

Treatment replanning in head and neck cancer radiotherapy: an investigation based on clinical dosimetry

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Abstract

Radiotherapy is a medical specialty based on controlled use of ionizing radiation for therapeutic purposes. Patients submitted to external beam radiation therapy of head and neck may suffer anatomical changes during the course of treatment. Frequent causes of such variations are the reduction of tumor volume, the progression of the disease during the course of radiotherapy, the loss of weight, and other causes. The conventional treatments are made of 33 to 35 fractions. Thus, the interval of time between the treatment planning computed tomography (CT) and the conclusion of the treatment surpasses two months. Monitoring significant anatomical variations and making adjustments to the plans of radiotherapy during the course of radiotherapy could be a relevant strategy to achieve the objectives proposed for the treatments. The objective of this study was to analyze how the variations in volume of interest, both target structures and healthy tissues could affect the dose distribution in the patient in radiation therapy treatment of head and neck cancer. This analysis will be made through investigation of metrics dose-volume, volumetric variations of target structures, as well as the parotid glands, patient thickness in the cervical region, image fusion, and isodose surfaces plotted on the CTs. The timing to Replan head and neck cancer appears to be around the 15th fraction of treatment, however a study with a larger number of patients is necessary. In case of adaptive radiotherapy, reduction of mean dose in the ipsilateral parotid was observed in 100% of patients, while in the contralateral parotid reduction was observed in 80% of patients. The decision to replan head and neck cancer has benefit in the spinal cord and brainstem since this study showed reduction in the maximum dose in 70% of patients in case of treatment replan. Decrease of dose including 95% of volume and minimum dose in the PTV (mean percentage decrease observed was 7.71%) was observed in case of no treatment replan. Increase in the maximum dose in the PTV was observed, for which the mean percentage increase observed was 2.42%. Adaptive radiotherapy improves the coverage of target volumes as well as the doses in OARs.

Keywords: radiotherapy, head and neck cancer, treatment replan, radiation dose.

Replanejamento terapêutico em radioterapia de câncer de cabeça e pescoço: uma investigação baseada na dosimetria clínica

Resumo

A radioterapia é uma especialidade médica baseada no uso controlado de radiação ionizante para fins terapêuticos. Pacientes submetidos à radioterapia externa de cabeça e pescoço podem sofrer alterações anatômicas durante o tratamento. As causas frequentes dessas variações são: a redução do volume do tumor, a progressão da doença durante o curso da radioterapia, a perda de peso e outras causas. Os tratamentos convencionais são feitos de 33 a 35 frações. Assim, o intervalo de tempo entre a tomografia computadorizada (TC) de planejamento do tratamento e a conclusão do tratamento ultrapassa dois meses. Monitorar variações anatômicas significativas e fazer ajustes nos planos de radioterapia durante o curso da radioterapia, pode ser uma estratégia relevante para alcançar os objetivos propostos para os tratamentos. O objetivo deste estudo foi analisar

como as variações no volume de interesse, tanto nas estruturas-alvo quanto nos tecidos saudáveis, podem afetar a distribuição da dose no paciente em tratamento radioterápico de câncer de cabeça e pescoço. Essa análise foi realizada por meio da investigação das métricas dose-volume, variações volumétricas das estruturas-alvo, bem como das glândulas parótidas, espessura do paciente na região cervical, fusão de imagens e superfícies de isodose plotadas nas TCs. O momento ideal para o replanejamento de câncer de cabeça e pescoço parece ser em torno da 15ª fração do tratamento, porém, é necessário um estudo com um número maior de pacientes. No caso da radioterapia adaptativa, a redução da dose média na parótida ipsilateral foi observada em 100% dos pacientes, enquanto na parótida contralateral, a redução foi observada em 80% dos pacientes. A decisão de replanear o câncer de cabeça e pescoço traz benefício na medula espinhal e no tronco encefálico, pois, este estudo mostrou redução da dose máxima em 70% dos pacientes em caso de replanejamento do tratamento. Diminuição da dose incluindo 95% do volume e dose mínima no PTV (redução percentual média observada foi de 7,71%) foi observada em caso de não replanejamento do tratamento. Observou-se aumento da dose máxima no PTV, para o qual o percentual médio de aumento observado foi de 2,42%. A radioterapia adaptativa melhora a cobertura dos volumes-alvo, bem como as doses nos OARs.

