Acta Med Croatica, 73 (2019) (Suppl. 1) 45-49 *Review*

Oncologic approach to the treatment of cancer-associated pain

ANTONIO JURETIĆ

University of Zagreb, School of Medicine and Zagreb University Hospital Centre, Department of Oncology, Zagreb, Croatia

Pain in cancer patients is a symptom especially prevalent in those in advanced or terminal stage of the disease. Pain, especially of chronic type, negatively affects patient quality of life, physical functioning, as well as his/her psychological, social and spiritual well-being. Cancer pain treatment planning and implementation should start with initial comprehensive assessment of the pain. Consequent treatment should be multimodal, encompassing pharmacological and nonpharmacological management options for pain, depending on pain etiology, intensity, location, patient performance status, cancer disease stage and comorbidities. Radiotherapy as a nonpharmacological treatment modality has its role in cancer pain treatment, especially in case of patients with painful localized metastatic bone lesions. Irradiation of these bone metastatic sites can provide effective pain control and decrease the probability of the occurrence of skeletal-related events. In the case of pain associated with primary and metastatic brain tumors (headaches), irradiation is applied on the endocranium (brain). This article provides a brief overview of clinical radiotherapy and palliative radiotherapy indications in cancer patients. Evidence suggests that in palliative treatment indications, low-dose hypofractionated short-course radiotherapy schedules can be as effective as high-dose protracted radiotherapy.

KEY WORDS: difficult intubation, prominence of upper incisors, interincisor gap, intubation difficulty scale

ADDRESS FOR CORRESPONDENCE: Professor Antonio Juretić, MD, PhD
School of Medicine, University of Zagreb
and Zagreb University Hospital Centre,
Department of Oncology
Kišpatićeva 12
10 000 Zagreb, Croatia
E-mail: ajuretic@kbc-zagreb.hr

INTRODUCTION

Pain is one of the more common symptoms of malignant disease. It is an extremely unpleasant and frightening symptom that as a rule manifests in more advanced stages of the disease. Due to the nature and spread of tumor disease (incurability), the pain experienced by oncologic patients is frequently of a chronic type. In such conditions, there is no doubt that pain adversely affects the patient quality of life. Alongside physical pain, patients suffering from a malignant disease can also experience mental (emotional) pain. Consequently, the pain felt by oncologic patients is not only a physical experience but a manifestation of a variety of psychological, social and spiritual elements. That is why the concept of 'total pain' is used. When treating pain, the focus should not be only on the pain itself (physical pain) but also on the person as a whole. Since all the components of pain must be attended, treating oncologic patients very often requires a multimodal and multidisciplinary approach. Pharmacological treatment of pain, which includes the use of non-opioid analgesics, opioids and other drugs, is the basis of treating pain (1-6). Radiotherapy also has its place in the treatment of pain, for example, pain caused by bone metastases and pain (headaches) associated with primary and metastatic brain tumors. This paper aims to briefly outline the role of radiotherapy in treating cancer pain. Since such clinical situations most often involve patients suffering from incurable diseases, palliative radiotherapy approach is adopted with the aim of alleviating discomfort (pain) and maintaining or improving the quality of life (2, 7-9).

Radiotherapy is a standard cancer treatment modality. It is based on the use of ionizing radiation, most commonly high-energy x-ray beams or high-energy electron beams. Nowadays, radiotherapy is used in the treatment of more than 50% of all patients suffering from a malignant disease. Since the discovery of x-ray in 1895 by Wilhelm Roentgen, this treatment modality has evolved considerably both in technical and clinical terms (8,10-13).

Technically, these beams are most frequently applied in the form of so-called external beam radiotherapy (EBRT) or teletherapy. This means that the beam source is outside the body or at a distance from the treated patient who is lying on the treatment couch. Nowadays, EBRT is administered using linear accelerator as a radiotherapy machine or beam source. In the linear accelerator, high-energy x-ray beams are produced by accelerating a stream of electrons and allowing them to collide with a metal target. High-energy electrons are obtained by removing the target from the stream of accelerated electrons. The resulting high-energy rays or beams are afterwards pointed at a particular part of the body, either the tumor (primary or metastatic tumor) or the tumor bed after the tumor has been surgically removed (adjuvant radiotherapy) (8,10-13).

