DIFFERENCES AMONG DOSES FOR NEURO-AXIS RADIOTHERAPY PLANNING IN THE GONADAL REGION

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RESUMEN

Radiotherapy can disrupt the functioning of the hypothalamic-pituitary axis, directly causing ovarian deficiencies, such as the decrease in fertility or damage that renders the uterus incapable of accommodating the growth of a fetus. However, these issues have become increasingly important to a growing number of pediatric and adolescent cancer survivors. The whole-body, cranial-spinal axis, as well as abdomen and pelvic region irradiations may expose the ovaries to radiation and may cause premature ovarian failure, whereas doses above 35 Gy cranial can affect the hypothalamic-pituitary functions. This study performed a comparison of four doses of radiotherapy planning techniques for the neural axis. For this analysis, technical simulations were performed for the treatment of medulloblastoma in four different planning, applied in a RANDO anthropomorphic phantom and dosimeters (TLD-100). The radiation fields in the 1st and 2nd planning were 40 x 5 cm^2 and 17 x 5 cm^2 with 4.0 cm depth, in which doses were 0.03 and 0.05 Gy / day and 0.11 and 0.09 Gy / days, on the right and left sides, respectively. The 3rd and 4th measured planning 32 x 7 cm^2 and 18 x 7 cm^2, with a 2 cm gap and a 4.0 and 5.0 cm depth, in which doses were 1.08 and 0.2 Gy/day and 1.14 and 0.14 Gy/day, on the left and right sides, respectively. It could be observed that the doses in the ovaries in the 3rd and 4th schedules proved to be larger than the doses in the 1st and 2nd planning. This is caused by the spinal field width and the depth of the second spinal field, which is 1.0 cm more than the field of the 1st and 2nd planning. These differences should be observed in image planning, as incorrect measures can cause damage in the treatment finish.

1. INTRODUCCIÓN

Advances in diagnoses and treatments have substantially improved the survival rate among cancer patients in recent decades. The growing number of survivors is due mainly to the attention given to the long-term effects caused by cancer treatments and their impacts on one's quality of life. [1].

A variety of complications brought about by treatments can be observed when followed up over the long-term. Among these complications, endocrine consequences are possibly the most commonly found [2, 3]. This form of treatment typically involves the combination of surgery, radiotherapy, chemotherapy with alkylating agents, or bone marrow transplants [4,5].

Craniospinal irradiation (CSI) is an essential component in the treatment of medulloblastoma. The neoplastic cells are disseminated through the cerebrospinal fluid, and

the CSI technique involves the irradiation of all areas that support the cerebrospinal fluid, which have the added risk of the tumor spreading. CSI radiotherapy can disturb the hypothalamic-pituitary functions, cause ovarian failure, or result in damage that can render the uterus incapable of accommodating the growth of a fetus [6].

The hypothalamic-pituitary radiation causes the destruction and fibrosis of the pituitary glands and can lead to the significant dysfunction of the hypothalamic-pituitary function. Signs of the dysfunction of the hypothalamus include amenorrhea, high prolactin, and suppressed levels of gonadotropins [4].

Children exposed to cranial irradiation are more likely to develop central precocious puberty due to the destructive effects caused to the inhibitory pathways of the hypothalamus. Girls are more susceptible than are boys when using lower doses of radiation (18-24 Gy), while both boys and girls are equally susceptible to precocious puberty when higher doses are used (30-50 Gy) and to delayed puberty due to the deficiency of gonadotropins and to hypogonadotropic hypogonadism, as well as oligospermia and azoospermia [2].

In male patients, the gonadal toxicity leads to the prolonged induction of azoospermia, which may or may not be reversible. This reversibility can immediately be observed in post-puberty patients; however, the same antineoplastic regime applied to pre-puberty male patients can induce permanent azoospermia. The probability of permanent azoospermia is related to the specific alkylating agents used and their doses [3].

The ganadotoxicity in women is age-dependent, with older women being more susceptible, as their total follicle reserve is diminished during the therapy. [7]. Whole-body and pelvis region, which includes the ovaries, irradiation can cause a reduction in the quantity of primary follicles, thus bringing about permanent damage, depending on the dose and the size of the field of radiation. The risk of menopause related to complications and infertility at a young age due to treatment can be devastating [8].