Palavras-chave: radioterapia, câncer de cabeça e pescoço, replanejamento de tratamento, dose de radiação.

1. Introduction

Head and neck cancer is the seventh most common cancer globally, accounting for more than 660,000 new cases and 325,000 deaths annually (Gormley et al., 2022). In Brazil, oral cavity cancer is the fifth most common cancer, and the estimate of new cases annually is 10,900 cases in men and 4,200 in women (Inca, 2023). Radiotherapy plays a key role in curative-intent treatments for head and neck cancers. Its use is indicated as a unique therapy in early stage tumors or in combination with surgery or concurrent chemotherapy in advanced stages (Alterio et al., 2019). At the Brazilian National Cancer Institute (INCA), 24% of the cases treated with radiotherapy from 2015 to May 2022 are head and neck sites.

Intensity modulated radiotherapy (IMRT) and volumetric modulated arc therapy (VMAT) are commonly used in head and neck cancer because these techniques can spare normal tissues such as parotid glands, larynx, oral cavity, and spinal cord (Schwartz et al., 2023). Another peculiarity is that the steep dose gradients characteristic of these conformal external beam methods allows better target coverage compared to less conformal external beam techniques. However, setup uncertainties and anatomical changes limit adherence to planned dose deposition throughout treatment fractionation (Weppler et al., 2018). For this reason, treatment replanning protocols are used to respond to anatomical changes to allow the target (tumor) to be covered and the OAR to be spared (Weppler et al., 2018).

For the adaptive radiotherapy to be practicable it is necessary to correctly identify patients who mostly will benefit from a replanned treatment. WEPPLER et al. point out three categories of replanning. Image-based methods, they compare periodic cone beam CT (CBCT) or CT images with the CT simulation (CTsim) to identify any systematic physical changes. Temporally based methods, they preselect the time at which a new plan should be calculated. Patient characteristic-based methods, they examine pretreatment parameters such as weight and tumor stage to predict if and when a replan may be necessary (Weppler et al., 2018). Patients with head and neck cancer have a high rate of viral association, resulting in a high response rate to radiotherapy (Brown et al., 2016).

This study focused on adaptive radiotherapy in head and neck cancer and aimed to analyze how the variations in volume of interest, both target structures and healthy tissues, could affect the dose distribution in the patient in radiation therapy treatment of head and neck cancer.

2. Materials and Methods

2.1 Patients and tumors

For the purpose of this study ten treatment plans of both male and female patients, stage III or IV, who received head and neck (oropharynx and nasopharynx) radiotherapy treatment at the Brazilian National Cancer Institute (INCA) were retrospectively analyzed. This study was performed with the institution's ethic committee consent.

2.2 Treatment planning

The techniques used were both IMRT and VMAT (Rapid arc). The linear accelerators used were both Trilogy and Clinac CX, both from Varian, with image system attached (CBCT - Cone beam computed tomography). 6 MV photon beam was used. The prescribed dose for the PTV high risk for all the patients was 70 Gy distributed in 33 or 35 fractions. The treatment planning system used was Eclipse, version 13.6. The calculation algorithm used was AAA (anisotropic analytical algorithm, version 13.6.23). For the CTs (computed tomography) Philips Big Bore was used and the immobilization accessories used were thermoplastic mask and footrest.

Besides the pretreatment tomography (CT1), all the patients were submitted to a new tomography (reCT); CBCT was used to decide reCT. The fractions from which the patients were submitted to a new tomography varied from patient to patient according to the necessity of treatment replanning. With this methodology for adaptive radiotherapy, it was possible to verify whether or not there were significant differences between the planned dose and the actual delivered dose (without treatment replanning).

Apart from that, it was also possible to estimate the volume variations in parotid glands during the course of treatment, as well as estimate the mean doses in parotid glands, maximum doses in the spinal cord and brainstem, dose including 95% of the volume, as well as minimum and maximum dose in the PTV – in the initial treatment plan (CT1), in the case that the patient does not replan the treatment (reCT) and in the treatment replan.

2.2.1 The methodology used was divided into three parts

1) At first the two CTs were compared (Figure 1), CT1 and reCT (pretreatment CT and CT for the treatment replanning). The two images were plotted one over another, thus significant anatomical variations could be seen by visual inspection as well as parameters such as patient thickness in the region of interest. After that, the same structures contoured in the initial CT were also contoured in the new CT. The contours were made by the same person to avoid interobserver variations. So, measurement of these structure volumes could be compared.

