Patient-Specific Fetal Dose Determination for Multi-Target Gamma Knife Radiosurgery: Computational Model and Case Report

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Abstract

A 42-year-old woman at 29 weeks gestation via in vitro fertilization who presented with eight metastatic brain lesions received Gamma Knife stereotactic radiosurgery (GKSRS) at our institution. In this study, we report our clinical experience and a general procedure of determining the fetal dose from patient-specific treatment plans and we describe quality assurance measurements to guide the safe practice of multi-target GKSRS of pregnant patients. To estimate fetal dose pre-treatment, peripheral dose-to-focal dose ratios (PFRs) were measured in a phantom at the distance approximating the fundus of uterus. Post-treatment, fetal dose was calculated from the actual patient treatment plan. Quality assurance measurements were carried out via the extrapolation dosimetry method in a head phantom at increasing distances along the longitudinal axis. The measurements were then empirically fitted and the fetal dose was extracted from the curve. The computed and measured fetal dose values were compared with each other and associated radiation risk was estimated. Based on low estimated fetal dose from preliminary phantom measurements, the patient was accepted for GKSRS. Eight brain metastases were treated with prescription doses of 15-19 Gy over 143 min involving all collimator sizes as well as composite sector mixed shots. Direct fetal dose computation based on the actual patient’s treatment plan estimated a maximum fetal dose of 0.253 cGy, which was in agreement with surface dose measurements at the level of the patient’s uterine fundus during the actual treatment. Later phantom measurements also estimated fetal dose to be in the range of 0.21-0.28 cGy (dose extrapolation curve R² = 0.998). Using the National Council on Radiation Protection and Measurements (NCRP) population-based model, we estimate the fetal risk of secondary malignancy, which is the primary toxicity after 25 weeks gestation, to be less than 0.01%. Of note, the patient delivered the baby via scheduled cesarean section at 36 weeks without complications attributable to the GKSRS procedure. GKSRS of multiple brain metastases was demonstrated to be safe and feasible during pregnancy. The applicability of a general patient-specific fetal dose determination method was also demonstrated for the first time for such a treatment.

Introduction

Gamma Knife stereotactic radiosurgery (GKSRS) has been widely adopted as a definitive or adjuvant treatment of various intracranial lesions, including multiple brain metastases [1-7]. It is rare for a pregnant woman to present with brain metastases and be referred for the GKSRS procedure. For some patients early delivery may be an option to facilitate more comprehensive oncologic imaging and management, however, the risks and benefits must be carefully assessed in a multi-disciplinary setting. One of the key concerns for the procedure is possible radiation toxicity to the fetus, which is dependent on the gestational age at the time of radiation exposure. In the first trimester during organogenesis, the major risks are teratogenicity and growth retardation, in the second trimester risk of growth retardation increases and there is a possible reduction in IQ with radiation exposure, and in the third trimester the primary risk is radiation-induced malignancy (leukemia) in the developing fetus [2]. There is limited data on the use of GKSRS for the treatment of brain metastases in pregnant patients and most studies describe managing patients on the 201-source configuration of the early GKSRS systems [1, 4].

With the introduction of Gamma Knife Perfexion (PFX) system, a single universal self-shielded tungsten collimator was employed [8-9], which significantly reduced the distal peripheral dose and external radiation exposures. The external radiation exposure is low enough such that some centers have considered installing a glass window in the treatment vault [8]. In light of enhanced technical capability and the low external radiation dose of the PFX system [10-11], we accommodated treatment of a rare GKSRS case at our institution, treating a pregnant patient with eight brain metastases of varying size throughout the cerebellum and cerebrum. Prior to treatment delivery, we endeavored to determine a reliable method to estimate the patient-specific fetal dose, and whether it is practical and safe to treat pregnant patients in general with multiple brain tumors with Gamma Knife Perfexion. To answer these questions, we developed an empirical computation method and concurrently performed in-phantom dose measurements to cross
To directly verify and cross check the computed value of Equation 2, direct dose measurements were carried out. Phantom measurements (LGP version 10.2) assumed \( D = \frac{2}{8} = 25\% \), \( w \) opening for a composite \( i \), where \( n \) is the relative sector weighting factor for the \( i \) sector, \( \theta \) the central dose rate and irradiation time for the \( i \) shot, \( b \) is the composite shot transit time including shuttle time between shots, \( (i=1) \), \( PFR \) is here defined as

\[
PFR (s,d) = \frac{PD (s,d)}{FD (s,d)} \tag{1}
\]

where \( PD (s,d) \) is the distal peripheral dose rate at a distance of \( d \) for the collimator size \( s \) and \( FD (s,d) \) is the dose rate of a given collimator at the focal point \( (d_0) \) corresponding to the Leksell G-frame coordinates of \( (x, y, z) = (100, 100, 100) \) mm. Once the \( PFR \)s were known, the patient-specific fetal dose \( (D_f) \) was computed as follows:

\[
D_f = D_0 \sum \left[ \sum (\frac{n_{s,b}}{d_t}) \right] + \sum \left[ \sum \left( \frac{n_{s,b}}{d_t} \right) \right] + \sum \left[ \sum \left( \frac{n_{s,b}}{d_t} \right) \right] + \sum \left[ \sum \left( \frac{n_{s,b}}{d_t} \right) \right] \tag{2}
\]

where \( N \) is the total number of isocenters for the treatment plan, \( D_0 \) is the reference dose rate, \( d_t \) and \( d_s \) are the central dose rate and irradiation time for the \( i^{th} \) shot, both of which values are provided in the treatment plan printout under the shot details section, \( b \) is the composite shot transit time including shuttle time between shots, \( (i.e., t_s = \sum t_b \) total treatment time – total beam-on time), \( (PFR_{0}, PFR_{b}, PFR_{d}) \) are the PRF values for 0-mm, 4-mm, 8-mm and 16-mm collimator, respectively, and \( \{w_{s,b}, w_{s,b}, w_{s,b}, w_{s,b}\} \) are relative sector weighting factor for the \( i^{th} \) shot, \( i.e., \{w_{s,b} = n_{s,b}/d_t; w_{s,b} = n_{s,b}/d_t; w_{s,b} = n_{s,b}/d_t; w_{s,b} = n_{s,b}/d_t\} \)

where \( n_{s,b}, n_{s,b}, n_{s,b} \) are the number sectors open for the \( i^{th} \) shot, respective. For example, if the 8-sector opening for a composite \( i^{th} \) shot is given \( b \), \( 4, 8, 8, 16, 16 \), then it follows that \( \{w_{s,b} = 1/8 = 12.5\% \}, w_{s,b} = 2/8 = 25\% \), \( 3/8 = 37.5\% \), \( 1/16 = 2/8 = 25\% \). Of note, the current GKSRS treatment planning system (LGP version 10.2) assumed \( D_b \), the background dose rate for the blocked shot, to be 0.00 Gy/min.

**Phantom measurements**

To directly verify and cross check the computed value of Equation 2, direct dose measurements were carried out.
out using computed tomography (CT) based planning (Figure 1a). The experimental setup for the measurements is illustrated in Figure 1b, where measurements were carried out using a compact ionization chamber (Wellhofer-CC13, IBA Dosimetry, Bartlett, TN) placed in a stack of solid water blocks and coupled with a humanoid head phantom (CyberKnife, Sunnyvale, CA) attached to the Leksell G-frame (Elekta, Atlanta GA).

The head phantom served as patient head simulation and solid water blocks approximated the dose scattering condition (Figure 1b). Thin-cut CT scans (1.5 mm) of the phantom were also obtained and actual patient treatment plan was projected on the phantom to simulate the actual treatment (Figure 1a). For each projected treatment plan, ionization chamber measurements were carried out by systematically shifting the chamber inferiorly inside a solid water block. Similarly, the PFR was measured by placing single shots (i.e., 16 mm, 8 mm, 4 mm and 0 mm) at the center of head phantom and taking measurements at locations approximating the patient’s uterine fundus, which was obtained by tape measure measurement during the time of initial patient consultation. Finally, the distal peripheral dose at any distance including the fetal locations was obtained by empirically fitting the measurement data. The results from the curve were compared with the direct computation result of Equation 2.

FIGURE 1: Projected treatment plan and experimental set-up.
Illustration of the patient's projected treatment plan on the computed tomography (CT) study of a head phantom (a and b) shows the experimental set up for the ionization chamber measurements.
Patient treatment planning and treatment

At the time of radiosurgery, the patient was 29 weeks pregnant, in her third trimester. The Gamma Knife planning MRI (Figure 2) was performed without gadolinium contrast, which is contraindicated during pregnancy, included T1 3D fast spoiled gradient echo (FSPGR), 3D fast spin echo (FSE) T2, increased signal intensity (ISI), and T2/FLAIR sequences. With guidance from neuroradiology, a total of eight lesions, including the left frontal resection cavity, were identified for treatment on the T2 FLAIR sequences. Axial isodose contours for the outlined targets are shown in Figures 2a-2d. The mean target volume was 2.83 ± 4.7 cc (range, 0.03-12.4 cc) and the targets were treated with prescription doses of 15-19 Gy based upon size and location. No margin for target uncertainty was added to the GTV, however, five of the eight targets were prescribed to isodose lines higher than 50% (range, 67-87%). The total target volume was 22.6 cc. The treatment plan used 4, 8 and 16 mm collimation and a total of 32 distinct isocenters. The total in-room treatment time was 143 min with a total beam-on time of 138 minutes. The surface dose measurement at the level of the uterine fundus for the entire treatment was <0.05 cGy.

FIGURE 2: Axial MR slices for target delineation.

