Introduction

Cranial irradiation is a common treatment modality for patients with primary or metastatic brain tumors. While current radiation techniques are improving in efficacy of dissolving tumors, they still have the potential to affect a range of normal bodily functions, including fertility, through the endocrine glands in the brain—the hypothalamus and the pituitary. The hypophalsum controls the release of gonadotropins, releasing hormone (GnRH), which controls the release of gonadotropins FSH (follicle stimulating hormones) and LH (luteinizing hormone) from the anterior pituitary. These hormones are responsible for crucial parts of the reproductive cycle, including maturation in males, and follicle development, ovulation, and estrogen production in females. This poster will evaluate the extent to which cranial irradiation impacts the levels of these hormones and their impact on fertility.

Commonly used as a treatment modality for cancer patients, radiation is known to have pernicious effects on the body, including organ toxicity and damage to soft tissue, among a myriad of others. While radiation to the abdominal and pelvic region is highly pernicious effects on the body, including organ toxicity and damage to soft tissue, it still has the potential to affect a range of normal reproductive functions, including fertility. This study examined cases of cranial radiotherapy (RT) on the hypothalamic-pituitary axis and preserved the fertility of neurological cancer patients. Given the growing number of adults with prepubertal tumors, it is necessary to understand the impact of cranial radiotherapy on reproductive health. In the present study, we assessed the impact of cranial irradiation on reproductive hormones in a cohort of patients with brain tumors who received cranial RT.

In the study, male survivors of brain tumors who were treated with cranial RT were compared to control group of patients who were not treated with radiation. Testosterone, luteinizing hormone (LH), follicle-stimulating hormone (FSH), luteinizing hormone-releasing hormone (LHRH), estradiol, and total testosterone were measured in the patients who received cranial RT and in the control group. The results showed that cranial irradiation impaired the pituitary gland's ability to secrete normal levels of gonadotropins, as well as other hormones essential for fertility, including testosterone and LHRH. The results indicated that cranial irradiation treatments with minimal dosage are essential to preserving pituitary function and that reproductive health and fertility. Similarly, limits on RT dosage should be enforced based on proximity of the tumor to the pituitary. Finally, as evidenced by the increasing prevalence of GD with time elapsed since diagnosis, it is necessary to continue performing long-term surveillance and pituitary assessment for cranial radiotherapy patients to ensure prompt detection of hypopituitarism.

Methodology

For this topic, the data used for analysis comprised of studies that recorded and parsed data from patients who were treated with standard cranial radiotherapy for brain tumors and compared these levels to those of matched controls. The first study performed by the Department of Stereotactic and Radiation Neurosurgery in Prague, Czech Republic, incubation of hypogonadism was tracked in 85 patients irradiated with Leksell gamma knife (LK). 38 of 45 patients were irradiated with a mean dose of ≤35 Gy (Gy) to the pituitary and 40 of whom were irradiated with a mean dose of ≥45 Gy. Serum testosterone or LH estradiol levels were evaluated before and every 6 months after LK irradiation. Finally, a study conducted by Littley et al. followed for ten years (patients aged 4-15) who underwent cranial RT and compared their hormone levels to the control group. The results showed that cranial irradiation impaired the pituitary gland's ability to secrete normal levels of gonadotropins, as well as other hormones essential for fertility, including testosterone and LHRH. The results indicated that cranial irradiation treatments with minimal dosage are essential to preserving pituitary function and that reproductive health and fertility. Similarly, limits on RT dosage should be enforced based on proximity of the tumor to the pituitary. Finally, as evidenced by the increasing prevalence of GD with time elapsed since diagnosis, it is necessary to continue performing long-term surveillance and pituitary assessment for cranial radiotherapy patients to ensure prompt detection of hypopituitarism.

Results

The results of the study indicated that there is a significant correlation between patients undergoing cranial radiotherapy (RT) for brain tumors and gonadotropin deficiencies. In the first study, 43% of patients (21 of 50) expressed hypopituitarism, and 23% displayed gonadotropin deficiencies. Biological effective dose (BED) values were significantly higher (–78 vs. 44 Gy) in patients with gonadotropin deficiencies, with a p value of 0.004.

