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USE OF PET-CT IN RADIOTHERAPIC GLIOMAS PLANNING

[1]Caroline Salvador, [2]Reginaldo Mortágua Gonçalves, [2]Tatiane Sabriela Cagol Camozzato, [3,*]Patrícia Fernanda Dorow, [4]Caroline de Medeiros and [5]Paulo Marcelo Rodrigues

[1]MSc, student in the Post-Graduation Program in Radiological Protection, Academic Department of Health and Services. Federal Institute of Santa Catarina, (IFSC), Santa Catarina, Brazil
[2]Doctoral in Medicine and Health Sciences, Professor of the Post-Graduation Programin Radiological Protection. Academic Department of Health and Services, Federal Institute of Santa Catarina. (IFSC), Florianópolis, Santa Catarina, Brazil
[3]Doctoral in Engineering and Knowledge Management, Professor of the Post-Graduation Programin Radiological Protection. Academic Department of Health and Services, Federal Institute of Santa Catarina. (IFSC), Florianópolis, Santa Catarina, Brazil
[4]Master in Education, Professor of the Post-Graduation PrograminRadiological Protection, Academic Department of Health and Services, Federal Institute of Santa Catarina (IFSC), Florianópolis, Santa Catarina, Brazil
[5]Doctor, Specialist, Radio-Oncologist, Doctor of the Oncology Research Center, Florianópolis, SantaCatarina, Brazil

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ABSTRACT

The use of positron emission computed tomography in radiotherapy planning has increased over the last decade. In this study, we analyzed, through a bibliographic research, the use of positron emission computed tomography examination in radiotherapy of gliomas. The research was conducted from October to November 2017, in the databases of "VHL", "Science Direct", "Pubmed" and "Web of Science", through the married descriptors: Positron Emission Tomography Computed Tomography OR pet AND Radiotherapy AND Planning and was constituted of 14 articles published in the period from 2013 to 2017. The literature has shown that the positron emission computed tomography technique when used for the radiotherapy of gliomas allows a safer treatment in the delivery of the dose in the delimited structures, thus saving the normal tissue, reducing the toxicity and reducing the probability of geographical errors in the definition of the target volume, thus having the potential to impact many aspects of the therapeutic approach. It was also noticed the increase of research related to the radiopharmaceuticals used in this examination, emphasizing the importance of further studies related to the topic.

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INTRODUCTION

Positron emission computed tomography is a PET-PET (PET-CT) device coupled to a CT (Computed Tomography) PET; therefore, the examination combines CT techniques and nuclear medicine, with indications in the specialties of a) oncology: for cancer staging and diagnosis, radiotherapy planning, response evaluation, relapses, metastases, follow-up and late toxicity, etc. b) cardiology: to determine cardiac blood flow, effect of heart attacks and myocardial infarction and; c) neurology: for studies of brain activity with evaluation of abnormality such as tumors, memory problems, Alzheimer's, location of epileptogenic focus in patients candidates for surgery, etc. The PET-CT exams perform the fusion of metabolic images of PET with the tomographic anatomical images.

***Corresponding author:* Patrícia Fernanda Dorow,**
Doctoral in Engineering and Knowledge Management, Professor of the Post-Graduation Programin Radiological Protection. Academic Department of Health and Services, Federal Institute of Santa Catarina. (IFSC), Florianópolis, Santa Catarina, Brazil

For Bailey, Maisey, Townsend and Valk (2005), PET-CT is a functional imaging tool that can improve the accuracy of target volume delineation from the definition of metabolic tumor volume along with morphological imaging and clinical examination findings. Positron emission tomography (PET) has been established as an efficient and safe diagnostic method, representing the most modern technology for image studies in oncology. The technological advance with the hybrid PET and CT (PET / CT) equipment is of great notoriety, thus enabling a more accurate and early diagnosis. Fluoride-18-fluoride-fluoride (FDG-18F) is the radiopharmaceutical used in PET and PET / CT examinations, a glucose analogue that allows glycolytic detection of the cell, aiding in the diagnosis of malignancies (Silva *et al*., 2017). Molecular imaging with PET is increasingly being implemented in neuro-oncology, as it provides additional metabolic information for the tumor, both for patient management and for evaluation of newly developed therapies (La fougère*et al*., 2011).The general objective of the present study is to analyze the use of PET-CT in the radiotherapy of gliomas.