Axial MR slices for the pregnant patient depicting the target locations (N = 8) and associated the isodose distributions. Note the small lesion inside the brainstem (2b), the large cerebellar metastasis (2a) and frontal lobe resection cavity (2d). The yellow lines show the prescription dose contours and the green lines show the
Of note, the patient delivered the baby via scheduled caesarian section at 36 weeks without complications attributable to the GKSRS procedure. At her two-month follow-up MRI with gadolinium contrast, there was significant decrease in five of the treated metastases, two areas of FLAIR hyperintensity which may represent treated metastases with resolution of enhancement, four new untreated metastases, and two lesions which in retrospect, were punctate dots of FLAIR abnormality at the time of her Gamma Knife planning MRI. At this point, the patient also had extra-cranial progression of the disease for which she was started on systemic chemotherapy. Since her initial Gamma Knife treatment, she has had three additional GKSRS procedures and whole brain radiotherapy. She remains alive 3.5 years after her initial presentation with intracranial disease and at last follow-up she had ECOG performance status of 1.

The PFRs for the 16-mm, 8-mm, and 4-mm collimators were determined to be 0.0013 ± 0.0000, 0.0048 ± 0.0001, and 0.00058 ± 0.00003, respectively. Although the GKSRS treatment planning system assumed $D_b = 0.00$ cGy/min, for more realistic estimate in the study we substituted the maximum in-phantom dose rate measurement when blocking all the sectors and applied PFR for the 0-mm for the calculation, i.e., $PFR_0 = 0.0055$ and $D_b = 0.028$ Gy/min. Substituting all the PFR values as well as the focal dose rate from the patient’s treatment plan, the maximum fetal dose at the location of uterus fundus was calculated to be 0.253 cGy, which was in agreement with surface dose measurements using MOSFETs at the level of the patient’s uterine fundus during the actual treatment. The robustness of the calculated value was further confirmed by varying all the PFR values by 3s or ~40% and the maximum fetal dose detected was found to be <0.35 cGy for all the cases. Figure 3a plots the individual collimator/combination contributions and the number of shots associated with such a calculation. As shown in Figure 3a, 51.8% of the calculated dose was from the 19.8-mm shots, whereas the three 16-mm shots contributed 27.5%. The total shot transit time only contributed approximately 0.005% of the total dose.

The extrapolation dose measurement result is plotted in Figure 3b, where nearly perfect exponential fit was obtained, i.e., $R^2 = 0.998$ from linear regression in logarithmic scaling of both x- and y-axis. From the fitted curve, the maximum fetal dose near the fundus of the uterus was estimated to be 0.278 to 0.211 cGy, which agreed well with the calculated value of 0.253 cGy from the patient’s treatment planning data. Noting excellent fitting result of Figure 3b, the dose to other critical structure of the patient was also obtainable. For example, the dose to the thyroid was found to be ~2.5 cGy, the maximum heart dose was ~1.5 cGy, etc.
FIGURE 3: Individual shot dose contribution and dose extrapolation.

Relative contributions from individual shots for the computed maximum fetal dose at the fundus of the uterus location based on the actual patient’s treatment planning (a) and the fitting results for the direct extrapolation dose measurements. Note the excellent fitting result yielding $R^2 = 0.998$ with the final fitted formula shown.

Discussion

GKSRS of a pregnant patient with multiple brain metastases ($N = 8$) is detailed in this report. Compared with previous Gamma Knife systems (Models U-4C) for which distal peripheral dose was reported to be on the order of 10 cGy for a simple treatment [1], distal peripheral dose was found to be 1-2 orders of magnitude lower for the PFX system, as in the current study. A patient-specific fetal dose computation procedure and extrapolation dosimetry measurements were developed and successfully carried out for the patient treatment.

Good correlation was found between calculations and measurements. The maximum fetal dose for this case was determined to be <0.3 cGy. Based on the current National Council on Radiation Protection and Measurements (NCRP) recommendation of 0.5 cGy whole-fetus dose limit for the general public [12], the treatment for the patient was deemed safe. A conservative estimate of the probability of toxicity, in this case radiation-induced malignancy, was <0.002% using NCRP population-based risk model (i.e., 0.006%/cGy to the whole fetus).

It is evident that the measurement and calculation method presented are readily translatable to other distal
locations given that patient-specific measurements are performed, as demonstrated in Equation 2.

Conclusions

In summary, the results of this study have demonstrated that GKSRS is a technically feasible modality and safe by a conservative standard for treatment of patients with multiple brain metastases during the 2nd-3rd trimesters of pregnancy. Special care must be taken by clinicians to ensure the dose to the fetus is reliably estimated via both the patient-specific treatment plan and in-phantom measurements as demonstrated by this study.

Additional Information

Disclosures

Human subjects: Consent was obtained by all participants in this study. Informed consent obtained.
Animal subjects: All authors have confirmed that this study did not involve animal subjects or tissue.
Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: Payment/services info: All authors have declared that no financial support was received from any organization for the submitted work. Financial relationships: Patricia K Sneed declare(s) Honorarium and travel expenses from Elekta. Received an honorarium and travel expenses from Elekta to attend a meeting regarding the Elekta Gamma Knife registry effort in New York City, February 2015. Other relationships: All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

References