Radiotherapy can affect one's fertility not by direct whole-body, lower abdomen, pelvis, or spinal radiation, but also by disseminated radiation, which can cause gonadal failure, even if the ovaries are outside of the field of radiation. In addition to the ovaries, the deleterious effects on the uterus can also cause damage, such as uterine vasculature, damage to the endometrium, and myometrial fibroids [1].

Radiation on the uterus, depending on the dose, can cause scars and diminish the blood flow in the uterus, resulting in a reduction in the uterine volume, whereas when radiation is applied directly to the pelvis region, the risk of infertility occurs, defined by the absence of spontaneous menstruation or pregnancies [4].

Today, many treatment options are available to prevent infertility in high-risk patients, including the freezing of embryos, gonadal shielding during radiotherapy, conservative gynecological surgery, and the cryopreservation of embryos, which is the only method that is well-established for women to preserve their fertility. Other such strategies, including ovarian suppression, ovarian transposition, and the cryopreservation of oocytes and ovarian tissue are still in their experimental stages [1, 4, 8].

The present study focuses on a comparison among the applied doses in four radiotherapy planning techniques for the neural-axis, considering the changes that occur in each planning, such as field size, field depth, and gap movement.

2. MATERIALS AND METHODS

To evaluate the nueroaxial techniques, simulations of the treatment for medulloblastoma were performed in four distinct planning: the first planning (half-cone beam

technique), the second planning (angled gantry technique), the third planning (angled gantry technique with mobile gap), and the fourth planning (angled gantry technique without mobile gap). The sections of the radiotherapy treatments were carried out using two distinct linear accelerators, which were applied in a solid anthropomorphic simulator from the Radiation Analog Dosimetry (RANDO) Laboratory, which represents the human body of a woman and 84 LiF:Mg,Ti thermoluminescent dosimeter units (TLD-100) in the form of chips.

The dosimeters were placed between the layers created by the simulator in the center of the fields and in the surrounding organs (Figure 1).

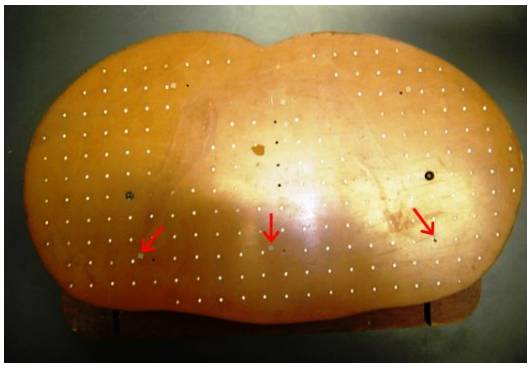


Figure 1- Position of the TLDs in one of the layers corresponding to the uterus and ovary

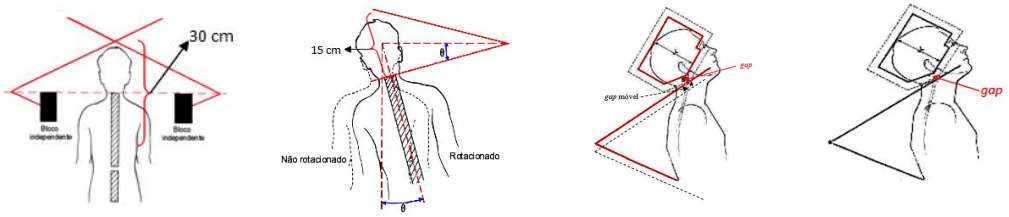
In the third schedule, in each section, the cranial and spinal fields varied one centimeter in length, making the 0.38 cm gap fluctuate its position both at the cranial-spinal junction as well as at the thoracic-lumbar junction. Table 1 shows the dimensions of the fields for radiotherapy planning techniques.

