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REVIEW ARTICLE

BIBLIOMETRIC REVIEW ON HYPERPROTECTED RADIOTHERAPY FOR THE TREATMENT OF BRAIN TUMORS

Peter Kühn, Reginaldo Mortágua Gonçalves and *Patrícia Fernanda Dorow

Department of Health and Services / DASS, Federal Institute of Education, Science and Technology of Santa, Catarina, 88020-300, Florianópolis-SC, Brazil

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ABSTRACT

Introduction: In recent years, there has been considerable interest in the application of advanced imaging techniques to improve the treatment of brain tumor. Objective: to analyze studies that deal with hyperfractionation in relation to the survival of patients submitted to radiotherapy of brain tumors.

Materials and methods: By choosing the keywords Hyperfrationation and brain for searching the database of Scopus, 102 documents were found. Due to the inclusion of the topic, the publications related to protonotherapy and anatomical areas different from those of interest were excluded after the cross (TITLE-ABS-KEY (hyperfractionation AND BRAIN)) AND (glioma) AND AND (glioblastoma) AND (EXACTKEYWORD, "Brain Neoplasms"), 26 papers were selected. The authors and articles with the highest citations and publications were searched for the most expressive information according to the research theme.

Results: The incidence of high grade glioma (HGG) is approximately 5 per 100,000 person-years in Europe and North America. According to Hingorini *et al.* 2012, the prognosis of patients with glioblastoma (GBM) remains poor, and the use of hyperfractionation or dose escalation beyond 60 Gy did not confer any survival benefit. Hypofractionated radiation therapy has been employed as a novel approach to achieve dose escalation with interesting results. For Lutterbach J. et al 2003, in addition to established prognostic factors, anemia and elevated serum LDH levels may negatively influence the outcome in a multivariate analysis in patients with glioblastoma.

Conclusion: hyperfractionation has not been able to obtain significant answers regarding the survival of patients submitted to radiotherapy of brain tumors.

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INTRODUCTION

According to the National Cancer Institute (INCA, 2017) radiotherapy is defined as "a method capable of destroying tumor cells by employing a beam of ionizing radiation," ie a spatial application process of a quantity and intensity of radiation predetermined by the physician, so that during the administration of the rays, spatial distribution and incidence of these occur in the greater amount of target tissue to be eradicated thereby protecting healthy tissues. According to the International Atomic Energy Agency (IAEA), radiotherapy planning should always be based on the most accurate diagnostic methods available to determine the spread of the disease (Vincent *et al.,* 2015). In recent years, there has been considerable interest in the application of advanced imaging techniques to improve the treatment of brain tumor, mainly in three areas:

a) Attempts to identify the best distribution of tumor cells and to locate tumor invasion, particularly relevant for the planning of radiotherapy.
b) Attempts to identify the borderline relationships of the tumor with the white matter and eloquent areas of the cerebral cortex to provide information that reduces complications in normal tissues.
c) Early prediction of response to conventional therapy, based on initial tumor characteristics or initial changes in response to therapy, which could be used to modify or adapt the radiotherapy treatment plan (WHITFIELD *et al.,* 2014).

The classification of brain tumors by groups, according to Margareth Todd (1949), is as follows:

Group 1: Radiorresistant tumors (astrocytomas, ependymomas, oligodendrogliomas, neuromas, resistant forms meningiomas);
Group 2: Localized radiosensitive tumors (neuroepitheliomas, hemangioblastomas, sensitive meningiomas);

Corresponding author: **Patrícia Fernanda Dorow,**
Department of Health and Services / DASS, Federal Institute of Education, Science and Technology of Santa, Catarina, 88020-300, Florianópolis-SC, Brazil.

Table 1. Classification of publications

Classification of publications							
Year	**Amount**	**Study area**	**Amount**	**Document type**	**Country**	**Source**	**Diomai language**
2016	2	Biochemistry, Genetics and Molecular Biology	17	Artigo 23	EUA: 12	Journal: 25	English: 25
2012	1	Chemistry	1	Revisão 3	Germany: 5	Book 1	Japanese: 1
2011	1	Health Professions	1		Japan: 5		
2004	1	Medicine	25		Canada:4		
2003	1	Neuroscience	4		Israel:1		
2001	2	Physics and Astronomy	7		Italy:1		
1999	1				England:1		
1997	4				Yugoslavia: 1		
1995	3				Undefined: 1		
1994	4						
1993	1						
1992	2						
1989	2						
1984	1						

Group 3: Radiosensitive tumors with metastases (medulloblastomas, ependimoblastomas, malignant papillomas of the coroid plexus, pineoblastomas);

Group 4: Malignant resistant tumors (glioblastomas, astroblastomas);

Group 5: Tumors of the pituitary gland (chromophobe resistant tumors, tumors less resistant to chromophils, basophilic tumors of unknown resistance).

Gliomas are the most common primary central nervous system (CNS) tumors in adults accounting for about one third of tumors of the central nervous system and 81% of all malignant CNS tumors reported in the United States. The most common and most malignant type of glioma is glioblastoma (GBM), with a mean overall survival rate (OS) of 15 months after surgical resection followed by adjuvant radiotherapy (RT) and Temozolomide (TMZ) chemotherapy. The prevalence of GBM is higher in patients aged 50 years or older and is likely to increase with the ongoing demographic change for the older ages (Kaul *et al.,* 2016). The objective of this study was to analyze studies that deal with hyperfractionation in relation to the survival of patients submitted to radiotherapy of brain tumors. According to Jason Fangusaro, 2012, high-grade gliomas (HGG) are one of the most common central nervous system (CNS) tumors found in adults, but represent only about 8 to 12% of all pediatric CNS tumors. Historically, pediatric HGG has been thought to be similar to adult HGG, since they appear histologically identical; however, molecular, genetic and biological data show that they are distinct.