2) The investigation continued with the stage of dosimetric reconstruction. Two scenarios were considered. The first scenario assumed to ignore the need to replan. To recreate such scenario, we applied on the new CT the same treatment plan created at the beginning of treatment. In this way, the patient would have an initial treatment plan, based on the anatomy of the initial CT, and even after having a new CT of the patient, the initial treatment plan was used to calculate the absorbed dose in the new CT. Treatment parameters such as radiation beam geometry, energy, monitor units, fluency and beam weight were kept.

3) The second scenario considered the dose accumulated by the patient, taking into account the adjustments of the treatment plan. Using tools of treatment plan analysis such as isodose curves plotted over CT projections (sagittal, coronal and transversal) and dose volume histogram (DVH), the two scenarios were compared and evaluated in terms of metrics dose-volume practiced for these cases in clinical routine. They are mean dose in parotid glands, maximum dose in both the spinal cord and brainstem, dose including 95% of the planning target volume (PTV), as well as minimum and maximum dose in the PTV.

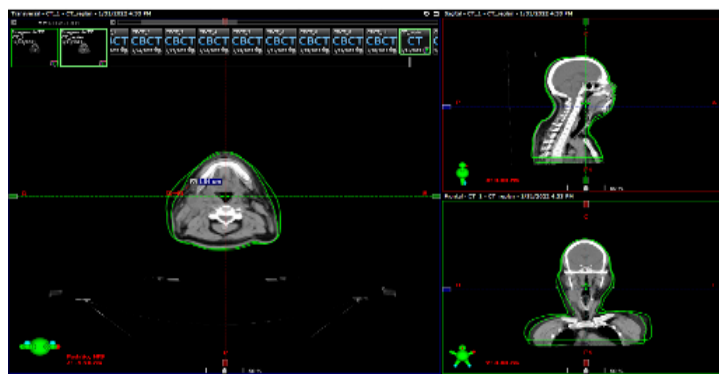


Figure 1. Comparison between CT pretreatment (outer) and CT for treatment replanning (inner). Source: Authors, 2023.

3. Results and Discussion

Table 1. below shows values of volume variations in the CTV for each patient.

Table 1. Values of volume variation in the CTV for each patient.

Patient	Volume of CTV (cm ³)		Percent variation
	CT1	reCT	
1	97.00	89.71	-7.52
2	711.21	556.63	-21.73
3	455.01	259.07	-43.06
4	216.08	204.33	-5.44
5	99.90	99.46	-0.44
6	267.51	250.99	-6.18
7	286.18	201.49	-29.60
8	636.73	662.06	3.98
9	105.61	103.74	-1.77
10	69.91	62.28	-10.91
Average			-12.27

Source: Authors, 2023.

From Table 1, one can notice that there was reduction in the CTV volume in 90% of patients. The mean percentage reduction observed was 12.27%. Figure 2 below shows the values obtained from volume variations in parotid glands for each patient both in the CT1 and in the reCT.

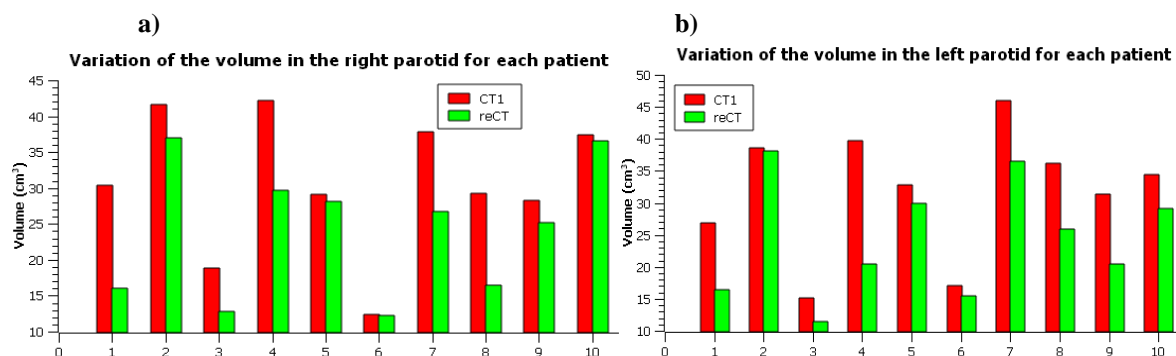


Figure 2. Variation of the volume (cm³) in both right (a) and left parotid (b) in both CT1 and reCT for each patient. Source: Authors, 2023.

