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Assessing the Risk of Secondary Cancer Induction in Radiosensitive Organs During Trigeminal Neuralgia Treatment With Gamma Knife Radiosurgery: Impact of Extracranial Dose

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Abstract

Purpose: Gamma knife radiosurgery (GKRS) delivers high-dose external radiation to a small intracranial lesion. However, scattering and leaked radiation can deposit a portion of the dose outside the radiation field, which may pose a risk to radiation-sensitive patients, such as pregnant women. Trigeminal Neuralgia (TN) is treated with one of the highest GKRS doses (80–90 Gy). This study aimed to estimate the risk of secondary cancer induction in the uterus, ovaries, thyroid gland, and eyes of TN patients undergoing GKRS.

Methods: Radiation doses to the uterus, ovary, eyes, and thyroid gland were measured for 25 female TN patients, with a mean age of 35 years, utilizing Thermo Luminescent Dosimeters (TLD).

Results: The mean absorbed dose for the uterus, ovary, thyroid gland, and eyes were .63 ± .24, .471 ± .2, 8.26 ± 1.01, and 10.64 ± 1.08 cGy, respectively. Lifetime Attributable Risk (LAR) has been calculated using BEIR VII (2006) method. LAR for the uterus, ovary, and thyroid gland was 1, 2, and 23, respectively.

Conclusion: The results of this study and its comparison with standard values demonstrate that on average, mean doses to mentioned organs were smaller than their tolerance doses, and there is no limitation to treating patients suffering from TN by GK.

Keywords

trigeminal neuralgia, gamma knife, peripheral dose, thermo luminescent dosimeters, lifetime attributable risk

Introduction

Trigeminal neuralgia (TN) is a chronic neuropathic pain condition that affects the innervated regions of the face by the trigeminal nerve. Typical TN causes severe and sudden volleys of shock-like facial pain that lasts a few seconds to a few minutes in the distribution of one or more divisions of the trigeminal nerve.[1] Medication therapy is nearly always introduced as the primary treatment. However, they may be associated with side effects or unable to control the pain.

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Several invasive surgical procedures are used as TN treatment methods, including mechanical balloon compression, percutaneous radiofrequency rhizotomy, microvascular decompression, glycerol rhizotomy, and peripheral nerve section. However, these techniques have problems such as pain relapse, loss of facial sensation, and hospitalization. Stereotactic radiosurgery is a painless successful alternative treatment for TN patients.[2-9] Sixty-nine percent of patients were reported to remain pain-free one year after GK surgery without additional medication.[10] GK has been the standard radiosurgery technique for trigeminal neuralgia treatments.[11,12] Technically, the GK utilizes 201 60Co sources to irradiate the root entry zone of the trigeminal nerve. In comparison to LINAC-based radiosurgery, the GK system's simultaneous activation of all radioactive sources with a single delivery setup provides a distinct advantage. This feature eliminates the necessity for multiple patient positioning and beam setups, thereby further reducing random setup errors commonly associated with LINAC-based radiosurgery. The GK's streamlined approach contributes to enhanced precision and accuracy in treating trigeminal neuralgia patients. The fixed radiation source design of the GK provides advantages such as precise targeting, fixed positioning, and reduced treatment time, which contribute to minimizing the exposure of surrounding tissue in the low-dose range.[13,14]

It has been applied to intracranial targets such as primary or metastatic brain tumors, benign tumors, vascular malformations such as arteriovenous malformations (AVMs), and functional neurologic diseases like TN. The stereotactic radiosurgical method was initially introduced by Lars Leksell in 1951. From around 1953, he began treating trigeminal neuralgia patients using radiation sources such as X-rays. However, it was not until the late 1960s that Leksell and his team developed the GK system, which utilizes the cobalt radiation source. The introduction of the gamma knife marked a significant advancement in the field of SRS for destroying the particular focus in the brain to relieve pain instead of neurosurgery.[15] Achieving long-term tumor control vs saving neurovascular elements and maintaining cranial nerve function are the two important goals that can be reached by stereotactic radiosurgery alone or in combination with a more conservative surgery.[16] A reasonable concern regarding this method is that a specific portion of the dose is always deposited outside of the radiation field[17] because of (1) photon leakage through the treatment head of the machine, (2) radiation scattered from the collimators and beam modifiers, and (3) radiation scattered within the patient body from the treatment beams[18] which is schematically shown in Figure 1. Amount of this radiation is related to the treatment time[17] and average organ to isocenter distance.