Table 1: Dimensions of the radiation fields in each radiotherapy planning

Planning	Cranial Field	(Thoracic) Field	(Lumbar) Field	Depth	
				Cranium	Spinal Column
1st Planning	30 x 18cm^2	5 x 40cm^2	5 x 17cm^2	7.5 cm	4.0 cm
2nd Planning	15 x 18cm^2	5 x 40cm^2	5 x 17cm^2	7.5 cm	4.0 cm
3rd Planning	19 x 26cm^2	7 x 31cm^2	7 x 21cm^2	7.5 cm	4.0 / 5.0 cm
4th Planning	19 x 28cm^2	7 x 31cm^2	7 x 17cm^2	8.0 cm	4.0 / 5.0 cm

2.2 Treatment

The treatment simulations were performed in two different radiotherapy units using four different radiotherapy techniques (Figure 2). The prescribed doses were of 1.5 Gy for the first and second schedules and of 1.8 Gy for the third and fourth planning.



A **B** **C** **D**

Figure 2 – Geometry of the planning field techniques. A – Half - beam technique, B – Angled field technique, C – Angled field technique with mobile gap, and D – Angled field technique without mobile gap.

In the planning procedure for the treatment of medulloblastoma, four regions were focused to apply the pre-set dose. These regions included the middle portion of the brain and the posterior cranial fossa, which are inserted in the medulla I and II cranial fields, which correspond to the thoracic and lumbar fields. The uterus and the ovary, organs in the surrounding regions of the radiation fields, are located in the medulla II, in the lumbar region.

In the third schedule, in each section, the cranial and spinal fields varied one centimeter in length, making the 0.38 cm gap fluctuate its position both in the cranial-spinal junction as well as in the thoracic-lumber junction. Table 1 presents the dimensions of the radiotherapy planning fields.

2.2. **Dosimetry method**

To execute the dose measurement, thermoluminescent dosimeters (TLD-100) were used. These dosimeters were treated thermally in a PTW-TLDO annealing oven, manufactured by BICRON-NE, according to their specific parameters. After irradiation, before each reading, the dosimeters were submitted to a thermal pre-treatment, which is a procedure geared toward the elimination of less stable peaks that could interfere in the reproducibility of the detector response. The dosimeter scanning was carried out using a model 5500 scanner, manufactured by Harshaw-Bicron, using synthetic air generated by a model 4488 air compressor made by the same manufacturer.

The TLD responses were also adjusted by a correction factor of the dose measured by irradiation, together with an ionization chamber in a simulator filled with water in each accelerator.

3. RESULTS AND DISCUSSION

The present work employed the methodology applied to perform the level III dosimetry intercomparison, according to the procedures of selection and calibration of the dosimeters and the simulation of the treatment with an anthropomorphic simulator so as evaluate the doses measured in the simulated treatments. The results are presented in tables 2 and 3 below.

Table 2 – Dose evaluated for different cranial-spinal radiotherapy planning techniques in the hypothalamic-pituitary region.

Sites	1°Planning	2° Planning	3° Planning	4° Planning
Medium planning field	(1.55±0.01)	(1.51±0.05)	(2.15±0.07)	(1.86±0.09)
Posterior fossa	(1.85±0.07)	(1.69±0.05)	(2.12±0.09)	(1.89±0.01)

The radiotherapy treatment consisted of the application of doses that vary from 30 to 35 Gy in the cranial-spinal axis, with a reinforcement of the dose in the posterior fossa of 15 to 20 Gy. These doses are fractioned at 1.5 or 1.8 Gy/day, according to that recommended by ICRU-50 (1993) and ICRU-62 (1999).

In the present study's results, the medium planning field doses correspond to that recommended in the first, second, and fourth schedules, whereas in the third schedule, the doses were 20% above the prescribed dose (2.15 ± 0.07). While in the posterior fossa the doses proved to be above the recommended levels, only in the fourth schedule was the dose observed at the recommended level (1.89 ± 0.01), that is, the total of the planned dose varied from 30 to 35 Gy. The difference of the dose between the first and second schedule was due to the size of the cranial fields (Fig. 1), given that the beam in the X axis (30cm) was halved by the independent blocks in the first schedule, according to the applied technique, whereas in the second schedule, the field proved to be half of the first schedule on the X axis (15 cm).

In the third and fourth schedule, the dimensions of the fields were greater (19 x 26 cm and 19 x 28 cm), and it could be observed that the variation in the dimensions of the fields, due to the mobile gap, did not in fact diminish the dose, but rather increased it.