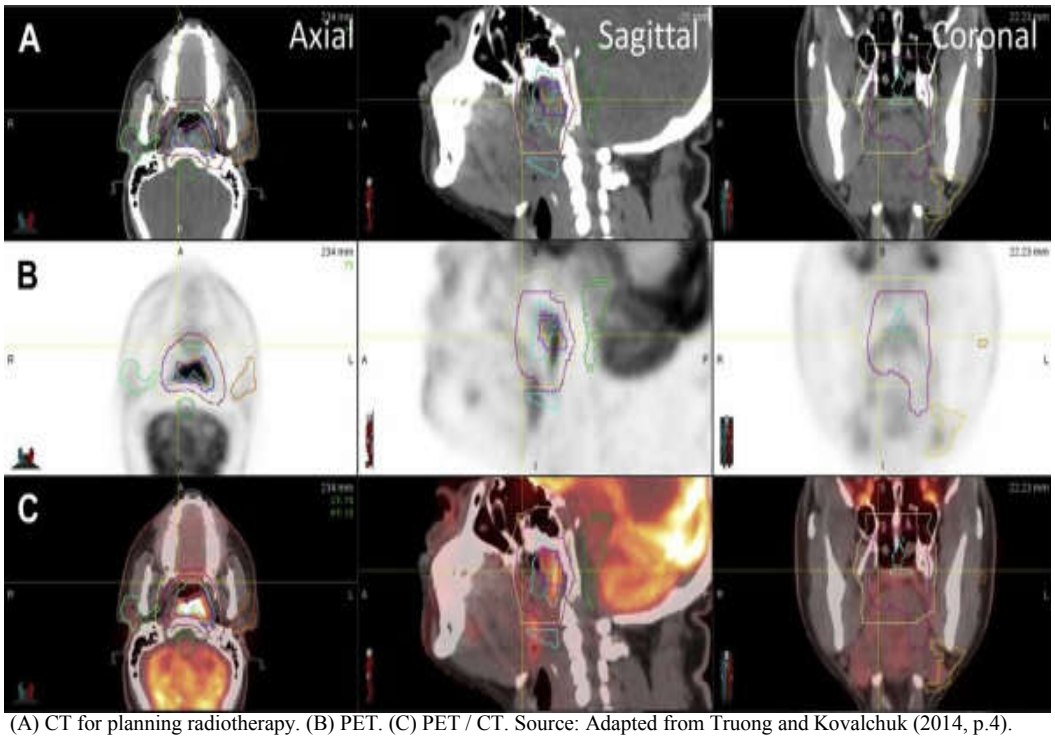
MATERIALS AND METHODS

The search was performed in the following databases and electronic addresses: "Virtual Health Library" (VHL), "Science Direct", "Pubmed" and "Web of Science", through the married descriptors: Positron Emission Tomography Computed Tomography OR PET AND Radiotherapy AND Planning. The result of the preliminary search is shown in table 1. In order to select the articles that were studied and discussed, the inclusion and exclusion criteria of the articles were defined, with inclusion items as follows: articles in Portuguese, English and / or German with the complete work available, dealing with subjects related to PET-CT examination in the planning of radiotherapy as the main focus in the research and articles published from 2013 to 2017. The primary study of the consulted journals addressed the abstracts of the articles, whose title was related to the theme of this work. We highlight the articles that made an association between PET-CT scan and gliomas. Data collection was performed in October and November 2017, and the final sample of the study was composed of 14 articles that met the selection criteria.