This peripheral dose may not be an important issue under normal circumstances, but it must be ensured that there is no particular danger in long treatment time for radiation-sensitive patients. One of the highest prescribed doses in GK treatments belongs to TN patients (85–90 Gy).[19] So, this high-prescribed dose increases the treatment time and remarkably rises in peripheral doses.[20] The decay of the radiation sources significantly influences exposure times in GKRS, with shorter times possible for fresh sources. However, these factors do not notably impact the efficacy or safety of the treatment for trigeminal neuralgia pain management. The examined dose rate range (1.21–3.74 Gy/min) did not affect pain control or morbidity, and outcomes remained unaffected.[21] Estimating the peripheral dose is essential in patients with long-life expectancy after treatment, significantly when the dose affects healthy anatomical structures with low tolerance to radiation like the fetus and ovary.[17] Trigeminal neuralgia affects females slightly more often than males. The male-to-female prevalence ratio ranges from 1/1.5 to 1/1.7. Although the exact incidence is unknown, TN affects 4 to 13 per 100,000 people annually.[22] By the way, the likelihood of treating a pregnant woman with trigeminal neuralgia is low and hypothetical, as TN predominantly affects older women who are typically beyond child-bearing age. It is worth noting that radiation protection legislation varies across countries, and in some cases, the use of radiation therapy in pregnant women is entirely prohibited, despite the theoretical and practical adherence to dose limit values.

Regarding radiation treatments, knowing the doses to be deposited outside the treatment volume beforehand may allow a risk estimation of detrimental effects and, if possible, precautions to minimize the probability of developing them.[17] Because of the well-founded concern regarding any radiation exposure to the fetus and also the higher prevalence of TN in females, the question is whether GKRS is an appropriate treatment for TN pregnant patients or alternative treatment(s) in many cases fewer effective ones accompanied by side effects, must be employed? Moreover, it is crucial to assess radiation doses at critical, normal structures for patients undergoing GKRS.[23] This study is the first assessment of extracranial absorbed dose and resulting side effects in Iranian patients with TN. Radiation doses to the uterus, ovary, eyes, and thyroid gland were estimated in 25 female patients using TLDs. Based on the prior studies, phantom measurements show that the absorbed dose at different depths does not differ significantly (P-value <.05). This result was expected since, as shown in Figure 1, the patient's head is a volume source of radiation, and doses to these extracranial sites are due to secondary radiation with nearly equal distance to the source of radiation. So, the surface dose is comparable to the depth dose, and we can place TLDs at the surface of the patients' skin to estimate the depth (organ) dose.[23] The Lifetime Attributable Risk (LAR), or the probability of being clinically diseased by (or dying from) specific cancer after radiation exposure until the end of life, has been calculated for the received dose to the mentioned organs using BEIR VII (2006) method[24] and also doses have been compared to the maximum tolerable dose reported by International Commission on Radiological Protection (ICRP).[25]

