Peculiarities of radiotherapy in the elderly*

Peculiaridades da radioterapia em idosos

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Abstract **It is known that the aging of the world population during the twentieth century and the beginning of this new century is a first-order challenge for nations, especially in the socio-economic field. An important aspect of the aging of global population is that, for older age groups, the prevalence of degenerative diseases is also higher, including malignancies. On the other hand, among the population of patients with cancer, half of these patients will receive radiation therapy at some point in their illness and their individual characteristics can somehow influence the prognosis, the indication and daily doses of treatment prescriptions. In this context, the health assistance for the elderly patient with cancer should be seen as an important challenge, mainly due to two factors: an increased demand for treatments, in quantitative terms, and physiological characteristics unique to this population, which can influence the therapeutic decision-making. This review proposes a discussion of some relevant aspects of both the physiology of the elderly, which may influence the course of radiation therapy, as well as of some technical advances in radiotherapy, which can in turn benefit these patients by offering, for example, lower toxicity, greater effectiveness and speed.**
Keywords: Radiotherapy; Elderly.

Resumo **É sabido que o envelhecimento da população do mundo durante o século XX e no início deste novo século constitui um desafio de primeira ordem para as nações, especialmente no campo socioeconômico. Um aspecto importante do envelhecimento populacional global é que, para grupos de idade mais avançada, a prevalência das doenças degenerativas também é maior, incluindo as doenças malignas. No universo de pacientes portadores de câncer, por outro lado, metade destes receberá radioterapia em algum momento de sua doença e suas características individuais podem influenciar, de alguma forma, o prognóstico, a indicação e as doses diárias de prescrição dos tratamentos. Neste contexto, a assistência à saúde do idoso portador de câncer deve ser vista como um importante desafio, principalmente devido a dois fatores: uma maior procura de tratamentos, em termos quantitativos, e características fisiológicas peculiares a esta população, que podem influenciar na tomada de decisões terapêuticas. Esta revisão propõe uma discussão sobre alguns aspectos relevantes tanto da fisiologia dos idosos, que pode influenciar o curso do tratamento irradiante, quanto de alguns avanços técnicos da radioterapia, que podem, por sua vez, beneficiar estes pacientes, oferecendo menor toxicidade e maior eficiência e rapidez, por exemplo.**
Unitermos: Radioterapia; Idosos.

Chen MJ, Nadalin W. Peculiarities of radiotherapy in the elderly. Radiol Bras. 2010;43(5):324–329.

THE CHALLENGE IN RADIOTHERAPY FOR ELDERLY PATIENTS

It is widely known that the world population aging along the twentieth century and in the beginning of this new century poses a great challenge to all nations, particularly from the socio-economic standpoint. According to data from the World Health Organization, in 2000 there were 600 million elderly individuals (with 60 years of age or more), and by 2050 such population is estimated to reach two billion individuals. Brazil will be the sixth country in the world with the largest number of elderly individuals[(1)] and, according to data from the Instituto Brasileiro de Geografia e Estatística (IBGE) (Brazilian Institute of Geography and Statistics), the life expectancy in the country, that reached 33.4 years in 1910, progressed to 64.8 years in 2000, with an elderly population of 14.5 million individuals[(2)].

A relevant aspect of the global population aging is that in the most advanced age groups, the prevalence of degenerative disorders, including malignant neoplasias, is also higher, because of the longer life span of the individuals and therefore longest exposure to risk factors, for example. In Brazil, for the population above 65 years of age, the data from Instituto Nacional de Câncer (National Cancer Institute) demonstrate that cancer is the second cause of deaths due to diseases, with a specific mortality ratio of 856/100,000 men and 536/100,000 women, in the period between 1995 and 1999[(3)].

In the universe of cancer patients, approximately one half will be submitted to radiotherapy at some point along the course of the disease[(4)] and, among the patients routinely treated by radio-oncologists, the individual characteristics of each one of these patients may influence on the prognosis, indication and even on the way the

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Received April 7, 2010. Accepted after revision May 26, 2010.

daily radiation treatment is prescribed. Matters linked to individual characteristics, including the socio-economic ones, many times cause the elderly patients not to receive such treatment modality, even when it is indicated and in spite of the potential benefits of the application of therapeutic radiation. Then, such patients are submitted to possibly less beneficial, non-standardized treatment schemes[5–7].

