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PROTON BEAM RADIOTHERAPY: THE USE IN ONCOLOGICAL THERAPY

Radioterapia com feixe de prótons: o uso na terapêutica oncológica

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Abstract: Understanding new approaches in the treatment of neoplasias is fundamental to instituting new indications and therapeutic options for patients with such pathology, especially in the current epidemiological scenario that shows an increase in the total cancer mortality rate. Proton therapy is an option with less effect on healthy tissues adjacent to the tumor. The objective of this work was to perform a literature review on the technique, advantages, limitations and uses of proton therapy in oncological practice. Consultation of national and international databases was made to achieve this goal. The use of proton therapy has been increasing worldwide, with conclusive studies showing its beneficial effects on uveal melanoma, hepatocellular carcinoma, esophageal cancer, among others. Due to the high cancer mortality in the world and the various adverse effects related to the healthy tissues adjacent to the tumor with conventional radiotherapy, there is a need for research on the real effects of proton therapy.

Keywords: Proton therapy; Radiotherapy; Neoplasms.

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Resumo: Compreender novas abordagens no tratamento das neoplasias é fundamental para instituir novas indicações e opções terapêuticas aos pacientes portadores de tal patologia, principalmente, no atual cenário epidemiológico que revela aumento na taxa de mortalidade total por câncer. A protonterapia se apresenta como uma opção com menor efeito sobre tecidos saudáveis adjacentes ao tumor. O objetivo deste trabalho foi realizar uma revisão bibliográfica sobre a técnica, as vantagens, as limitações e os usos da protonterapia na prática oncológica. Consulta a bases de dados nacionais e internacionais foi feita para alcançar tal objetivo. O uso da protonterapia vem aumentando em todo o mundo, com estudos conclusivos mostrando seus efeitos benéficos sobre o melanoma uveal, carcinoma hepatocelular, câncer de esôfago, dentre outros. Devido à alta mortalidade por câncer no mundo e aos diversos efeitos adversos relacionados aos tecidos saudáveis adjacentes ao tumor com a radioterapia convencional, surge necessidade de investigação sobre os reais efeitos da protonterapia.

Palavras-chave: Terapia com prótons; Radioterapia; Neoplasias.

INTRODUCTION

The rapid industrial growth and technological progress, and the intense process of urbanization in recent decades have enabled the increase in life expectancy of the world population and control of various diseases. In contrast, the aging of the population increased the incidence of chronic and degenerative diseases, such as cancer and cardiovascular diseases[1]

Cancer has therefore become an important public health problem in Brazil due to increased population exposure to risk factors; This is evidenced by the death rate over the years, in 1979, the neoplasias represented 7.91% of the total deaths in Brazil. Whereas in 2014 this number reached 16.23% of the total number of deaths in the country, revealing the importance of proper therapy to decrease both mortality and morbidity associated with this disease.[1,2]

Due to genetic abnormalities, cancer cells acquire the ability to proliferate more rapidly than normal cells and irregular, this division becomes autonomous, regardless of physiological stimulus for growth, i.e., cells remain growing even after the end of the stimulus that generated such changes. The malignant lesion also has the ability to invade and destroy surrounding tissue and spread to distant sites, metastasizing.

The early diagnoses are critical to establish the appropriate therapy according to the stage of cancer and determine the prognosis and survival of patients involved. Some cancers rely on strategies for screening to promote early diagnosis, others will benefit from various procedures such as endoscopy, histopathology, cytology, imaging and laboratory studies with tumor markers.[1,3]

The treatment has as main goals to cure, prolongation of life and improvement in the quality of life of patients. The main modalities of treatment are surgery and radiotherapy (RT) and chemotherapy (QT). The combination of methods is used in the majority of cases, using the QT or RT prior to surgical practice. The main objective of treatment is to destroy the cancerous cells with the preservation of healthy tissues surrounding the tumor.[4] Generally, surgery and RT are appropriate for local and regional disease, curing some cancers in early stages. QT can cure some cancers and have effective action in spread diseases, as in Hodgkin's disease and non-Hodgkin lymphomas of high degree and leukemias, in addition to the palliative use in other diseases.