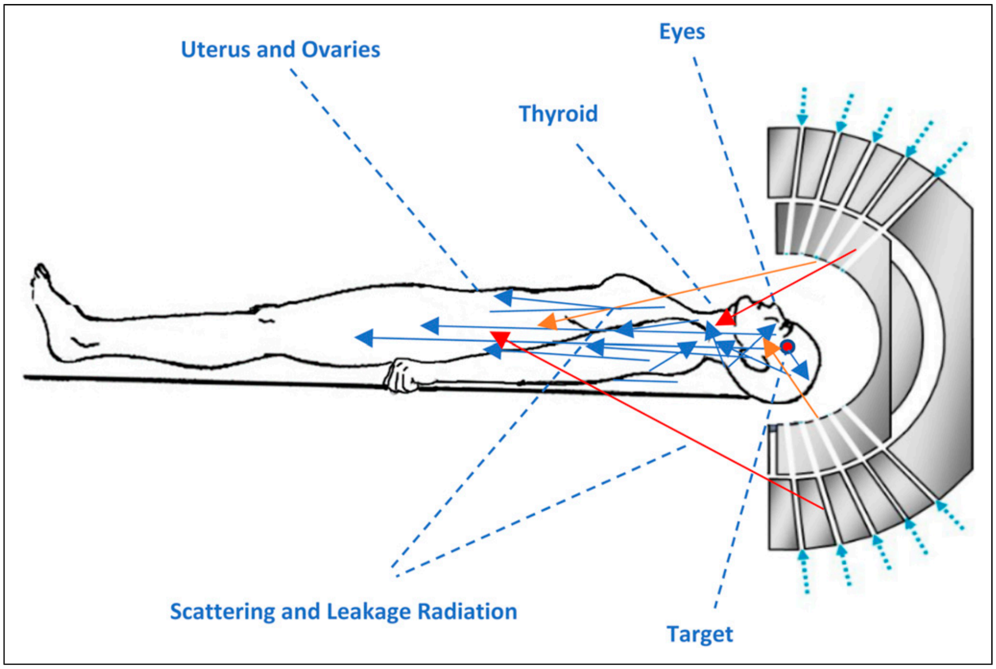

Figure 1. Sources of extracranial dose in GK radiosurgery.

Materials and Methods

Phantom Modification and Calibration of the TLDs

A relative radiation dosimetry system is a system whose response to ionizing radiation must be calibrated in a known radiation field before its radiation-induced signal can be used to provide an absorbed dose or dose rate in the dosimeter chamber cavity.[26] TLD is a relative dosimeter, so to have a valid measurement, it is necessary to obtain its calibration curve by delivering specific multi-level doses to the dosimeter to derive the dosimeter's response curve. In this study, the dose rate of GK was measured utilizing the Semiflex ionization chamber (PTW-TM31010 0.125 cm^3), which is suitable for small-field dosimetry.[27] Background radiation in 10 consecutive time intervals has been measured to calculate the net dose rate.[28,29] The ionization chamber was inserted into the Acrylonitrile Butadiene Styrene (ABS) spherical plastic phantom used for quality assurance in GK.[30]

For this measurement, cubic chips (TLD-100), composed of lithium fluoride crystals doped with Magnesium and Titanium, with sizes of 3.2 × 3.2 × .9 mm^3 and a usable energy range of 50 μGy to 500 Gy, were used. Annealing procedures for TLDs have been done based on the manufacturer's instructions. TLDs were kept at 285°C for 30 min to remove residual effects of previous irradiations, followed by fast cooling. TLDs were numbered, and calibration was performed individually and in groups. The purpose of the individual calibration was to compensate for random inherent individual variation of TLD detectors. For this purpose, each TLD chip was placed in specific holes on a Perspex slab at the depth of the maximum dose irradiated by the Co-60 beam. A dose of 100 cGy was delivered to TLDs to gain the ECC, which is calculated using equation (1).[31]

A correction factor for each detector, using the below equation, was calculated:

$$ECC_j = \frac{<TLD>}{TLD_j} \quad (1)$$

In this equation, ECC_j, $<TLD>$ and TLD_j are the correction factor of j-th TLD, mean response of irradiated TLDs, and response of j-th TLD in the same field, respectively.[28] TLDs whose response was out of range (Avg ± SD) were discarded. The remained TLDs were divided into six groups to perform the group calibration process at different dose levels of 0,5,7,10,11, and 12 cGy.

For group calibration, the standard spherical phantom was modified according to Figure 2A. This phantom is made of two hemispheres so that different Perspex layers dedicated to ion chamber, film, and TLD dosimetry can be inserted between them.[33,34]

For group calibration, TLDs were placed in sockets made by a laser in the center of a circular Plexiglas tissue-equivalent plate, 10 cm in diameter and 10 mm in thickness (Figure 2A). Then, the entire plate was placed inside the gamma-knife's spherical standard phantom (Figure 2B), centered at the device's isocenter, and irradiated uniformly by 18 mm collimator size with different doses (Figure 2C).