Although more thorough studies on the matter are required, from the medical professional standpoint some factors may be pointed as possible reasons for considering the management of elderly cancer patients as "difficult". On one hand, it is rare to reach a consensus on the most appropriate approach for the treatment of elderly patients, as a great number of scientific studies are focused on a young adult population, and therefore patients with better overall health conditions, with less clinical comorbidities. In these cases, the relative lack of treatment guidelines based on scientific evidences, and that are truly focused on the elderly patient population, provides the grounds for some uncertainty on the best way to assist this group with appropriate therapy[8].

On the other hand, an important bias is the association of a normal life condition of the human being with the progression of physiological changes with the aging process, the *senescence*, with a set of morbid processes that may occur parallel to normal aging, the *senility**. In some cases, for example, it may be really appropriate to deprive the elderly patient of a treatment with clear curative indication due to the presence of multiple comorbidities (which on their turn would be responsible for the actual reduction in patient's life expectancy), but it is also an important conceptual error to directly correlate age *per se* with a smaller patient's tolerance to radiation treatment. Additionally, if by one hand some clinical studies suggest that, for selected patients, the age factor does not decrease tolerance to more aggressive treatments[10–13], on the other hand the biological aggressiveness of tumors also seems to be variable in relation to the individual's age, being lower for some histological types, in older patients[14–16].

NEW TECHNIQUES AND RADIOTHERAPY APPLICATIONS

Several recent scientific medical developments have created an array of therapeutic options for the oncologic patient. Specifically in the field of geriatric oncology, such developments may translate into both more effective therapeutic resources in the fight against cancer and into mechanisms that allow the physician to bypass eventual physiopathological "imbalances" in elderly patients more easily and with less risk for excessive toxicity[17,18]. Similarly, in radiotherapy, new options of interventional techniques allow the reduction of possible side effects inherent to the intrinsic toxicity of radiations on healthy tissues, providing more efficient treatments in terms of radiation dose to tumors and areas at risk. Additionally, patient treatment time can also be shortened favoring, in this case, those patients facing logistical and socio-economic difficulties (access to radiotherapy services, for example).

Intensity modulated radiation therapy (IMRT) has been becoming popular in Brazil since the early 2000's, allowing, for example, by means of advanced computational techniques, a greater control of radiation dose distribution in the treatment. The utilization of such treatment modality allows the reduction of inherent radiation toxicity side effects on healthy tissues without significantly reducing the dose in the tumor targets (for example tumors and risk areas). For the elderly patients, the potential benefit of this new technique comes from lower intolerance risks along the course of the radiation treatment, because of the lower incidence of acute side effects and, consequently, allowing doses scaling, thus increasing the probability of tumor management[19–21]. In the long term, with lower toxicity risks, potentially beneficial results with respect to survival and quality of life of such patients are expected.

Not less interesting, and from the "indirect" benefits standpoint, some of the new radiotherapy techniques may also be very useful as a tool to facilitate the treatment without losing focus on treatment proposal, whether curative or remissive/palliative therapy, and, for the elderly patient, treatments with a reduced course minimize logistical and socio-economic barriers which are fundamental but many times underestimated points[5–7]. Techniques involving a single or few applications (in general completed after five or six applications), and utilizing tools that allow millimetric accuracy, are feasible alternatives for patients requiring palliation or radical treatment for certain types of brain tumors or tumors in organs such as the lung and liver, for example. Such techniques, known as radiosurgery, fractionated stereotactic radiotherapy and most recently, whole-body stereotactic radiotherapy, may represent alternatives for the elderly patients facing difficulties for accessing radiotherapy services or even with eventual psychosocial and cognitive deficits, which, on their turn, may impair their cooperation during long and conventional treatments that usually are administered on a daily basis, during two to four weeks, or longer[21,22].

As regards treatments with exclusively curative indication, patients with malignant prostate neoplasia at early clinical stage may opt for brachytherapy with radioactive iodine (I-125) or palladium (Pd-103) seeds implants as a sole modality of treatment, certainly a therapeutic option with lower risks than a radical prostatectomy (a major surgery), and certainly less prolonged than conventional fractionated radiotherapy, lasting from seven to eight weeks[21].