From Figure 2, one can notice that the volume of both right and left parotid decreased in the course of treatment, as expected, whereas there was tumor shrinkage. Reduction in the parotid glands was observed in 100% of patients. The mean percentage reduction observed for the right parotid was 21.13%, while for the left parotid it was 23.02%. Morgan & Sher (2020) reported a decrease in parotid glands as much as 14.7, 37, and 48% by the end of weeks 2, 4, and 7 (Morgan; Sher, 2020).

The timing to replan head and neck cancer treatment seems to be around the 15th fraction, since in this study greater volume percentage variations were observed in patients who did replan from the 15th fraction of treatment. For a more precise conclusion about the timing to replan, a larger number of patients is needed, Brown et al. (2016) in their prospective study with 10 patients found that the timing to Replan is at the commencement of week three and in week four (Brown et al., 2016).

The mean dose in the parotid glands is correlated with the risk of xerostomia (Lou et al., 2018). Figure 3 below shows the values of mean doses in parotid glands for each patient in the initial plan (CT1), in the case that the patient does not replan (reCT) and in the treatment replan.

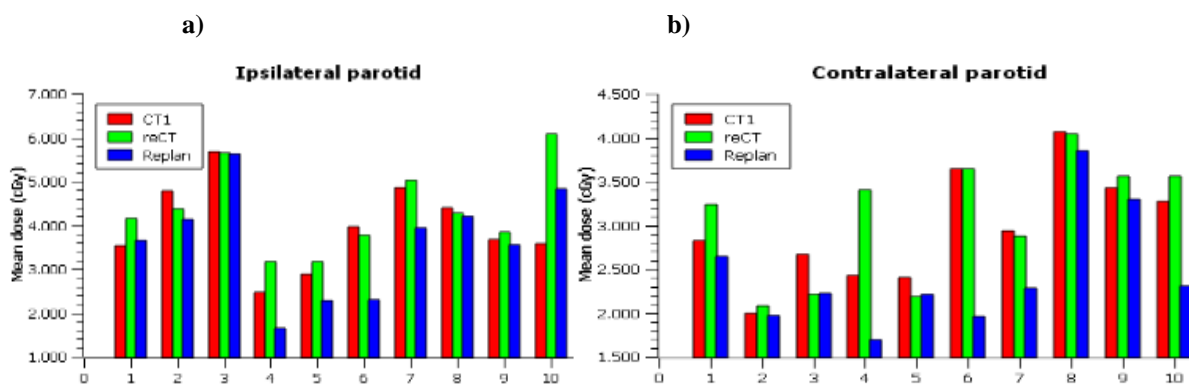


Figure 3. Mean dose in both ipsilateral (a) and contralateral parotid (b) for each patient. Source: Authors, 2023.

From Figure 3, in case of adaptive radiotherapy, reduction of mean dose in the ipsilateral parotid was observed in 100% of patients, while in the contralateral parotid reduction was observed in 80% of patients. In this study, in case of adaptive radiotherapy, the mean dose in the ipsilateral parotid decreased from 0.73 to 14.83 Gy, while in the contralateral parotid the mean dose decreased from 2.63 to 19.28 Gy. Among a total of 134 articles published between 2005 and 2016, 29 articles were ultimately retained for Castelli and cols review in which they found that adaptive radiotherapy decreases the mean dose to the parotid gland from 0.6 to 6 Gy (Castelli et al., 2018).

This study found a negligible correlation (*Pearson's r* = -0.1) between the volume and the dose in parotid glands, meaning that the dose in parotid glands does not only depend on the volume of the parotid glands. The present study also found a negligible correlation (*Pearson's r* = 0.2) between the volume of the CTV and the dose in the parotid glands.

The maximum dose in the spinal cord is a limiting parameter in the treatment planning of head and neck cancer radiotherapy. Figure 5 below shows the values of maximum doses in the spinal cord for each patient in the initial plan (CT1), in the case that the patient does not replan (reCT) and in the treatment replan.