The readout process has been done by Fimel LTM TLD Reader model HF15001 for all TLDs. To stabilize electrical circuits and reduce system noise, a 30-minute warm-up was

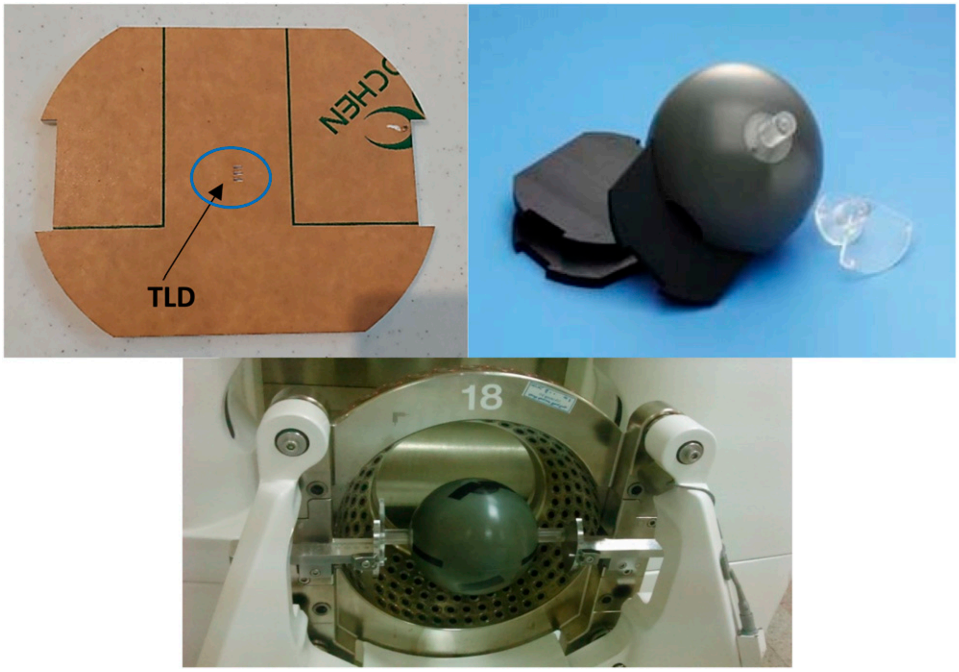

Figure 2. (A) Sockets made by a laser in the center of a circular Plexiglas tissue-equivalent plate, 10 cm in diameter and 10 mm in thickness. (B) Plexiglas tissue-equivalent plate inside the standard spherical phantom. (C) Irradiation of TLDs inside the modified standard phantom in the Leksell GK system.[32]

performed, and before any readout, PMT (Photo Multiplier Tube) noise and reference light tests were made.[35] Then, the calibration curve was obtained by fitting the best curve to the points in MATLAB and Excel software.

Patient Information, Positioning, and Treatment Planning

In the first step, head immobilization to localize the target in stereotactic radiosurgery was performed by rectangular stereotactic frame under local anesthesia. After fixing the frame to the patient's skull, the head coordinate was determined using a glass sphere to simulate the skull shape in the treatment planning system. Twenty-five female patients with normal weight and height were selected among TN patients referred to the Iran GK center. The specialist team did the treatment, including a neurosurgeon, radiation oncologist, and medical physicist.[16,36] Then, patients were referred to a 1.5 T MRI unit to capture T1 and T2 images for treatment planning (Figure 3). For all patients, a 90 Gy dose was prescribed at the 100% isodose line to the trigeminal root entry zone of the nerve, and specific attention to confining the brain stem dose to 13 Gy.[16,24] TN treatment was carried out with one single shot using the 4 mm collimator size and dose rate of around 70 cGy/min resulting in a typical treatment time of about 130 min.

Patient Dosimetric Measurements

Three groups of TLDs were sealed in thin 1×1 cm^2 plastic envelopes and then fixed on top of patients' thyroid gland, eyes, uterus, and ovaries. Moreover, three separate dosimeters were used for background dose monitoring in each measurement, whose readings were subtracted from mean value readings reported in the main measurements.

