological processes, results both in tumor growth and metastasis, which cause OP²².

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.

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