The proton therapy or radiation therapy with protons beam mainly used in eye neoplasms as uveal melanoma, emerges as a therapeutic option with the ability to decrease the radiation dose used in surrounding tissues, keeping the tumor's dose high.[5] It is presented as a method highly accurate and with radiation of high energy, using beams of protons instead of X-rays and electrons for treatment of cancer. Many specialized centers in proton therapy are being built around the world, especially in developed countries, with optimistic results in the treatment of certain types of cancer.

The present work of review is the product of bibliographical, qualitative and exploratory research of data obtained in books and scientific production indexed in electronic databases of national and international data such as Bireme, Scielo and Pubmed, published between January 2000 and July 2017. For this study, the following keywords in Portuguese and in English were used: terapia com prótons (proton therapy), efeitos de radiação (radiation effects), radioterapia (radiotherapy), neoplasias (neoplasms).

The inclusion criteria were those who responded to the research objectives in the period, mentioned above. Articles without full availability of content and duplicated articles were excluded.

LITERATURE REVIEW

PROTON THERAPY

The use of protons for therapy in cancer was proposed in 1946 by Robert Wilson, but the first tests were in fact in Uppsala, Sweden, in 1957. With the development of diagnostic techniques enhanced in image, such as computed tomography, positron emission tomography and nuclear magnetic resonance, the proton therapy gained great visibility, allowing the more accurate location of tumor.[4] According to data from the Particle Therapy Co-Operative Group (PTCOG) of November 2016, there are 54 international facilities in operation, making a total of 131240 treated by protons.[6]

TECHNIQUE, ADVANTAGES AND LIMITATIONS

The radiation exerts its effect to destroy the ability of cells to divide and grow in both cancerous cells and normal cells, because it is not selective for a particular cell type.

Because of its technique and physical and radiobiological properties, proton therapy allows a more precise tumor control or abrasion, preventing damage to the perilesional tissues. This allows, also to maintain an increases radiation in the tumor while maintaining that dose reduced in tissue adjacent to the lesion, something which is not possible with the conventional radiological techniques. Generally, when conventional radiological technique is used, the dose of radiation irradiated to the tumor is usually inferior than the required dose in an attempt to minimize the damage to neighboring tissues, something which, as already mentioned, is necessary when proton therapy is used.

The control of radiation on, almost exclusively, tumor cells is possible thanks to the effect of "Bragg Peak ", a particularity of the protons and other subatomic particles electrically charged, which allows the concentration of energy of particles irradiated at a stopping point. To the extent that they penetrate the human body, the protons lose energy due to collisions with atoms and stop after traveling at a specific depth, something around 30 cm, where most of energy is deposited . Thus, when the beams of protons are irradiated in a high speed (approximately 25% of that of light) on the human body, they penetrate the individual without causing damage to the tissues during penetration, and the most part of this energy radiated locates on the place where the protons ceased its movement, the stop point. This point can be controlled with a lot of accuracy and precision, allowing to direct it against a tumor with a high dose of radiation (higher than that achieved with conventional radiotherapy) at the same time that saves the neighboring tissues, increasing the effectiveness against the tumor cells and tissues.

The protons have their Bragg peak with a milimetric precision and a way inferior width when compared to the size of a large part of the tumors, but this is adaptable and may be extended depending on the need and specificity of the tumor. This modulation is performed with the use of modulation of energy and with the use of scrubbers.

Despite of the benefits already cited from the peak of Bragg, the proton therapy is still not widely used around the world, especially in poor and developing countries, the high cost to establish and operate centers for proton therapy are limitations of its use in oncologic care. The few randomized clinical studies with high levels of evidence also limit satisfactory results and precise and reliable

information on its use.