Calculation of LAR

Lifetime Attributable Risk (LAR) is the probability of being clinically diseased by (or dying from) specific cancer after radiation exposure until the end of life and has been calculated for the received dose to the mentioned organs using BEIR VII (2006) method.[24]

$$LAR(D,e) = \sum_{a=e+L}^{a_{\max}} M(D,e,a)S(a)/S(e) \qquad (2)$$

D represents dose, and S(a)/S(e) is the probability of surviving to the attained age (a) conditional on survival to exposed age (e) and was derived from the life span tables of the UK Office for National Statistics 2006–2008. L is the risk-free latent period (L = 5 for solid cancers). $M(D,e,a)$ is associated with excess absolute risk EAR (D, e, a) and extra relative risk ERR (D, e, a).[37]

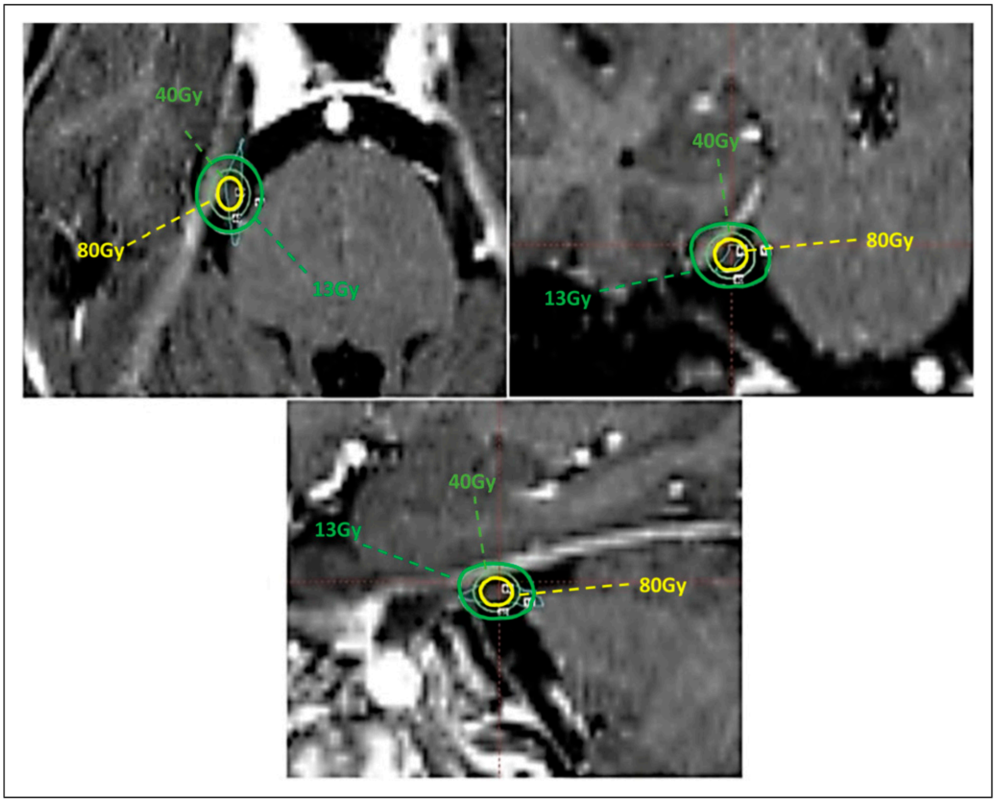

Figure 3. Illustration of the trigeminal nerve and brain stem as target and critical radiosensitive organ on MRI images.

Results

Calibration of TLDs

The actual output of TLDs during heating inside the TLD reader is light. The amount of this emitted light is directly related to the absorbed dose of radiation by the dosimeter, and the TLD reader convert emitted photons to an electrical current using a Photo Multiplier Tube (PMT). This current is collected by the TLD reader and reported in the nano-Coulomb (nC) unit as TLD response.[38] Calibration curves of TLDs at different dose levels are shown in Figure 4. The regression coefficient and matched line equation are specified too.

Extracranial Doses

Table 1 represents the measured doses in different organs:

The risk of secondary cancer induction has been calculated employing the BEIR VII (2006) method,[24] and LAR values and the related factors are given in Table 2.

Figure 5 gives the absorbed dose changes as a function of the average organs to isocenter distance. Regardless of the prescribed dose, the absorbed dose in various organs decreases by increasing the organs to isocenter distance. These results are in agreement with other studies by Di Beta,[17] Ioffe,[39] Novotny,[33] and Maarouf.[40] But in Berk's study,[41] because of different head angles (125° vs 72° in the current study) (Figure 1), the thyroid dose was more than the eyes' dose.