MATERIALS AND METHODS

Data collection was performed from 27.09.2017 to 02.12.2017 in the Scopus database. At first, 102 documents were found with the keyword Hyperfrationation and brain. In a second moment the publications referring to protonotherapy and anatomical areas different from the one of interest, after the crossing (TITLE-ABS-KEY (hyperfractionation AND BRAIN)) AND (glioma) AND (glioblastoma) AND (LIMIT-TO (EXACTKEYWORD, "Brain Neoplasms", 26 papers were selected, of these 25 in the English language and one in Japanese, with dates from 1984 to 2016. The authors and articles with the highest citation and publication highlights were searched for the most expressive information according to with the research theme.

RESULTS AND DISCUSSION

All 26 articles were classified according to the year of publication, study area, type of document, country of origin, source of publication and language according to Table 1. Some authors deserve recognition for their publications and quotations. We highlight that the author Wara, W.M. published 7 articles with the research theme, being 6 in the International Journal of Radiation Oncology Biology Physics. The author, Kaul, David, Charite - Universitatsmedizin Berlin, Department of Radiation Oncology, Berlin, has 32 documents in his name, was cited in 541 and as coauthor in 149. The article entitled Metronomic photodynamic therapy as a new paradigm for photodynamic Rationale and preclinical evaluation of technical feasibility for treating malignant brain tumors, published in the year 2004 was cited 113 times in other works.

Already the work entitled Hyperfractionated radiotherapy of human tumors:

Overview of the randomized clinical trials published in the year 1997 was referenced 122 times. The article Fluorodeoxyglucose uptake and survival of patients with suspected recurrent malignant glioma published in 1997 is cited 132 times and the article entitled White matter changes are correlated significantly with radiation dose. Observations from a randomized dose-escalation trial for malignant glioma (radiation therapy oncology group 83-02) published in 1994 is cited 101 times. According to Khan *et al.* 2016, the incidence of high grade glioma (HGG) is approximately 5 per 100,000 person-years in Europe and North America. According to Hingorini *et al.* 2012, the prognosis of patients with glioblastoma (GBM) remains poor, and the use of hyperfractionation or dose escalation beyond 60 Gy did not confer any survival benefit. More recently, hypofractionated radiation therapy has been employed as a novel approach to achieving dose escalation with interesting results. For Lutterbach *et al*. 2003, in addition to established prognostic factors, anemia and elevated serum LDH levels may negatively influence the outcome in a multivariate analysis in patients with glioblastoma. In the Phase III trial of accelerated hyperfractionation with or without difluromethylornithine (DFMO) versus standard fractionated radiotherapy with or without DFMO for newly diagnosed patients with glioblastoma multiforme, Prados *et al.,* 2001, concluded that the standard fractional irradiation for 59.4 Gy remains the treatment of choice for patients newly diagnosed with glioblastoma multiforme in relation to accelerated hyperfractionated irradiation to 70.4 Gy because in this prospective Phase III study, no benefit survival was observed. In the article the treatment of brain stem and thalamic gliomas with 78 Gy of hyperfractionated radiation therapy, Prados MD *et al.,* 1995 concluded that for patients with brainstem gliomas or thalamus, increasing radiotherapy dose of 72 to 78 Gy did not significantly improve survival. Different treatment strategies are clearly needed. In the article Hyperfractionated radiation therapy (hfx rt) followed by multiagent chemotherapy (CHT) in patients with malignant glioma: A phase II study. Jeremic *et al.* 1994, concluded that hypofractionated radiation therapy followed by multiagent chemotherapy was well tolerated with mild toxicity and virtually no late toxicity. More patients and longer follow-up are needed for a more in-depth assessment of its activity and late effects in patients with anaplastic astrocytoma. In the article Accelerated hyperfractionation in the treatment of malignant glioma, Sugawara T. et al. 1994, performed a retrospective evaluation to determine whether accelerated hyperfraction (AHF) improves the survival rate of patients with malignant gliomas and the results showed that multivariate analysis using the Cox proportional hazards model revealed that AHF significantly increased the survival rate. In addition to pointing to the selection of the AHF method as a treatment regimen, the multivariate analysis showed the following factors to be indicators of favorable prognosis: a different histopathological diagnosis of glioblastoma multiforme, age less than 40 years and supra-assentorial localization of the tumor.

Conclusion

By the characterization of the analyzed publications, even with the highlighted keywords, some articles did not present the expected relevance and also the little publication about the subject in the last 5 years was observed. However, some authors are often referred to in other publications. We also observed that hyperfractionation has not been able to obtain significant responses regarding the survival of patients submitted to radiotherapy of brain tumors, whereas hypofraction seems to be the most appropriate form, but it is clear also the recommendations of new researches with a greater number of patients. On the other hand there is no increase in late toxicity using hyperfractionation.The relationship of dose effect to radiation therapy is not clear when treating patients diagnosed with glioma with increasing doses of radiation gradually. There is no statistically significant difference in any of the tumor progression or survival times even with increasing dose intensity of radiation using hyperfractionation and no response effect.

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