USES:

The peak Bragg effect enables the use of proton therapy in tumors located near vital organs and radiosensitive tissues, such as tumors of head, neck and pelvic region, in addition to the pediatric use, reducing the chance of injury to healthy and developing adjacent tissues. Some studies have been carried out to prove the effectiveness of this type of therapeutic approach in certain tumors.

One of the most well-documented and explored use of the radiation therapy with protons beam is the uveal cancer. Wang et al[7] (2012), in a systematic and meta-analysis review, sought to compare the use of therapy with particles radioactively charged in uveal cancer with brachytherapy or enucleation, analyzing variables such as the recurrence of tumors, impact on mortality, adverse clinical effects, among other factors. The particles radioactively charged consisted mainly of protons beam, but also, to a lesser number, therapy with helium ions and ions of carbon. In total, 27 studies and 8809 patients were included. The authors found no statistically significant differences in mortality between the two groups. However, the therapy with particles radioactively charged (which includes the proton therapy) was superior in preventing local recurrence of tumor, retinopathy of radiation and formation of cataracts. As to the risk of enucleation, metastasis or the patients' life expectancy, there was no statistically significant difference between the two groups. The authors, however, classified as a low degree of recommendation of the conclusions of the analysis, with a view to the heterogeneity of the samples of included studies and the risk of bias.[7]

Patients with hepatocellular carcinoma (HCC) and prior cirrhosis, diagnosed by biopsy or abdominal imaging exams (CT or magnetic resonance imaging), were recruited by Loma Linda University Medical Center (LLUMC), in the United States, in a prospective study to evaluate the efficacy and safety of radiotherapy of protons beam of high dose in this type of cancer. 76 patients were evaluated between April 1998 and October 2006, the age range varied from 40 to 83 years. The acute toxicity of the treatment was minimal and included a slight fatigue and cutaneous reactions consisting of erythema (grade 1), no acute toxicity caused the interruption of the treatment, the most important toxicities were gastrointestinal complications (when the primary tumor was located near the small intestine there was an incidence of ulceration and bleeding GI). Levels of liver enzymes, bilirubin and albumin were used to evaluate liver disease induced by radiation, no significant change was observed after 6 months of treatment. The *média de sobrevivência livre de progressão* (Progression-Free Survival [PFS]) for the whole group was 36 months, with an average of PFS of 03 years of 60% for patients within the criteria of Milan. The patients received 63 degrees (Gy) of radiation over a period of 3 weeks with proton therapy[8]

Other uses of the therapy with protons to local HCC were reported by treatment centers in Japan. In a retrospective study conducted with 162 patients with HCC 192 treated from November 1985 to July 1998, Chiba et al[9] reached the conclusion that the therapy of protons beam for patients with HCC is not resectable, it is effective, safe, well-tolerated and repeatable. This is the mode of treatment useful for cure or palliation for patients with non- resectable HCC regardless of the size of the tumor, location of the tumor in the liver, insufficient supply of the tumor with arteries, presence of vascular invasion, liver failure and coexistent intercurrent diseases. The total median dose of irradiation of protons in this study was 72 Gy in 16 fractions over 29 days.[9] Hata et al[10] observed similar results in retrospective

review with 21 patients with HCC to whom other treatment modalities were contra-indicated or were not viable due to cohabiting illness and unfavorable conditions, doses of 63 Gy until 84 Gy were used (mean of 73 Gy) in 13 to 27 fractions (average of 18 fractions) for tumors treatments (Table 1).[10]

Table 1 - Use of proton therapy in hepatocellular carcinoma

Study	Bush et al[8]	Chiba et al[9]	Hata et al[10]
Number of patients	76	162	21
Dose irradiated	63 Gy	72 Gy	63-85 Gy
Average duration of proton therapy	21 days	29 days	23-63 days
Adverse documented effects	Gastrointestinal complications (ulceration and bleeding)	Elevation of total bilirubins, total drop of hemoglobin and elevation of hepatic transaminases	Erythema, loss of appetite and abdominal discomfort.