When x-rays or electrons are passing through the cells, energy is absorbed, which results in ionization of a number of atoms and generation of fast moving electrons and free radicals. The ionization of atoms can alter both the structure and function of cell (macro)molecules. Biologically, the most significant damage at the molecular level is that of deoxyribonucleic acid (DNA) impairments in the form of strand breaks. Since DNA molecules are cell genetic or hereditary material, any damage to them can, unless repaired, block their ability to further divide and proliferate. Cells whose DNA is damaged beyond repair are expected to stop dividing and die. Consequently, the main goal of radiation therapy is to deprive cancer cells of their multiplication potential and eventually kill cancer cells. Radiation therapy can kill cancer cells by a variety of mechanisms, i.e. apoptosis, mitotic catastrophe, necrosis, senescence and autophagy. The SI unit for the absorbed dose of radiation is the gray (Gy), i.e. the energy absorbed *per* unit mass (joules *per* kilogram) (8,10-13).

Although radiation damages both normal cells and cancer cells, the goal of radiation therapy is to maximize the radiation dose to abnormal cancer cells while minimizing exposure to normal cells, which are adjacent to cancer cells or in the path of radiation. Clinical radiotherapy came to be applied in clinical practice as a result of the fact that normal cells are usually able to repair themselves at a faster rate and more effectively than cancer cells. EBRT is normally delivered over multiple sessions (or fractions), usually as once-daily doses, to exploit the differences in repair and repopulation between tumor cells and normal cells. Radiotherapy can be applied with either curative or palliative intent to relieve the symptoms caused by cancer. Radiotherapy treatment intent thus depends on tumor extent (disease stage), tumor location, patient performance status and comorbidities, availability of modern radiotherapy treatment machines and their technical and software capabilities. It can be used as the sole treatment modality or combined with other treatment modalities, for example, concomitantly or sequentially with chemotherapy and surgery. The concomitant use of chemotherapy with radiotherapy can achieve a better overall response, albeit with an increased number of treatment-related toxicities. In combination with surgery, it can be administered postoperatively as adjuvant, which is a form of radiotherapy with curative intent. It is directed at the operated tumor bed with the aim of reducing the chances of a local tumor relapse as a result of any potentially remaining tumor cells. If administered preoperatively (neoadjuvantly), its aim might be to shrink the tumor and make it operable or easily operable. Also, if preoperative staging indicates that the patient will need adjuvant radiotherapy, neoadjuvant application of radiotherapy can have less side effects and consequently result in better patient compliance. Radiotherapy can also be applied, albeit rarely, intraoperatively (8,10-13).

In clinical radiotherapy, the radiation tolerance of normal tissue and organs surrounding the tumor limits the radiotherapy dose that can be given safely. As the dose is increased, the incidence and severity of normal tissue damage rise. When severe, normal tissue damage can produce life-threatening morbidities. Multiple parameters such as total radiation dose, fraction size, overall treatment time, volume and type of normal tissue to be irradiated, definition of target volume, and quality control of radiotherapy techniques should be taken into account. Reduction of radiotherapy-related toxicity is fundamental to the improvement of clinical results in oncologic patients. The present knowledge of radiation toxicity is derived from conventional and more recent 3-dimensional (3D)-conformal radiotherapy (3D-CRT) data. The QUANTEC project produced data that are currently used to predict the side effects of radiotherapy and the plausibility of evaluated treatment plans. Before being approved, all radiotherapy treatment plans have to be evaluated for the probability of organ-specific radiation toxicity (8,10-13).

Most EBRT is planned using computed tomography (CT) imaging to locate the tumor and provide information on the patient shape and tissue density. As a result of evolving radiation imaging and computer technology, there have been a number of innovations

in radiotherapy practice over the past several decades. Conventional 2-dimensional (2D) treatment simulation has been replaced with CT planning, with volumes delineated according to the International Commission on Radiation Units and Measurements (ICRU) report and ICRU supplements. This CT-based planning, as well as the possibility of implementing other imaging methods such as positron emission tomography/computed tomography (PET/CT) and magnetic resonance imaging (MRI) have enabled more precise target border and volume determination, with the consequence of radiotherapy treatment plans having better tumor dose conformity and sparing the surrounding normal tissue (10-13).