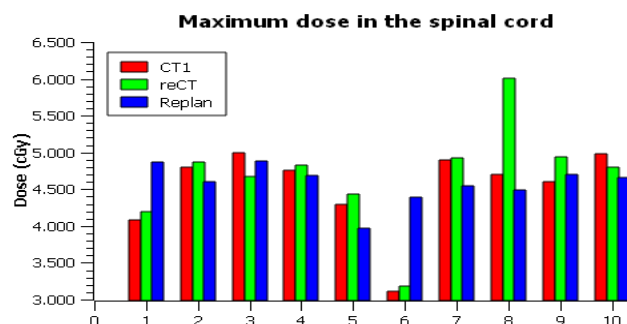


Figure 4. Maximum dose in the spinal cord. Source: Authors, 2023.

Reduction in the maximum dose in the spinal cord was observed in 70% of patients in case of treatment replan, while in case of no treatment replan the observed reduction was in 20% of patients. In the present study the maximum dose in the spinal cord decreased from 1.34 Gy to 15.1 Gy, in case of treatment replan (paired t-test; $p = 0.0045$, CI (confidence interval) = 95%). An investigation conducted by Castelli et al. (2018) found that adaptive radiotherapy decreases the maximum dose to the spinal cord from 0.1 to 4 Gy (Castelli et al., 2018); Hansen et al. (2006) in their retrospective study of 13 patients found that the maximum dose to the spinal cord increased in all patients who did not replan the treatment (range, 0.2–15.4 Gy; $p = 0.003$).

Another important metric dose-volume is the maximum dose in the brainstem. Figure 6 below shows the values of maximum doses in the brainstem for each patient in the initial plan (CT1), in the case that the patient does not replan (reCT) and in the treatment replan.

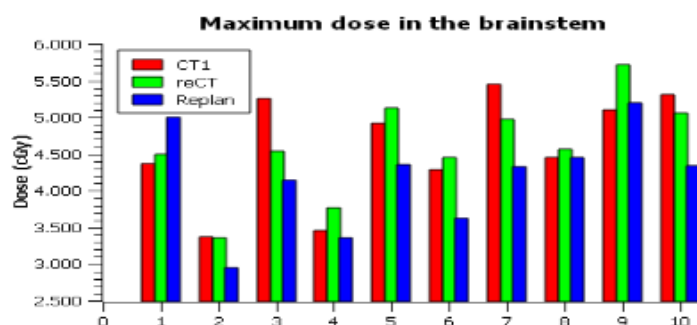


Figure 5. Maximum dose in the brainstem. Source: Authors, 2023.

Increase in the maximum dose in the brainstem was observed in 60% of patients in case of no treatment replan, range 0.14 – 6.64 Gy (paired t-test, $p = 0.007$, CI = 95%). These results are in accordance with those reported by Hansen and cols (2006) in their retrospective study of 13 patients in which they found an increase in the brainstem maximum dose in 85% of patients without replanning (range, 0.6 – 8.1 Gy; $p = 0.007$).

One of the objectives in a radiotherapy treatment is to deliver the prescribed dose in the PTV. Typically, the desire is to cover 95% of the PTV with the prescribed dose. Figure 7 below shows the values of doses including 95% of the PTV for each patient in the initial plan (CT1), in the case that the patient does not replan (reCT) and in the treatment replan.

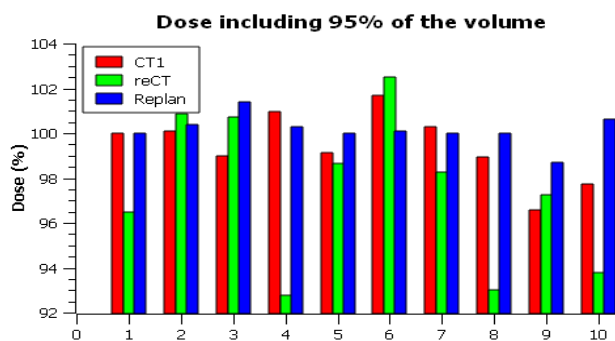


Figure 6. Values of doses including 95% of the PTV. Source: Authors, 2023.

In the present study, 60% of the plans without treatment replan (reCT) lost coverage. In case of no treatment replan an average decrease of 2.17% of the dose including 95% of the PTV was observed, from which the decrease of 1/3 of cases was greater than 4%. In case of treatment replan an average increase of 0.71% was observed (paired t-test; $p = 0.007$, CI = 95%). Castelli et al. (2018) in their study found that during IMRT without adaptive radiotherapy, a tumor underdose was observed for a majority (76%) of the patients, which justifies the use of adaptive radiotherapy. On the other hand, Hansen et al. (2006) found that the doses to 95% (D95) of the planning target volumes were reduced in 92% of patients, by 0.8 – 6.3 Gy ($p = 0.02$).