Discussion

Comparing the measured dose in studied organs with related tolerable doses reported by valid references demonstrates no serious concern regarding pregnant patients suffering from Trigeminal Neuralgia undergoing typical GK treatment. The duration of SRS treatment using a GK can vary significantly. For example, when a single isocenter is used for SRS in trigeminal neuralgia (TN) cases, the total treatment time shows relatively smaller variation, around a factor of ~4. However, when multiple isocenters are employed, this variability can increase by up to a factor of 10. Several factors contribute to this variability. Traditionally, the decay of Cobalt-60 sources, with a half-life of 5.26 years, has been considered a significant factor. Over time, for comparable treatment plans, the beam-on time increases proportionally, doubling after one half-life. However, the introduction of progressive plugging/sector blocking can have a similar impact. Additionally, collimator factors and individual patient geometry also affect the beam-on time. While scheduled or unscheduled time gaps in treatment may occur, they are less likely in TN cases, where treatments are typically administered as a continuous exposure. It is suggested that prescribing a specific biologically effective dose (BED) rather than a

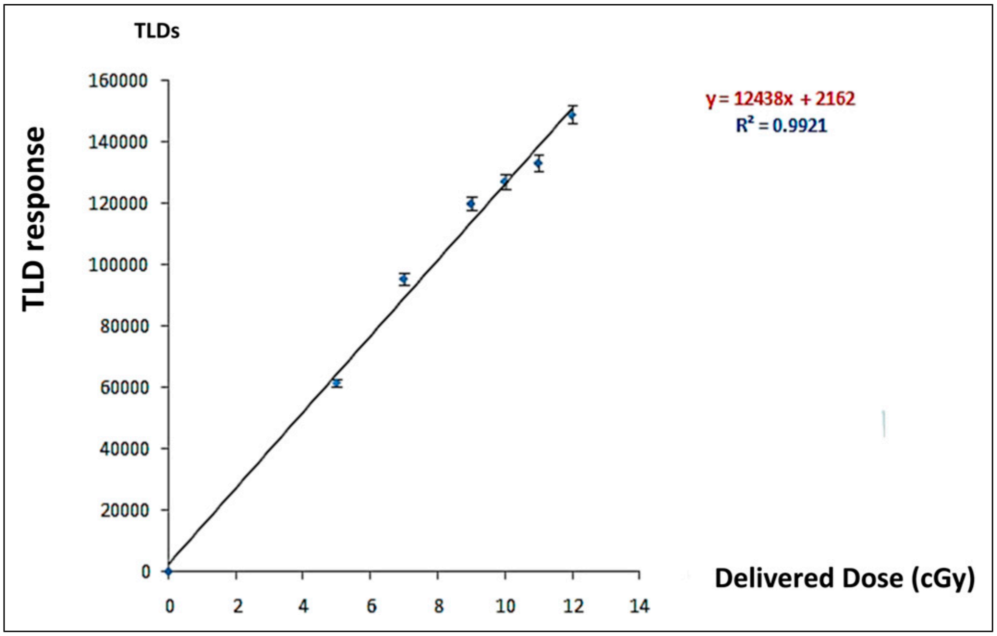

Figure 4. Calibration curves of TLDs in low-level doses.

Table 1. Measured Dose (cGy) of Extracranial Organs for Treated Patients by Gamma Knife.

Organ	Measured Mean Dose (cGy)	Mean Dose ± SD	Mean Dose to Prescribed Dose (90 Gy) (%)	SE
Eye	10.64	10.64 ± 1.08	.110	.160
Thyroid	8.26	8.26 ± 1.01	.090	.110
Ovary	.47	.471 ± .21	.005	.024
Uterus	.63	.63 ± .24	.006	.028

Table 2. The LAR Values for Treated Patients With Trigeminal Neuralgia by GK.

