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Technical Notes

Radiation dose to the fetus during CyberKnife radiosurgery for a brain tumor in pregnancy

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ABSTRACT

Purpose: Pregnancy during radiosurgery is extremely rare in clinical practice. We report fetal dose results during CyberKnife radiosurgery for a brain tumor in pregnancy.
Methods and materials: A 26 year old pregnant woman with a rapidly growing deep-seated grade-III glioma was treated during the third trimester of gestation using CyberKnife. Ultrasound imaging was used to determine the position of the embryo prior to treatment. A dose of 1400 cGy was prescribed aiming to control tumor growth until delivery of the child. Prior to radiosurgery, the treatment was simulated on an anthropomorphic phantom. Radiation dose to the embryo was measured using a Farmer chamber and EBT3 films.
Results: Fetal doses of 4.4 cGy and 4.1 cGy were measured for the embryo's head and legs, lying at 56 cm and 72 cm from the isocenter, respectively, using the Farmer chamber situated at 8.5 cm depth beneath the phantom surface. Dose results of 4.4 cGy, 3.5 cGy and 2.0 cGy were measured with the films situated at depths of 6.5 cm, 9.5 cm and 14.5 cm, respectively. An average dose of 4.2 cGy to the fetus was derived from the above values. A corresponding dose of 3.2 cGy was also calculated based on results obtained using EBT3 films situated upon the patient skin.
Conclusions: The measured fetal doses are below the threshold of 10 cGy for congenital malformations, mental and growth retardation effects. The radiogenic cancer risk to the live-born embryo was estimated less than 0.3% over the normal incidence. The treatment was administered successfully, allowing the patient to deliver a healthy child.

Introduction

The incidence of malignant brain tumors during pregnancy is rare, ranging between 0.025‰ and 0.05‰ [1,2]. In treating a pregnant woman with a malignant brain tumor, surgical resection and decompression should be performed as soon as possible if the tumor is large and causing progressive symptoms or surrounded by edema that is causing considerable mass effect. If the tumor is not producing much mass effect and the patient is clinically stable any invasive procedure can be postponed until after child delivery [3]. In the meantime, careful monitoring using frequent neurological examinations and neuroimaging studies should be performed. In case of tumors located in deep or eloquent brain regions where radiotherapy and/or chemotherapy is in order, a careful balance between the mother's benefit and the fetus risk should be performed [4,5]. As far as radiotherapy is concerned, radiation exposure in utero is associated with an increased risk of multiple severe complications, including lethality, malformations, mental and/or growth retardation, as well as cancer induction [6–8]. These effects have been reviewed in two reports by the International Commission on Radiological Protection and depend on pregnancy stage and the absorbed fetal dose [9,10].

In brain tumor radiotherapy, fetal dose is due to radiation leakage from the linear accelerator (linac) head, the scattered radiation from the beam collimation systems, the flattening filter and wedges (if applicable), as well as the scattered radiation from the patient body [11]. In contemporary radiotherapy techniques, like Intensity

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Modulated Radiation Therapy (IMRT) and Stereotactic Radiosurgery/Radiotherapy (SRS/SRT), the dose delivered to the tumor and surrounding organs at risk (OARs) is optimized using an increased number of intensity modulated small radiation beams utilized by specifically designed collimation systems. While these techniques are capable of creating conformal and steep spatial gradient dose distributions, introducing a paradigm shift in radiotherapy, they are associated with an increased number of Monitor Units (MUs) and consequently an accountable peripheral dose [12,13]. Moreover, the aforementioned techniques are usually combined with image guidance subsystems to ensure accurate registration of the planned dose distribution with the treated lesion. In case x-rays are used for guiding treatment delivery, the additional dose to the fetus from this procedure should also be considered [14].

In this work, we describe dosimetry measurements performed for a pregnant patient with a deep-seated malignant brain tumor treated in our clinic using the CyberKnife™ (Accuray Inc. Sunnyvale, CA, USA) stereotactic radiosurgery system [15,16].

Methods

Patient details

The presented case involves a 26 year old female who developed sudden headache with nausea and vomiting during the 13th week of pregnancy. The patient underwent CT and MR scans that that showed a 2.5 cm of maximum dimension (~4.2 cm^3) lesion located deeply in the right posterior hemisphere close to the occipital horn of the lateral ventricle, and a severe tetraventricular bleeding. A stereotactic brain biopsy was carried out which revealed a high-grade glioma (WHO grade III). The patient was offered the option of pregnancy cessation and subsequent surgery or to postpone surgery until delivery and perform a closer follow up using serial imaging. Due to the patient's wish to deliver her child and as her mental capacity was intact, surgery was deferred. A subsequent MR scan was carried out 4 weeks later and showed progressive disease with an increase of the lesion size to $(3.6 \times 3 \times 2.5)$ cm^3 and a volume of 8.7 cm^3. The rapid increase of tumor size, the challenging surgical location deep in the hemispheric white matter and the chance of repeated bleeding, together with the absolute refusal of a therapeutic abortion, posed indeed a grim prognosis quoad vitam to both mother and child.