Owing to better delineation of tumor margins and reduced rates of radiation-associated toxicity, the currently standard radiation treatments based on the implementation of these various technical and technological advances in radiation planning and delivery have allowed for the design of clinical studies with radiotherapy dose escalations and modified fractionation schemes. The goal of radiation treatment is to improve clinical outcomes while reducing damage to normal tissue. Newer radiotherapy equipment, techniques and treatment planning software can, owing to better delineation of tumor margins and reduced rates of radiation-associated toxicity, allow tumor dose escalation to improve local control and possibly lead to tumor cure. Advances in radiotherapy techniques were achieved by using functional images for target definition (PET/CT), 4D-computed tomography (CT), intensity modulated radiation therapy (IMRT) techniques with image guidance (image-guided radiation therapy; IGRT), adaptive radiotherapy and stereotactic (ablative) radiation therapy (SRT) (10-13).

Since protons not only have the ability to potentially reduce the dose of radiation applied to normal tissue but are radiobiologically more effective than high-energy x-rays, proton therapy has found its place among the new therapeutic approaches. However, this type of therapy also has its limitations, so the number of radiotherapy centers using this type of machines is relatively small (10-13).

Internal radiation or brachytherapy is delivered from inside the body directly to the tumor site by radioactive sources sealed in catheters or seeds. It is especially used in the routine treatment of gynecologic malignancies (10-13).

FRACTIONATION

Radiation therapy delivered in a fractionated regimen is based on differing radiobiological properties of cancer and various normal tissues. These regimens in general amplify the survival advantage of normal tissue over cancer cells, largely as a result of better sublethal damage repair of radiation damage in normal cells as compared to cancer cells. A typical radiation therapy regimen with curative intent consists of daily fractions of 1.8 to 2.0 Gy given over several weeks. Commonly used doses for conventional fractionation with curative intent radiotherapy with or without chemotherapy range from 60 to 70 Gy with daily fractions of, as has already been mentioned, 1.8 to 2.0 Gy *per* fraction. Postoperative or adjuvant radiotherapy doses range from 50 to 60 Gy, 1.8 to 2.0 Gy *per* fraction (10-13). Palliative radiotherapy treatment aims at alleviating symptoms (for example, pain) and improving the patient quality of life. The stage of the patient's disease or his/her medical condition is such that cure, unfortunately, is not expected. Therefore, in the case of patients with a limited expected survival time, late side effects of radiotherapy are of secondary importance. Another aim is to spare disabled patients and their families and accompanying persons from having to visit too frequently radiotherapy centers when the aim of their treatment is palliative radiotherapy. Consequently, palliative radiotherapy uses much shorter courses of larger fraction size (hypo-fractionation). In terms of the equieffective dose delivered in 2-Gy fractions (EQD2), these palliative doses are below the radical doses with standard size fraction (for example, with 60 Gy dose in 30 fractions, 2 Gy *per* fraction). Examples of palliative radiotherapy doses include 30 Gy in 10 fractions, 20 Gy in 5 fractions or 8 Gy in 1 fraction (2,7,9). The 30 Gy dose in 10 fractions is considered to be biologically equivalent to the dose of 40 Gy or 33 Gy in 2 Gy fractions (EQD2; calculated with the alpha/beta (a/b) ratio of 1 and 10, respectively). The 20 Gy dose in 5 fractions is considered to be biologically equivalent to the dose of 33 Gy or 23 Gy in 2 Gy fractions (EQD2; calculated with the a/b ratio of 1 and 10, respectively). The 8 Gy dose in 1 fraction is considered to be biologically equivalent to the dose of 24 Gy and 12 Gy in 2 Gy fractions (EQD2; calculated with the a/b ratio of 1 and 10, respectively) (14-16).

Figure 1 shows schematic presentation of several fractionation schedules in radiation treatment. Figures 2 and 3 present simple palliative treatment plans with treatment fields.