In the second study, it was revealed that median basal LH levels were significantly lower in patients who were given radiotherapy than in the control group (2.45 ± 3.33 IU/L vs. 5.17 ± 2.45 IU/L; p < 0.0003). In addition, 48% of patients (23 of 56) expressed hypopituitarism, and 23% displayed gonadotropin deficiencies. Another study confirmed the correlation between gonadotropin deficiency and strength of radiation (dose measured in gray, or Gy) to a non-pituitary brain tumor, and a similar study determined that 98% of the tested population was gonadotropin deficient eight years following radiation therapy of 4 Gy for pituitary tumors. As determined from these studies, while cranial irradiation does not seem to be strongly correlated to infertility, the exposure clearly alters normal gonadotropin hormone levels and may reduce fertility as a result of oligospermia, amenorrhea, hypogonadism, and other fertility limiting conditions caused by abnormal hypothalamic lesions. Targeted cranial radiation treatments must be furthered in order to prevent damage to the hypothalamo-pituitary axis and preserve the fertility of neurological cancer patients.

In the third study, hypopituitarism developed in only 1 of 45 (2.2%) of patients irradiated with a mean dose of ≤35 Gy, compared to 72.5% of patients irradiated with a mean dose >35 Gy, indicating that dosage of radiation to the brain, particularly to the hypothalamic-pituitary axis, is correlated to fertility preservation.

In the study by Littley et al. LHH and FSH levels were tracked based on RT dose and schedule, and as time elapsed following treatment, by 4 years following treatment, 99% of the studied patient population were gonadotropin deficient, and by 8 years 96% of patients were deficient. These patients were also shown to have deficiencies in growth hormone (GH), adrenocorticotropic hormone (ACTH) and thyroid-stimulating hormone (TSH).

In the present study, the data used for analysis comprised of studies that recorded and parsed data from patients who were treated with standard cranial radiotherapy for brain tumors and compared these levels to those of matched controls. The first study performed by the Department of Stereotactic and Radiation Neurosurgery in Prague, Czech Republic, incubation of hypogonadism was tracked in 85 patients irradiated with Leksell gamma knife (LK). 38 of 45 patients were irradiated with a mean dose of ≤35 Gy (Gy) to the pituitary and 40 of whom were irradiated with a mean dose of ≥45 Gy. Serum testosterone or LH estradiol levels were evaluated before and every 6 months after LK irradiation. Finally, a study conducted by Littley et al. followed for ten years (patients aged 4-15) who underwent cranial RT and compared their hormone levels to the control group. The results showed that cranial irradiation impaired the pituitary gland's ability to secrete normal levels of gonadotropins, as well as other hormones essential for fertility, including testosterone and LHRH. The results indicated that cranial irradiation treatments with minimal dosage are essential to preserving pituitary function and that reproductive health and fertility. Similarly, limits on RT dosage should be enforced based on proximity of the tumor to the pituitary. Finally, as evidenced by the increasing prevalence of GD with time elapsed since diagnosis, it is necessary to continue performing long-term surveillance and pituitary assessment for cranial radiotherapy patients to ensure prompt detection of hypopituitarism.

Applications to biotechnological therapy

Though this analysis has shown that cranial irradiation has potent effects on both the tumor and its proximal structures and tissues, it is an undeniably effective modality for destroying the cancer. Therefore, means for delivery of radiation should be targeted and localized to the cancer, aiming to minimize radiation exposure of normal, healthy tissue. Intensity Modulated Radiation Therapy (IMRT) was implemented throughout the early 21st century (and is currently most commonly used), proven to control the beam’s dose to be consistent with the 3D-shape of the tumor. However, as the diagrams to the left demonstrate, IMRT does not guarantee radiation to healthy tissue on the border of the end of the proton’s range, determined from initial intensity modulated by a variety of factors. However, PBT, available in very few medical centers, is more expensive, and due to its novelty, has known long-term side effects. Further research and clinical trials must be conducted before PBT may be safely incorporated as a cancer treatment modality.

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References