Furthermore, for elderly female patients, intraoperative radiotherapy is another example of a quite promising modality as an alternative to conventional and adjuvant radiotherapy for breast cancer. In carefully selected cases at early clinical stage, this treatment modality can be utilized, reducing treatment time from up to six weeks to a single application at the same surgical moment of the breast tumor resection. Likewise, new studies that have given greater attention to the so called "partial irradiation of the breast" whose principle is the irradiation of only the tumor bed and the adjacent breast tissues, have utilized, among others, brachytherapy as a

* Note from the author: This misperception refers inclusively to ageism, defined as "the approach that leads to treatments denial to a person due to discrimination against this person solely because of age", whose expression is deeply rooted in many aspects of human social behavior, for example, in language, attitudes, beliefs and values[9].

modality of radiation treatment in a reduced number of fractions[21,23].

Finally, along this same line, several studies have also point out to rapid treatment schemes, of the "hypofractionation" type (with higher daily doses and shorter total treatment time) as a viable alternative for the same patient profile, both for the purposes of short term palliation/remission and with curative indication[24].

PHYSIOLOGICAL ASPECTS OF THE ELDERLY PATIENT AND THEIR IMPACT ON THE RADIATION TREATEMENT

Cardiovascular system

Primary malignant cardiovascular system neoplasias are extremely rare events in the daily oncologic practice. However, the association of physiological/cardiological changes in the elderly patient (with reduced functional reserve and limited capacity to tolerate effort), clinical cardiovascular comorbidities (frequent at advanced ages) and the commonly utilized chemotherapeutic drugs (such as anthracyclines and the new monoclonal antibodies) presents an extremely high cardiotoxicity potential[25]. Literature data documenting the radiotherapy effects on the heart originate mainly from the evaluation of patients treated for breast cancer or mediastinal lymphomas. In such cases, conditions such as heart rhythm disorders, coronary diseases and cardiomyopathies, are associated with the use of older treatment techniques, such as conventional radiotherapy and irradiation of a substantially larger volume of the heart (for example, in the irradiation of the chest wall and mediastinal lymph node drainage system). Additionally, one should bear in mind that such effects present a variable latency until they manifest, ranging from months to up to a decade[26].

Besides the reduction in the volume of radiation on the cardiac area during the irradiation treatment, one should be particularly careful in the cases of patients with pacemakers or implanted defibrillators/cardioverters. The exposure of such devices to ionizing radiation and to the action of electromagnetic fields generated by linear accelerators may interfere with their normal functioning, resulting in risks to the patient's health. The manufacturers' recommendations on specific precautions for each device are quite divergent, however, it seems to be a consensus that both pacemakers and implanted defibrillators/cardioverters should not be directly exposed to radiation fields, and some type of cardiological evaluation, particularly during and after the course of the treatment, should be performed[27].

Upper gastrointestinal tract

Functional alterations observed in the mucosal protection mechanism predispose the elderly patients to a smaller tolerance to therapeutic radiations with a higher susceptibility to mucositis episodes with significant, negative effects on their quality of life[16]. The development of mucositis on the oral cavity surface and in upper gastrointestinal tract is very frequently observed in the course of radiotherapy for head and neck tumors. During the treatment symptoms such as pain and local discomfort are generally observed, with feeding difficulties and nausea, with the consequential risk for nutritional impairment and worsening of the patient's functional status.

Some artifices may be utilized in such cases to prevent and reduce the intensity of oral and upper gastrointestinal symptoms, in order to maintain adherence to the therapeutic plan and to avoid unplanned interruptions. Pharmacological and non-pharmacological measures should be aggressively instituted, even if only prophylactically, as well as the frequent monitoring of their application[28]. The use of topical agents (anesthetics, local protectors) and oral medications (analgesics, antiemetics), superinfection (oral moniliasis) treatment and the use of radioprotectors (amifostine), LASER and of the IMRT technique must occur in parallel with simple measures, such as guidance for appropriate dental hygiene, removal of irritating factors (alcohol, smoking, prostheses) and specialized dental and nutritional follow-up. However, one should bear in mind that in spite of the of the high number of available interventional options, the results of scientific studies on many such agents are many times conflicting or even non-existent, a fact that imposes a judicious use of those agents[28,29].

Pulmonary system

It may be difficult to differentiate the changes normally observed in the elderly patient on what concerns to causes that can be attributed to a purely physiological component and causes that can be attributed to chronic exogenous factors such as exposure to tobacco, fumes, environmental pollution and to infectious agents, for example. However it is a fact that during the senescence process, a variety of progressive physiological changes is detectable, representing contributors to a lower tolerance of the elderly to harmful agents such as infections, cytotoxic drugs and ionizing radiation. Such physiological changes, including both structural changes of the thoracic framework and functional changes of regulatory mechanisms of the respiration (for example gas exchange and respiratory control), as well as local defense mechanisms[30], may be associated with morbidities that usually affect the elderly population, such as chronic obstructive pulmonary disease (COPD) and with the typical effects of radiotherapy, leading the elderly patients to a lower tolerance to the treatment. Both in acute character (during the therapeutic course or even few months after the treatment), with acute pneumonitis caused by radiation, as in a late character, with pulmonary fibrosis, the association of irradiation with respiratory diseases and physiological functions decrease pose an "explosive" potential for clinical decompensation of the elderly patient, including elevated mortality risk[31].