Organ	Weighing Factor (W_T)	Mean Dose (cGy)	LAR
Thyroid	.04	8.26	23
Uterus	.01	.63	1
Ovary	.08	.47	2

physical dose may lead to optimal safety and efficacy in stereotactic radiosurgery (SRS) for trigeminal neuralgia (TN). The findings indicate that a therapeutic ratio for TN treatment could be achieved by targeting a BED range of 1820–1962.5 Gy. Within this range, a long-term pain-free incidence of 90% and a low risk (less than 10%) of developing hypoesthesia can be expected. However, it is important to note that higher BED values do not correspond to a higher probability of pain control, but rather an increased risk of complications.[42] The possibility of receiving the scattered and leaked radiation to tissues out of the radiation field will increase in longer treatments. Regarding radiation treatments, knowing the doses to be deposited outside the treatment volume beforehand may allow a risk estimation of detrimental effects and, if possible, precautions to minimize the probability of developing them. Absorbed doses in mentioned organs, reference values, and results of similar studies are discussed below in detail:

Eyes

The mean eyes absorbed dose was 10.64 ± 1.08 cGy, .11% of the prescribed dose (Table 1), much lower than the cataractogenic dose of 200 cGy and the permissible dose of 500 cGy causing blurry vision.[43,44] Consequently, there is no risk of developing cataracts in TN treatment by GKRS. In other studies, investigating the eyes' received dose on patients and Rando phantoms, higher delivered doses of .25, 1, .7, and 7% of prescribed doses compared to the .11% of this work have been reported (Table 3). These discrepancies have pertained to many influencing factors, such as collimator size, the number of isocenters and shots applied, and eye-lesion distance. Larger collimator sizes in diameters of 18, 14, and 8 mm led to more scattering delivered to extracranial organs than the 4 mm collimator in the current study.[40,41,45,46]

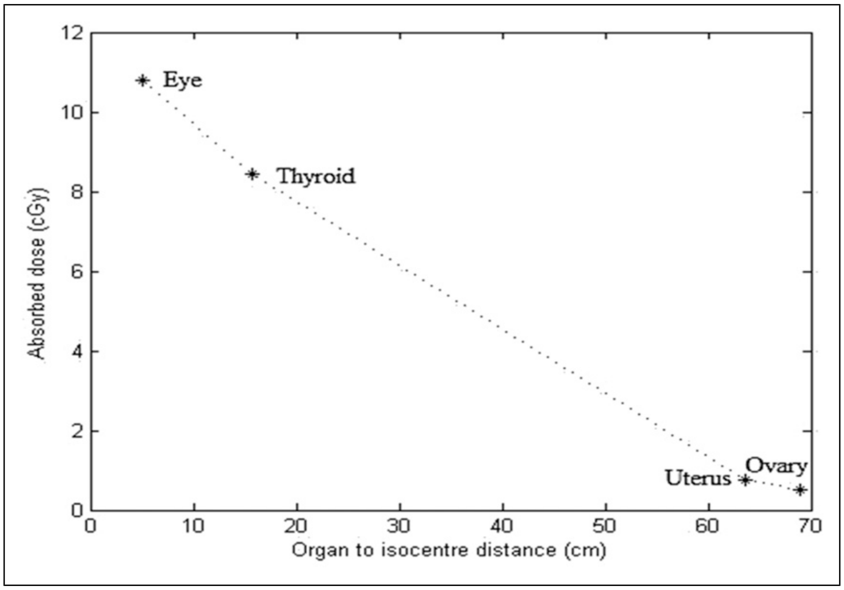

Figure 5. The absorbed dose as a function of organs to isocenter distance.

Table 3. Comparing Absorbed Dose of Organs With Previous Studies.

Study	Eye (cGy)	Thyroid (cGy)	Ovary (cGy)	Uterus (cGy)
Di Betta 2010[17]	—	1.32	.036	—
Miljanic 2013[20]		8.5	0.8	0.7
Ioffe 2002[39]	—	—	1.8	8.1
Hasanzadeh 2007[23]	—	9.15 ± 3.89	.47 ± 0.3	—
Novotny 1996[33]	22.3 ± 16.8	8.1 ± 5	—	1.2 ± 0.8
Maroof 2005[40]	27.6 ± 20	15.5 ± 8.3	2 ± 1.2	—
Berk 1993[41]	9 ± 8	15 ± 7	3.5 ± 2	3.0 ± 2.0
Yu 2003[45]	—	—	0.6	.26
Zitcovich 2007[46]	23.8	19.6 ± .073	—	2.1 ± .05
Chao 1996[47]	—	—	—	2.5
Yu 1997[48]	36.9 ± .39	5.8	—	4.0
Current study	10.64 ± 1.08	8.27 ± 1.01	.471 ± .21	.63 ± .24

Likewise, three and four isocenters applied in previous studies[40,46] caused an increase in absorbed doses.