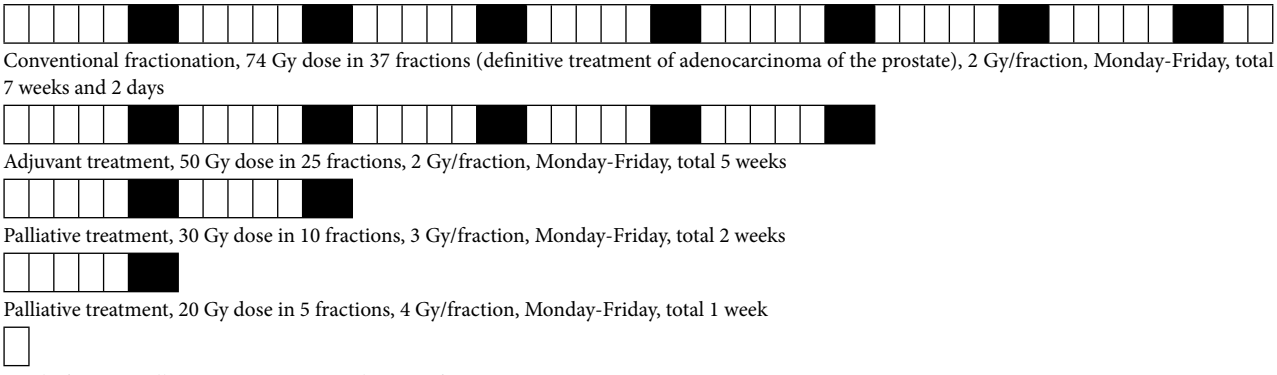

Fig. 1. *Schematic presentation of several fractionation schedules in radiation treatment. Days of treatment are shown as white squares (Monday to Friday) and weekend days (Saturday and Sunday) as black squares.*

Fig. 2. *Radiotherapy treatment plan for a bone metastatic cancer located in the upper thoracic vertebra. Applied dose was 30 Gy in 10 fractions (3 Gy/fraction). It was executed by using two opposite anteroposterior 15 MV photon beams.*

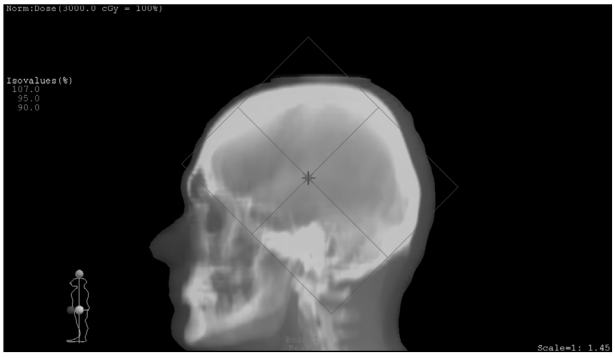

Fig. 3. *Treatment field for whole brain irradiation in a patient with multiple brain metastases. Applied dose was 20 Gy in 5 fractions (4 Gy/fraction). It was executed by using two opposite lateral 6 MV photon beams*

PALLIATIVE RADIOTHERAPY INDICATIONS

Palliative radiotherapy rarely improves overall survival. Also, since radiotherapy is a local anti-cancer treatment option, palliative radiotherapy should supplement and not replace holistic palliative care. Palliative radiotherapy is indicated for a relatively wide range of local symptoms such as pain resulting from bone metastases (the most frequent indication and application in clinical practice), obstructive cancer disease in the mediastinum (superior vena cava syndrome), pain and neurological compromise due to malignant spinal cord compression, symptoms due to brain metastases, alleviation of symptoms due to advanced head and neck and pelvic cancers, tumor compression of surrounding tissue and organs in the head and neck region, abdomen and pelvic region, control of bleeding, pain, and malodor due to skin cancer or skin or subcutaneous skin metastases resulting from other tumors (for example, locoregionally advanced breast cancer) (2,7,9).

Radiotherapy side effects depend on which tissues in cancer vicinity are receiving substantial radiotherapy doses. Since on the basis of tumor anatomical location it is possible to predict side effects, symptomatic therapy for preventive purposes can be administered as early as and concomitantly with radiotherapy. In other situations, it can be applied later on, with the appearance of relatively severe symptoms, if such symptoms appear at all (2,7,9).

CONCLUSIONS

In conclusion, in the case of oncologic patients with advanced cancer, palliative radiotherapy has a wide range of indications and is aimed at decreasing the intensity of their suffering due to pain and other cancer-related symptoms. In clinical practice, it has proven to be an effective treatment modality for the majority of patients with indications for palliative radiotherapy. In the majority of such patients, the effects of radiotherapy are visible within several weeks of finishing treatment, in some even during treatment. Based on these findings, major oncologic and pain societies have included in their guidelines radiotherapy and palliative radiotherapy (17-19). Also, there are publications of updated results of palliative radiotherapy (20, 21).