The minimum dose in the PTV is a metric associated with the PTV coverage. Underdosage in the PTV can lead to a failure in the accomplishment of the goals of treatment. Figure 8 below shows the values of minimum dose in the PTV for each patient in the initial plan (CT1), in the case that the patient does not replan (reCT) and in the treatment replan.

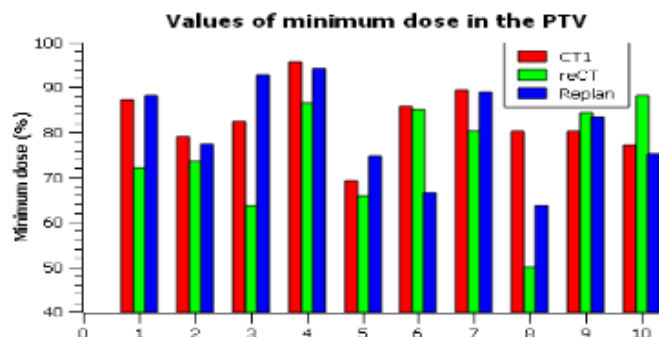


Figure 7. Values of minimum dose in the PTV. Source: Authors, 2023.

Analyzing the graphic from figure 8 above one can realize that in 80% of cases the minimum dose in the PTV in the case that the patient does not replan the treatment (reCT) is smaller than in the case that the patient does replan the treatment, strengthening the conclusion that the coverage of dose is better in case of treatment replan. In case of no treatment replan an average reduction of 7.71% of minimum dose in the PTV was observed (paired t-test; $p = 0.008$, CI = 95%).

The maximum dose in the PTV is a metric which is associated with dose homogeneity within the target volume. Figure 9 below shows the values of maximum dose in the PTV for each patient in the initial plan (CT1), in the case that the patient does not replan (reCT) and in the treatment replan.

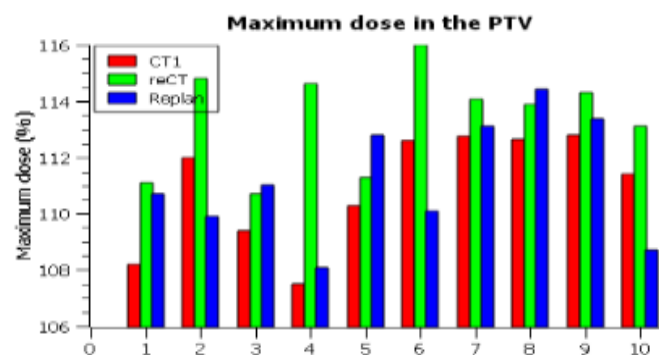


Figure 8. Values of maximum dose in the PTV. Source: Authors, 2023.

Analyzing the graphic from figure 9 one can realize that the dose gradient is greater in 100% of plans in case of no treatment replan (reCT), in which an average increase of 2.42% of the maximum dose in the PTV was observed (paired t-test; $p = 0.007$, CI = 95%).

4. Conclusions

The present study investigated the influence of adaptive radiotherapy in head and neck cancer. Evaluating, for 10 patients, three different scenarios: initial plan (CT1), the case that the patient does not replan (reCT) and the treatment replan, it has been demonstrated that variations in volumes of interest, target structures or OARs affects the dose distribution delivered to the patient in the head and neck cancer radiotherapy treatment. The results of this study suggest that adaptive radiotherapy improves the coverage of target volumes as well as the doses in OARs.

5. Acknowledgments

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6. Authors' Contributions

Sérgio Domingos Dunduma Paca: experimental design, data collection, article writing, scientific reading, submission and publication. *Saulo Santos Fortes*: experimental design, data collection, article writing, scientific reading and review. *Leonardo Peres da Silva*: experimental design, data collection, article writing, scientific reading and review. *Juliana Carvalho*: experimental design, data collection, article writing, scientific reading and review.

7. Conflicts of Interest

No conflicts of interest.

8. Ethics Approval

Yes. "Parecer N° 6071052200005274. Parecer Brasileiro do Comitê de Ética Humana N° 5602700"

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