These doses were also received on the hypothalamic-pituitary axis, which indicates that the patient is susceptible to developing gonadal disturbances. Kim C.H. and Jeon G. (2012) [8] affirm that the greater cranial radiation doses of 35-40 Gy can harm the hypothalamic-pituitary functions and can cause hypogonadism. By contrast, Green D.M. et al. (2011)[11] reported that deficiency occurred in the luteal phase in adult patients that received a dose of 24 Gy in cranial radiotherapy treatment, whereas in child patients doses of 22 to 27 Gy also caused a deficiency in the luteal phase, leading to infertility. Very low levels of radiation in the pituitary glands can also harm fertility [4].

Male patients tend to be more susceptible to the problems of infertility and can present problems in the development of puberty or the sexual function after receiving a dose of 12 Gy. Although the testicles are rarely irradiated directly, exposure due to the dispersion of radiation can bring about negative consequences in reproduction, since a dose of 0.1 Gy can cause oligospermia, and a dose of 0.35 Gy can cause reversible aspermia

In the medulla II region (Table 3), the lumber field, despite the slightly higher doses, corresponded to that expected in the first and second schedule, while in the third and fourth schedules, the doses were 30% higher than expected. In this field, the radiation beam, by dissemination, reached the uterus, which received, in the first and second schedule, 35% and 34% of the prescribed dose, whereas in the third and fourth schedule, it received 28% and 30% of the prescribed dose, respectively. Regardless of the dose, the uterus received doses of less than 14-30 Gy. According to the authors [5], these doses can cause the reduction in the uterine length, poor endometrial thickness, and the absence of blood flood in the uterine

artery. The risk of uterine dysfunction increases with both the higher doses and the radiation fields, which involve a greater uterine volume.

Table 3 - Doses evaluated in the interest regions for different cranial-spinal radiotherapy planning techniques in the lumbar region.

Sites	1st Planning	2nd Planning	3rd Planning	4th Planning
Medulla II	(1.64±0.11)	(1.63±0.01)	(2.46±0.10)	(2.38±0.05)
Uterus	(0.52±0.03)	(0.51±0.03)	(0.50±0.20)	(0.54±0.08)
	(0.03±0.05)	(0.11±0.02)	(1.08±0.20)	(1.14±0.06)

The doses in the ovaries proved to be quite low; only in the third and fourth schedules did the right-side ovary receive higher doses. This fact is due to a deviation in the simulator's column and in the width of the lumbar field (7 cm); in addition, the depth of the lumbar field was 1 cm larger than in the prior two schedules.

Some authors [1] affirm that radiotherapy can cause gonadal failure, even when the ovaries are not in the radiation field. The human oocyte is extremely sensitive to ionizing radiation, the dose of direct radiation causes a reduction associated with age in the ovarian follicle reserve; the dose with less than 2 Gy is sufficient enough to destroy half of the population of oocytes; and doses of above 6 Gy generally provoke irreversible ovarian failure.

In comparison to younger women, older patients present a greater risk of developing infertility after radiotherapy due to the low reserve of primary follicles and the high damage to the chromosomes caused by induced radiation in the oocytes [11].

Low doses with values of between 4 and 6 Gy in adults and between 10 and 20 Gy in children can lower the ovarian function, in turn accelerating follicular atresia, destroying the quantity of follicles. Prior studies have demonstrated that females treated with doses of pelvic radiation in excess of 2 Gy present a high-risk of permanent ovarian failure [4,7].

4. CONCLUSIONS

In the present study, the doses evaluated in the uterus and ovaries presented divergences in the four schedules, with the differences appearing much more accentuated in the third schedule. The changes implemented in the procedures used to apply the techniques, such as the field sizes, which were greater in both the cranial and spinal fields, and the depth, contributed to the increase in dose. The prescribed dose in the first and second schedules was less (1.5 Gy) than in the third and fourth (1.8 Gy). The width of the spinal field of the first two schedules was 2 cm narrower than in the third and fourth schedules. In addition, the depth of the lumbar field in the third and fourth schedules, which was 1 cm greater, contributed to the increase in the doses in the ovaries.

This study's results demonstrate that the application of a periodic dosimetry to analyze the doses used in the treatments can serve as a good parameter to avoid undesirable consequences resulting from high doses in the medulla II region.

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