In another study, Makishimaet al11 (2015) demonstrated decrease of doses of irradiation at marginal tissues to tumor and, consequently, of the adverse cardiac and pulmonary effects when evaluating patients with esophageal cancer undergoing therapy with protons, when compared to those patients undergoing conventional radiotherapic therapy with x-rays. It is worth mentioning that these adverse effects are the major concern when radiotherapy is used, more specifically, in this type of tumor. The randomized clinical trial with 44 patients with esophageal cancer, in which 19 patients received conventional radiotherapy with x-rays and 25 patients received treatment with protons. Despite the 44 patients in the study present some degree of cardiopulmonary alteration when evaluated, not all of them had these findings with severity and/or clinical importance. In the 19 patients who underwent radiotherapy, the following cases were reported: 10 cases of pericardial effusion, four of pneumonia by radiation, two pleural lung, one of the pharmacological pneumonitis and one of pulmonary infection. Whereas in the group of patients undergoing proton therapy, only one showed pericardial effusion of clinical relevance, not being reported other adverse effects (Table 2). The median dose of radiation was similar for both groups. The patients had the same histological type of cancer, squamous cell carcinoma, and all of them also received chemotherapy during the first five days of radiotherapy and subsequently additional cycles, but none received a combination of x-rays and beams of protons.[11]Even though the surgical treatment is the standard for the treatment of this type of cancer, it is well-documented that when used concurrently, chemotherapy and radiotherapy bring additional benefits in relation to the prognosis, with reduction of mortality and increasing the quality of life of individuals after treatment. In this context, the therapy with protons optimizes such benefits, with a view to reducing the likelihood of complications of normal tissues and the adverse effects of radiation with its use. However, in the study of Makishima et al [11] (2015) the group undergoing radiotherapy with conventional x-rays contained some patients with more advanced disease than that has undergone the

therapy with protons, this may have affected the rates of morbidity, and it is important this consideration in the interpretation of the results, besides the small sample of patients followed in the clinical trial. Still, it was possible to observe that in patients with the same disease stage submitted to different therapies, the adverse events were less frequent than in those who made use of proton therapy .[11]

Table 2 - Comparison between proton therapy and conventional radiation in esophagic cancer

		Protons beams	Conventional radiation
Number of patients		25	19
Dose irradiated		60-70 Gy	60 Gy
Average duration		24 months	20 months
Number of patients with relevant adverse effects	Pharmacological pneumonitis	00	01
	Pulmonary infection	00	01
	Radiation pneumonitis	00	04
	Pulmonary stroke	00	02
	Pericardial stroke	01	10

Ohriet al[12](2013) concluded, in a meta-analysis of 20 studies, lower rates of late toxicity in patients with prostate cancer treated with proton therapy when compared to other types of treatment that employs technique of external radiotherapy. The systematic review included a total of 11.835 patients, seeking to assess the rates of late gastrointestinal and genitourinary toxicities when made use of therapy with protons or intensity-modulated radiation and comparing with patients who made use of conventional radiotherapy. The assays used as assessment tool the RTOG (Late Radiation Morbidity Scoring Schema). There was a decrease in the rate of gastrointestinal toxicity in patients who made use of proton therapy or intensity-modulated radiation, but the same was not observed for the genitourinary adverse events. It is important to stress that the gastrointestinal and genitourinary toxicities are events that can be caused by a number of factors beyond the radiation, although symptoms considered rare by the low incidence (5%), which, however, are important due to their respective clinical repercussions and severities presented..[12]