Focusing on these important factors from the thoracic irradiations "risk *versus* benefit" evaluation standpoint, it is clear that eventual deficiencies in the pulmonary "reserve" of the elderly patients may make them ineligible for a potentially curative treatment, because of the negative impact of doses and large treatment volumes on a sometimes subtle balance. However, it is elusive to believe that the anguish in contraindicating a more aggressive treatment considering the clinical status of the patient (or otherwise, indicating the treatment and causing an intolerable damage) may be settled by means of an eminently technical

evaluation of the planned treatment. Studies published in the late 1990´s point dosimetric factors of radiotherapy plan (thus recommending the use of conformal 3D radiotherapy as standard technique) as fundamental predictors of pulmonary toxicity/pneumonitis in patients treated for lung cancer[32]. But, although the greatest risk factor seems to be the radiation dose administered to the normal lung tissue, ideal dosimetric parameters are still to be determined as the reduction in the symptoms severity is considered. Equally, other factors may also play a relevant role, such as the simultaneous use of chemotherapy drugs, radioprotectors, and clinical parameters (age, performance and respiratory functional parameters), and therefore cannot be considered as being of lesser importance[33].

Renal system

The aging of the kidneys is characterized by morphological changes such as decrease in the organ´s weight and volume, decrease in the cortical thickness with atherosclerosis and intimal thickening of the intrarenal vessels, glomerulosclerosis and interstitial fibrosis with local tissue infiltration by inflammatory cells, and physiological changes such as reduction of the tubular function, of patency and glomerular filtration rate and of the renin-angiotensin system activity[34]. All such changes increase the difficulty in manipulating volumes and electrolytes by the elderly patient, increasing the risk of intolerance to the oncologic treatment, in particular, due to excessive toxicity to chemotherapy and radiopharmaceuticals. As regards radiotherapy, attention must be given to radiation treatment fields in patients already treated or under treatment with remarkably nephrotoxic drugs (cisplatin for example), in which concomitant or sequential irradiation of one or both kidneys, even if inadvertently, may cause additional and irreparable damage[35].

Cerebrovascular system

Radiotherapy plays an important role in the treatment of both primary and metastatic cerebral tumors, whether as a curative tool or with palliative purposes. Unfortunately the greatest majority of central nervous system (CNS) neoplasias present a very high aggressiveness potential, with severe consequences, when not fatal, imposing a high risk for neurocognitive deficits. It is also widely known that additionally to the deleterious action of the disease itself, radiotherapy acts as a risk factor for complications but, in most of cases, the need to utilize such treatment modality and the unfavorable prognosis of the patients take precedence over any fears of possible toxic effects. In some specific groups, such as patients presenting with low-grade gliomas, primary CNS lymphomas, patients submitted to prophylactic cerebral irradiation and patients treated with radiotherapy of the CNS are particularly more susceptible to the development of radiogenic effects, given their higher probability of local control and long term survival[36].

Additionally to the progressive behavior of CNS neoplasias (by the tumor progression or associated paraneoplastic syndromes, for example), other factors potentially associated with neurocognitive deficits in the elderly patient can be mentioned: CNS surgery, chemotherapy drugs (and medications such as corticosteroids), clinical comorbidities (such as diabetes mellitus and systemic arterial hypertension) and associated neurological comorbidities[37]. In addition, typical changes of the cerebrovascular physiology predispose to neurological complications. As the age progresses, a decrease in the vascular flow and cerebral metabolism is observed, with decreased cerebral perfusion reserve, neuronal tissue atrophy and noticeable functional impairment with memory and cognition loss, sensory and motor reflexes loss in a greater or lesser degree[38].