REFERENCES

1. Paice JA, Ferrell B. The management of cancer pain. CA Cancer J Clin 2011; 61: 157-82. doi: 10.3322/caac.20112.
2. Portenoy RK. Treatment of cancer pain. Lancet 2011; 377: 2236-47. doi: 10.1016/S0140-6736(11)60236-5.
3. Schmidt BL. The neurobiology of cancer pain. J Oral Maxillofac Surg 2015; 73(12 Suppl): S132-5. doi: 10.1016/j.joms.2015.04.045.
4. von Moos R, Costa L, Ripamonti CI, Niepel D, Santini D. Improving quality of life in patients with advanced cancer: targeting metastatic bone pain. Eur J Cancer 2017; 71: 80-94. doi: 10.1016/j.ejca.2016.10.021.
5. Portenoy RK, Ahmed E. Cancer pain syndromes. Hematol Oncol Clin North Am 2018; 32: 371-86. doi: 10.1016/j.hoc.2018.01.002.
6. Scarborough BM, Smith CB. Optimal pain management for patients with cancer in the modern era. CA Cancer J Clin 2018 Mar 30. doi: 10.3322/caac.21453.
7. Ahmad SS, Duke S, Jena R, Williams MV, Burnet NG. Advances in radiotherapy. BMJ 2012; 345: e7765. doi: 10.1136/bmj.e7765.
8. Baskar R, Lee KA, Yeo R, Yeoh KW. Cancer and radiation therapy: current advances and future directions. Int J Med Sci 2012; 9: 193-9. doi: 10.7150/ijms.3635.
9. Spencer K, Parrish R, Barton R, Henry A. Palliative radiotherapy. BMJ 2018; 360: k821. doi: 10.1136/bmj.k821.
10. Schaue D, McBride WH. Opportunities and challenges of radiotherapy for treating cancer. Nat Rev Clin Oncol 2015; 12: 527-40. doi: 10.1038/nrclinonc.2015.120.
11. Baumann M, Krause M, Overgaard J *et al*. Radiation oncology in the era of precision medicine. Nat Rev Cancer 2016; 16: 234-49. doi: 10.1038/nrc.2016.18.
12. Choi WH, Cho J. Evolving clinical cancer radiotherapy: concerns regarding normal tissue protection and quality assurance. J Korean Med Sci 2016; 31 Suppl 1: S75-87. doi: 10.3346/jkms.2016.31.S1.S75.
13. Citrin DE. Recent developments in radiotherapy. N Engl J Med 2017; 377: 1065-75. doi: 10.1056/NEJMra1608986.
14. Barton M. Tables of equivalent dose in 2 Gy fractions: a simple application of the linear quadratic formula. Int J Radiat Oncol Biol Phys 1995; 31: 371-8.
15. Bentzen SM, Dörr W, Gahbauer R *et al*. Bioeffect modeling and equieffective dose concepts in radiation oncology-terminology, quantities and units. Radiother Oncol 2012; 105: 266-8. doi: 10.1016/j.radonc.2012.10.006.
16. Fowler J. Bioeffect modeling and equieffective dose concepts in radiation oncology: comments on Bentzen *et al*.'s paper from ICRU in Radiother Oncol 2012; 105: 266-8. Radiother Oncol 2013; 108: 354. doi: 10.1016/j.radonc.2013.07.009.
17. Persoli M, Juretić A, Lončarić M. Smjernice za liječenje karcinomske boli odraslih. Bol 2011; 1: 2-14. Available at URL: http://www.hdlb.org/wp-content/uploads/2012/01/Bol_glasilo_br_2_2011_web.pdf. Accessed on May 25, 2018. (in Croatian)
18. Ripamonti CI, Santini D, Maranzano E, Berti M, Roila F; ESMO Guidelines Working Group. Management of cancer pain: ESMO clinical practice guidelines. Ann Oncol 2012; 23 Suppl 7: vii139-54. doi:10.1093/annonc/mds233.
19. NCCN clinical practice guidelines in oncology (NCCN guidelines). Adult cancer pain.Version 1.2018.NCCN.org (47 pages). Available at URL: https://www.nccn.org/professionals/physician_gls/default.aspx#supportive. Accessed on May 25, 2018.
20. Pin Y, Paix A, Le Fèvre C, Antoni D, Blondet C, Noël G. A systematic review of palliative bone radiotherapy based on pain relief and retreatment rates. Crit Rev Oncol Hematol 2018; 123: 132-7. doi: 10.1016/j.critrevonc.2018.01.006.
21. Rich SE, Chow R, Raman S *et al*. Update of the systematic review of palliative radiation therapy fractionation for bone metastases. Radiother Oncol 2018; 126: 547-57. doi: 10.1016/j.radonc.2018.01.003.