CONCLUSION

Because of the increase in the incidence of malignant neoplasms in recent years and the survival of patients when treated early, the use of an effective therapy and which reduces adverse events in the short and long term is essential in order to decrease morbidity and improve the quality of life of patients with cancer. Therapy with protons beam, although still limited to a few countries due to its high cost and its technological complexity, has much to offer in the present and in the future in the treatment of cancer patients. This is thanks to its physical and technical characteristic that allows to focus a high degree of radiation on some point at the same time that saves the normal tissues. The literature shows promising results with its use in which there are many studies that corroborate the fact that the reduction in adverse events with the use of proton therapy in specific types of cancer, however there are limitations in the work so far carried out which should be taken into account in

time to interpret the results. In this way, the therapy with protons beams is an alternative that seems to offer advantages in the treatment of certain types of cancers, although more studies are needed to provide security and compare their effectiveness in different types of cancer, which although present this title in common, vary greatly in events, developments and behavior regarding the therapy.

REFERENCES

1. BRASIL. Ministério da Saúde. Secretaria de Atenção à Saúde. Instituto Nacional de Câncer. Coordenação de Prevenção e Vigilância. *A situação do câncer no Brasil*. Rio de Janeiro, RJ, 2006.

2. INCA. Instituto Nacional de Câncer. Atlas de mortalidade por câncer. Disponível em:<https://mortalidade.inca.gov.br/MortalidadeWeb/>. Acesso em: 24 de Julho 2017.

3. KRUMAR, V. et al. *Robbins e Cotran, bases patológicas das doenças*. 8. ed. Rio de Janeiro: Elsevier, 2010.

4. CARUSO, F.; CARVALHO, B.H.V.; SANTORO, A.F.S. A física de altas energias e a terapia de câncer com prótons: motivações e perspectivas. In: ALVES, G.; CARUSO, F.; MOTTA, H.; SANTORO, A.(Org.). *O Mundo das Partículas de Hoje e de Ontem*. 1.ed. São Paulo: Ed. Livraria da Física, 2000. p. 117-130.

5. CHRISTOVAO, M.T.; CAMPOS, T.P.R. de. Análise da distribuição espacial de dose absorvida em próton terapia ocular. *Radiol Bras*., São Paulo, v. 43, n. 4, p. 249-254, Agosto 2010.

6. PTCOG: Particle Therapy Co-Operative Group. Disponível em: <http://ptcog.web.psi.ch>. Acesso em 24 Julho 2017.

7. WANG, Zhen, et al. Charged Particle Radiation Therapy for Uveal Melanoma: A Systematic Review and Meta-Analysis. *Int. J. Radiation Oncol. Biol. Phys.*, Rochester, v. 86, n. 1, pp. 18e26, Junho 2013.

8. BUSH, D.A.; KAYALI, D.; GROVE, R.; SLATER, J.D. The safety and efficacy of high-dose proton beam radiotherapy for hepatocellular carcinoma: a phase 2 prospective trial. *Cancer*, Loma Linda, v. 117, n. 13, p. 3053-3059, Janeiro 2011.

9. CHIBA, T. et al. Proton beam therapy for hepatocellular carcinoma: A retrospective review of 162 patients.*Clin. Cancer Res.*, Tsukuba, v. 11, n. 10, p. 3799-3805, Maio 2005.

10. HATA, M. et al. Proton beam therapy for hepatocellular carcinoma with limited treatment options. *Cancer*, Tsukuba, v. 107, n. 3, p. 591-598, Agosto 2006. Disponível em: <http://onlinelibrary.wiley.com/doi/10.1002/cncr.22039/abstract>. Acesso em 24 Julho 2017.

11. MAKISHIMA, Hirokazu, et al. Comparison of adverse effects of proton and X-ray chemoradiotherapy for esophageal cancer using an adaptive dose–volume histogram analysis. *Journal of Radiation Research*, Oxford, v. 56, n. 3, p. 568–576, Março 2015.

12. OHRI, Nitin, et al. Late toxicity rates following definitive radiotherapy for prostate cancer. *Can. J. Urol.,* Philadelphhia, Agosto 2012. Disponível em: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3808959/?tool=pubmed>. Acesso em 24 Julho 2017.