Radiogenic neurotoxicity mechanisms, on their turn, are more present in the white substance of the cerebral tissue and are attributed to diffuse tissue demyelination, vasculopathy and, eventually, to focal necrosis. The acute symptoms typically observed are dizziness, headache, nausea and vomiting, which later associate with sleepiness, fatigability (few months after the end of radiotherapy), eventual worsening of neurological deficits, and finally with convulsions and signs of intracranial hypertension (a late condition). Such effects seem to be more present in patients treated with irradiation of large cerebral volumes ("whole brain radiotherapy", for example), with higher daily doses (hyperfractionation: for example, ≥ 3 Gy daily), increased total doses and association with neurotoxic chemotherapy drugs[37].

Again, because of the greater frequency of previously mentioned factors and the predisposition resulting from typical physiological changes, elderly patients seem to be more susceptible to radiation-induced neurotoxicity. The weight of evidence supports the safety of focal radiotherapy using more modern techniques, with conventional fractionation and up to commonly prescribed doses (45–60 Gy)[37].

Musculoskeletal system

The musculoskeletal system shows changes related to age progression in the muscles, bones and joints. A decline in the muscular mass and functionality (strength) and increase in tissues adiposity are typical consequences of aging, in addition to bone mass loss (with greater incidence of osteoporosis, most prominent in women and after the beginning of menopause), and increased frequency of degenerative changes and osteoarthrosis of articular cartilages[39]. The elderly also present with a greater deterioration of postural balance and sensory decline (of the vestibular, auditory, visual and proprioceptive systems), with greater risk for falls and consequential fractures[40]. Although there appears to be no direct correlation between radiation treatment with normally utilized doses and the risk of osteomuscular complications, there are certain groups of patients that require greater attention, in principle, because of the multifactorial characteristics of hip fractures in the elderly, and by the severe consequences from the social point o view and in terms of quality of life.

Two of the most common causes leading cancer patients to be submitted to radiation therapy are prostate adenocarcinomas in men and uterine cervix carcinomas in women. In the first case, there is a high frequency of concomitant use of androgenic blockers, whose the known side effect is accelerated bone mineral loss, with greater risk for fractures[41]. In the second case, the use of radiotherapy as a modality of treatment for pelvic tumors (in general)

also seems to be strongly associated with a substantial increase in the risk for pelvic fracture for elderly female patients[42]. Both facts justify a greater attention to patients submitted to pelvic irradiation, with special care, for example, with respect to overdose in the hip joint and femoral head regions[43]. Tools such as the use of IMRT or the simple protection of such structures in the external radiotherapy fields can be very useful for the patients, including the youngest ones, with the intent of reducing the occurrence of fractures in the long term.

Hematologic and immune systems

For the elderly, hematopoietic and immune systems functional deficiencies present in the aging process seems to have little physiological importance in healthy individuals. In such cases, changes in these systems, including decrease in hemoglobin concentration, decrease in bone marrow cellularity and functionality, decreased polymorphonuclear function, lymphocytes and monocytes (with concomitant deficiency of cell-mediated immunity)[44,45] do not seem to have a great impact on the quality of life of physically healthy individuals, although it is known that there are impacts regarding anemia detectable by laboratory tests, capacity of bone marrow to respond to more intensive demands and greater susceptibility of the elderly patient to infections[46].

For the elderly patient with indication for radiation treatment, one must bear in mind that there is always the possibility that such patient may have already been submitted to other treatment modalities with prospects of severe myelotoxicity, such as chemotherapy that implies, for example, symptomatic anemia, pancytopenia and risk for infections, with progression to sepsis and death. In the irradiation of bone marrow compartment (for example, bones of the axial spine and hip), the recovery of peripheral blood cell count occurs more rapidly than bone marrow regeneration by the compensatory effect of the non-irradiated bone marrow; and, additionally to age, the recovery of the irradiated bone marrow is influenced by associated chemotherapy, dose and irradiated volume and survival after irradiation[47].

Specifically as regards anemia, there are indications that lower hemoglobin levels may be associated with worse treatment outcomes, for certain neoplasias, and in such cases specific therapeutic approaches should be considered[48].

CONCLUSION

With a view on the global population aging, the health assistance, particularly oncological assistance for the elderly, must also be seen as a first-order challenge in this new century. Two factors related to the population aging justify this preoccupation: a greater demand for treatment, in quantitative terms, and the peculiar physiological characteristics of this population. Although typical factors of the elderly physiology may influence the course of the radiation treatment, their correct identification and appropriate management, as well as the use of new technical developments in radiotherapy, may benefit such patients, allowing lower toxicity, greater efficiency and swiftness, for example, contributing to avoid the omission in utilizing radiotherapy when it is indicated.

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