RESULTS AND DISCUSSION

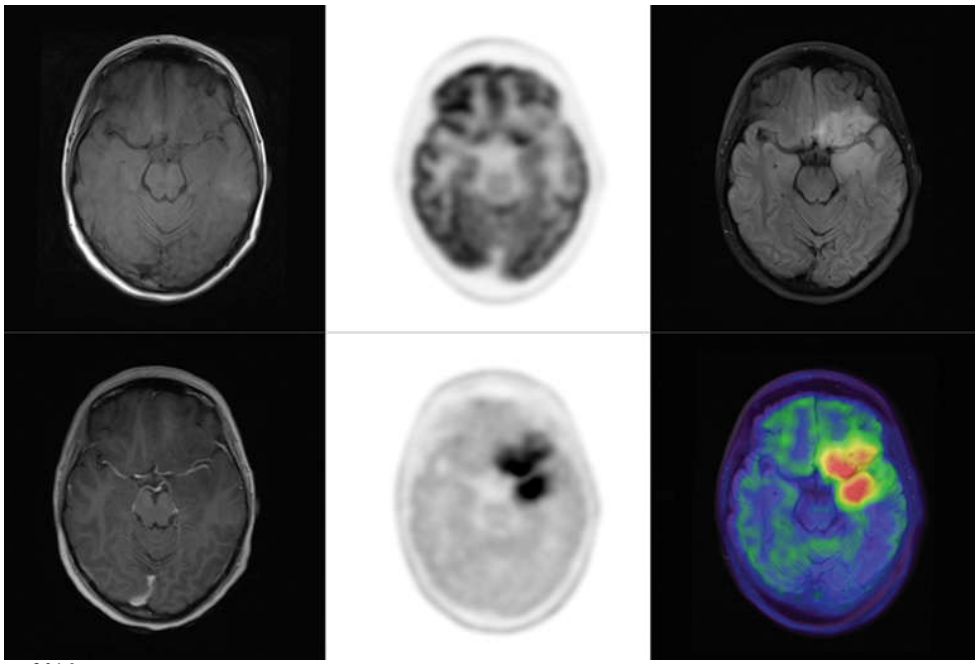
Gliomas are the most common primary brain tumors, accounting for more than 80% of all Central Nervous System neoplasms and are currently classified by the World Health Organization as astrocytomas, oligodendrogliomas, mixed tumors, and ependymomas. The diagnosis and classification of these tumors are based on histopathological features that are sometimes difficult to define. Despite advances in neurosurgery, chemotherapy and radiotherapy, the prognosis of patients with gliomas is still very restricted (Mendes *et al*., 2014). The World Health Organization (WHO) proposes a classification for these tumors, from grade I to grade IV, being made from the histology and architectural pattern of the primary lesions. In addition to this type of evaluation, techniques of immunohistochemistry, cytogenetics and molecular biology are also employed to subclassify these tumors. Meningiomas represent the most frequent primary CNS tumor (35.5%), followed by glioblastoma (15.8%), and a total of 311,202 meningiomas (35.5%), according to a survey conducted by the Central Registry of Brain Tumors in the United States between 2005 and 2009). The most common sites are meninges (35.2%) and pituitary (15.3%). Meningiomas represent the most common CNS tumor, involving mainly adults over 65 years old, uncommon in children, and twice as common in females. Glioblastomas are the second most frequent tumor, representing about 16% and, like meningiomas, are more prevalent in adults over 65 years and rare in children. Glioblastomas are 1.6 times more common in men (Mendes *et al*., 2014). Gliomas classified by the World Health Organization (WHO) as a high grade [grade III and IV] represent the majority of malignant tumors of the central nervous system that affect adults; with predominance of glioblastoma multiforme, also known as GBM and grade IV astrocytoma. Low-grade gliomas are much less common in adults, and most are grade II gliomas according to WHO classification (Whitfield *et al*., 2014). 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).