Thyroid

The thyroid equivalent dose was 8.27 ± 1.01 cGy, (.009% of the prescribed dose), and according to the calculated LAR value, the risk of secondary cancer is 23 per 100,000 people, which is the highest LAR between mentioned organs. In previous studies performed on thyroid dose measurement, higher thyroid doses of .4, .1, .2, .4, .5, and .13% of prescribed dose (Table 3) were seen owing to larger collimators size used (8, 14, 18, and 30 mm), multiple isocenters, multiple shots, and larger angle (125°) resulting in increased scattered radiation.[17,20,23,33,40,41,45,46]

Uterus and Ovaries

The measured doses of the uterus and ovaries were .63 ± .24 cGy and .471 ± .21 cGy, which are .006 and .005% of the prescribed dose, respectively (Table 1). These values are under the permissible dose threshold of the uterus and ovary.[43,44] In other studies reported in Table 3, due to the previously mentioned reasons for eye and thyroid, the reported doses for the uterus and ovaries were higher than the corresponding dose in this study.[20,33,39,40,47] Calculated LAR values for the uterus and ovaries were 1 and 2, respectively, meaning that if 100,000 patients are treated with this method, one or two people will probably develop secondary cancer.

Table 4. Comparing Absorbed Dose to Selected Organs With NCRP and ICRP.

Organ	$TD_{50/5}$ cGy 3/3	$TD_{5/5}$ cGy 3/3	Mean Dose cGy	Equivalent Dose Limit
Eye	1800	1000	10.64	
Thyroid	15000	4500	8.26	
Fetus	—	200	—	NCRP5 ICRP2
Ovary	—	200–300	.63	NCRP5 ICRP2
Uterus	1000	7500	.47	NCRP5 ICRP2

TD5/5 and TD50/5

The tolerance dose TD5/5 represents the radiation dose that would result in a 5% risk of severe complications within five years after irradiation, and TD50/5 represents the dose that would result in a 50% probability of developing severe complications within five years of irradiation.[49] Cataract formation as a result of exposure is a controversial topic. The threshold dose for cataracts is 300 cGy for gamma radiation.[50] TD5/5 for eye lens is 1000 cGy for 3/3 whole organ, TD5/5 of the thyroid gland is 4500 cGy for 3/3 entire organ, and TD50/5 of the thyroid is 1500 cGy for 3/3 whole organ. TD5/5 and TD50/5 of the uterus are, respectively, 7500 and 10,000 cGy for the organ's total volume. TD5/5 of ovaries is 200–300 cGy for 3/3 of the whole organ.[51] The effects of radiation on embryos and fetuses include fetal death, fetal or neonatal physical abnormalities, retardation or developmental disorders, congenital malformations, and cancer induction. The dose of studied organs has been presented in Table 4 in comparison with ICRP and NCRP announcements. According to Table 4, there is no significant risk regarding pregnant patients suffering from Trigeminal Neuralgia undergoing typical gamma knife. Therefore, we can conclude that organs out of the radiation field of the GK machine are safe, and their risk of secondary cancer is low.

Conclusion

In this study, the average absorbed dose of the eye, thyroid, ovaries, and uterus were 10.64 ± 1.08, 8.26 ± 1.01, .471 ± .21, and .63 ± .24 cGy, equivalent to .11, .09, .005, and .006% of the prescribed dose (90 Gy), respectively. Leakage radiation, collimator scattering, and internal scattering comprise the most important factors leading to extracranial organs' receiving dose. The out-of-field organs' absorbed dose is a function of the organs to isocenter distance, collimator size, and target location in the patient's head. On average, mean doses to mentioned organs were smaller than their tolerance doses, and it seems there is no significant limitation to treating TN pregnant patients by gamma knife. In the case of ovaries and fetuses, due to the fetus's sensitivity to radiation and long-life expectancy, particular strategies (such as positioning) should be considered to reduce radiation as low as reasonably achievable (ALARA).

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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