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; Castrejón; Londoño, 2015). High-grade gliomas are lethal brain tumors with median survival for 12 to 15 months. Computed tomography (CT) and magnetic resonance imaging (MRI) have so far provided limited information on the degree of malignancy, infiltration and effects on surrounding normal tissue, and differentiation between necrotic tissues and recurrent tumor (FROSINA, 2016). Since its advent in 1970, PET (Positron Emission Tomography) has gained importance in the evaluation of patients with gliomas. The PET image allows a highly sensitive measurement using active biochemical molecules labeled with positron-emitting radionuclides, also known as radiotracers (MIYAKE *et al*., 2016). Positron emission tomography is a diagnostic procedure that allows the integration of computed tomography and MRI information with metabolic, pharmacokinetic, and pharmacodynamic data. With the increasing availability of radiolabelled markers, P*Et al*lows generalized applications in the diagnosis, prognosis and therapy of high-grade gliomas (Frosina, 2016). Due to its superior spatial resolution, magnetic resonance imaging is favored in the management of high-grade gliomas, but its superiority to computed tomography is not clinically demonstrated (Dhermain, 2014). It is conceived that PET-CT (Positron Emission Tomography - Computed Tomography) has added a new dimension to the cancer image. It can be used in the radiotherapy planning of different types of cancer with better precision and result compared to conventional imaging methods (Sharma; Mukherjee, 2016). According to Albert *et al*. (2016), the biological and metabolic information provided by PET can identify tumor sub-regions with a higher risk of



(A) CT for planning radiotherapy. (B) PET. (C) PET / CT. Source: Adapted from Truong and Kovalchuk (2014, p.4).

Figure 1. Images to aid in the delimitation of the target volume in radiotherapy planning



Source: Law, 2016.

Figure 2. F-18 FDG PET / CT (upper row) and F-18 FDOPA PET / CT (lower row) of a low-grade non-highlighting low-grade frontotemporal cerebral glioma showing the high contrast background tumor of amino acid images in comparison with metabolic image

Table 1. List of keywords and their results

Database	Descriptors	Total Articles
BVS	Positron Emission Tomography Computed Tomography OR PET AND Radiotherapy AND Planning	771
Web of Science		8532
Science Direct		3206
Pubmed		600

Source: Prepared by the authors, 2018.

recurrence, which may be included in the volume of radiation increase. The ability to improve the definition of tumor extension and its biology can be used to improve the therapeutic relationship of radiation treatment. The current recommendations focus on the role of PET in the radiotherapy planning of WHO class III / IV gliomas, as the role of PET imaging in WHO grade II glioma irradiation is not well established. For Truong and Kovalchuk (2014), the interest and the use of PET-CT in the planning of radiotherapy treatment have increased over the last decade. According to the aforementioned authors, many institutional studies examined the impact of PET and / or PET-CT on the delineation of GTV (visible tumor volume or gross tumor volume) for radiotherapy planning, most demonstrated PET-CT superiority over PET or CT alone for diagnosis, staging and consistency of the target volume definition. According to Frosina (2016), treatment of high-grade gliomas usually requires radiotherapy and a close-up image plays a central role in radiotherapy planning, where at least two major volumes must be delineated: a) GTV that identifies the position and extent of the visible tumor volume, and b) CTV containing GTV plus a margin for the spread of subclinical disease that may not be fully visualized and is crucial for maximizing the dose of radiation to the tumor. The delineation of GTV based exclusively on CT planning may be difficult, especially due to the limited contrast between the tumor and surrounding tissues with similar density (Vincent; Castrejón; Londoño, 2015).

As quoted by Truong and Kovalchuk (2014), conformational radiotherapy techniques depend on the precise delimitation of the target volume to ensure coverage of the tumor with the prescribed radiation dose, in addition to sparing adjacent normal tissue. New imaging techniques that improve the definition of invasive tumor routes, allowing modification of the expansion to a CTV area that better reflects the risk of recurrence, and provide some insight into the major biological steps preceding tumor-induced tumor size reduction radiotherapy, may improve treatment planning, diagnosis and prognosis of high-risk gliomas (Frosina, 2016).

In this context, according to Vicente, Castrejón and Londoño (2015), the use of PET-CT in the planning of radiotherapy has the potential to impact many aspects of the therapeutic approach: indication of treatment (ie curative or palliative), volume delineation tumor reduction, radiation reduction for non-pathological tissues, and reduction of interobserver variability in geometric planning. This optics has affinity with the propositions of Send *et al*. (2017), the authors cite that accurate primary staging is essential for therapeutic planning and, therefore, for patient prognosis. In this sense, PET-CT has a significantly higher precision and this may have a considerable influence on the choice of therapy regimen and, therefore, also on the prognosis of patients. For Truong and Kovalchuk (2014), PET-CT is a functional imaging tool that can improve the accuracy of target volume delineation from the definition of metabolic tumor volume along with morphological imaging and clinical examination findings. According to the aforementioned authors, data from PET-CT scans and tomographic data from the simulation are transferred to a radiotherapy treatment planning system. The images are merged and the radio-oncologist defines GTV using all available diagnostic information, including clinical examination and imaging to accurately define the lesion. Volumetric expansions are created from the GTV (visible tumor volume) to form a clinical target volume (CTV) that considers the microscopic spread of the tumor and ensures coverage of subclinical or suspected disease sites. An additional final expansion of the CTV creates PTV which considers errors in treatment and tumor movement both during each treatment (intra-fraction) and between treatments (inter-fraction). As cited by Christensen *et al*. (2017), PET-CT has great potential to optimize the radiotherapy treatment plan. It can be used to predict outcome of treatment using interleaved tests, which can be used to modify the treatment plan based on the therapeutic response. It may also provide information for a more accurate staging if performed as a full-body examination. In this sense, in several studies PET / CT resulted in changes in treatment plans and target volumes for patients with head and neck cancer. In the study by Christensen *et al*. (2017), PET-CT gave rise to the suspicion of unknown metastases in 13% of the 207 patients with head and neck cancer, where 10% of patients had a major change in treatment strategy. In the PET-CT tests, substances composed of two elements are used: the drug and the radionuclide. When these elements are united, a drug is formed marked with radioactive material that we call radiopharmaceuticals. The most commonly used radionuclide for high-grade gliomas PET is fluorine-18 (18F), due to its high reactivity and versatility, as well as intrinsic spatial resolution (Frosina, 2016).

Fluoride-18-labeled fluordeoxyglucose ([18F] FDG) is the major radiopharmaceutical used in PET-CT scans. In contrast to glucose (the energetic substrate of most cells in the human body), glycolytic mapping of tissues, the difference in glucose consumption between normal tissues and malignant cells, favors the detection and diagnosis of malignancies (SILVA and BOLOGNESI, 2017). For Vicente, Castrejón and Londoño (2015), the use of [18F] FDG provides a valuable imaging technique, its implementation in the radiotherapy image protocol, improves the selection of candidates for curative and palliative radiotherapy and allows a greater management optimization of treatment. In addition, the functional image of PET can provide biological information that allows dose painting or dose escalation to tumor subvolumes. According to Cammaroto *et al*. (2016), PET-CT with [18F] FDG is considered a powerful molecular imaging technique that demonstrates the increase in the metabolic activity of cancer cells, thus finding a way in clinical practice for the diagnosis and staging of various types of cancer. However, misleading findings have been reported due to absorption in non-malignant tissues caused by peritumoral inflammation and physiological changes, especially in the region of the head and neck.[18F] FDG is widely used in PET of high-grade gliomas, although its high absorption in normal gray matter may limit its use to the image of some gliomas that may not be visualized. According to Miyake *et al*. (2016), [18F] FDG-PET is applicable for the gliomas image due to increased glucose metabolism in high-grade gliomas and the positive correlation between glycolytic rate and malignancy. However, due to the high physiological metabolism of glucose in normal brain tissue (cerebral cortex, basal ganglia and thalamus) and inflammatory tissue (ie, macrophages), the identification of glioma in such tissues is difficult. Thus, the decreased sensitivity of [18F] FDG-PET in the detection of injury is a major limitation for assessing gliomas. According to Law (2016), late imaging (e.g., 6 h) following administration of FDG instead of the usual post-radiotracer image of 60-90 minutes may improve the discrimination between tumor and physiological background absorption, a as the FDG is retained in the tumor longer than in the normal brain parenchyma.

Another approach to radiopharmaceuticals comes from Albert *et al*. (2016) for the authors [18F] FDG PET has limited utility in the WHO III / IV radiotherapy planning of gliomas, and the radio therapeutic planning using amino acid PET, such as [11C] MET, [18F] FET or [18F] FDOPA PET, seems feasible, having preliminary evidence of potential benefit. According to the aforementioned authors, the metabolic markers of glucose exhibit good sensitivity, but a reduced specificity for malignant tumors, whereas the metabolic pathways of amino acids provide better delimitation of tumors and cell proliferation. With similar reflections is Dhermain (2014), citing that in PET, measurement of amino acid absorption using [11C] -methionine (MET) or [18F] -fluoroethyl-L-tyrosine (FET) has been shown to be more reliable in visualizing metabolism of the brain tumor than the use of [18F] -fluoro-deoxy-2-glucose (FDG). According to Law (2016), FDG PET has a limited utility for conventional treatment planning because of the relatively low contrast between tumor and background / normal gray matter. More recently, the addition of PET images from some radiotracers - in particular the amino acid analogues - in radiotherapy planning has been shown to be promising in the identification of post-surgical microscopic residual tumor and differentiation of brain tissue tumor, thereby improving local and reduce radiation to the healthy brain parenchyma.

For Albert *et al*. (2016), PET imaging techniques are useful for detecting biopsy focal points, deciding on tumor resection, radiotherapy planning, monitoring therapy, and distinguishing recurrence of brain tumor or progression of post-radiotherapy effects. However, it is not possible to use only one PET marker to make all clinical decisions because each plotter has advantages and disadvantages (Miyake *et al*., 2016).In this way, we can highlight in agreement with Vicente, Castrejón and Londoño (2015), that PET-CT is an emerging and highly complex technique for radiotherapeutic planning; requiring further studies related to the topic.

Conclusion

The indication of PET-CT in the specialty of oncology encompasses the planning of radiotherapy, which has been increasingly using PET-CT in the last decade. Its use in the radiotherapy of gliomas allows a safer treatment in the delivery of the dose in the delimited structures, saving the normal tissue, reducing the toxicity and reducing the probability of geographical errors in the definition of the target volume. The PET-CT technique improves the precision of the target volume delineation by defining the volume of metabolic tumor, together with the morphological image and clinical examination findings, with the potential to impact many aspects of the therapeutic approach. However, it was observed that there is no consensus regarding the best radiopharmaceutical, or the best combination of radiopharmaceuticals to be used in PET-CT examinations for clinical decision-making in the radio therapeutic planning of gliomas. This topic should be validated in prospective studies in order to evaluate the impact of amino acid PETs on the definition of target volume and the importance of the biological definition of tumor tissue for overall patient survival. Being, in this way, a wide field of research. It is concluded, therefore, that PET-CT is a relevant tool for the accurate evaluation of new treatment strategies and should be considered in prospective studies.

In addition, it is emphasized that early adjustment of patient care can avoid unnecessary treatment toxicity and reduce the costs of ineffective therapies.

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