CyberKnife radiosurgery was then considered as an alternative to achieve tumor growth control until delivery. Ultrasound imaging was performed to determine the position of the embryo prior to radiosurgery. The distance of the embryo's head and legs from the midline of the patient's head was measured equal to 56 cm and 72 cm respectively. Radiosurgery preparation included the construction of a customized thermoplastic mask of the patient's head in treatment position and acquisition of a contrast enhanced CT scan with 0.1 cm slice thickness and 0.1 cm slice separation, using a 256-multi-slice SOMATOM Definition Flash CT scanner (Siemens AG, Erlangen, Germany). While the dose to the fetus from a head CT scan has been reported to deliver a dose of less than 5×10^{-4} cGy [9] to the fetus, a 0.2 cm thick shielding apron was positioned around the abdomen of the patient. An additional set of 0.1 cm isotropical resolution T1- and T2-weighted axial MR images of the patient's head was also acquired using a 3T MAGNETOM Trio scanner (Siemens), to aid delineation of the target and surrounding OARs. All image series were imported into the MultiPlan™ Treatment Planning System (TPS) (Accuray). The anatomical MR images were registered with the CT volume using the registration algorithm of the TPS. The target and the critical structures of the brain (i.e., brain stem, optic chiasm and optic nerves) were delineated using the CT and the fused anatomical MR images. Both eyes were also contoured and used as blocking structures (i.e., avoid beam direction passing through them) in treatment planning. The TPS sequential optimization tool was used to create a conformal treatment plan with optimum tumor coverage, maintaining minimal: the dose to surrounding healthy brain tissue, OARs and total MUs.

Fetal dose measurements

Dose measurements were performed using the RANDO™ anthropomorphic phantom (The Phantom Laboratory, Salem, NY). The specific phantom is constructed with a natural human skeleton, which is cast inside soft tissue simulating material. Lungs are molded to fit the contours of the natural rib cage. The phantom is sliced at 2.5 cm intervals. The intervals comprising the abdomen of the RANDO phantom were replaced with RW3 (PTW, Freiburg, Germany) slabs of (30×30) cm^2 lateral dimensions and 20.5 cm total thickness (Fig. 1). A 0.6 cm^3 PTW-30013 Farmer ionization chamber was placed at 8.5 cm depth beneath the surface of the phantom using an appropriate drilled RW3 slab. Besides the ion chamber, the dose to the fetus was also measured using Gafchromic EBT3 films (ISP, Wayne, NJ). Three (20.3×25.4) cm^2 sheets of EBT3 films were positioned between the RW3 slabs at depths of 6.5 cm, 9.5 cm and 14.5 cm (Fig. 1). Two additional sets of three (3×3) cm^2 EBT3 films were positioned 56 cm away from the isocenter on the surface of the RW3 phantom and the patient, respectively, for surface dose measurements and verification purposes.

Film dosimetry was performed according to the protocol suggested by Devic and colleagues [17]. The calibration curve of the used film batch was obtained beforehand by irradiating two sets of 15 pre-cut (3×3) cm^2 EBT3 films situated 1.5 cm beneath the surface of a 20 cm thick RW3 phantom, with doses in the range of 0 cGy–300 cGy using the 6 cm in diameter CK reference beam. Absorbed doses to the films were measured using a Farmer chamber situated at 10 cm depth inside the RW3 phantom. All EBT3 films were scanned one day post irradiation to allow post irradiation optical density growth, using an Epson Expression 1680Pro flatbed optical scanner. The scanner was used in transmission mode and all films were scanned in 48-bit RGB mode with a resolution of 72 dpi, but only the red color channel of the image was used. It is noted that film dosimetry was performed using the red channel of the scanned images since for the dose range of interest the sensitivity (defined as net optical density (netOD) change per unit absorbed dose) of the EBT dose–response is the higher compared to the corresponding sensitivity for the green and blue channels [18]. All films were placed in the same area of the scanner bed, maintaining the same orientation throughout the scanning procedure. Custom written routines were employed to obtain the net optical density (OD) of each film on a pixel by pixel basis and to convert

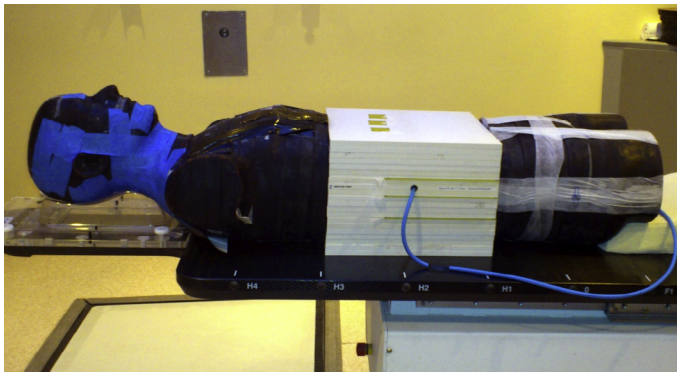

Figure 1. A photograph of the anthropomorphic phantom used to measure the dose to the fetus.

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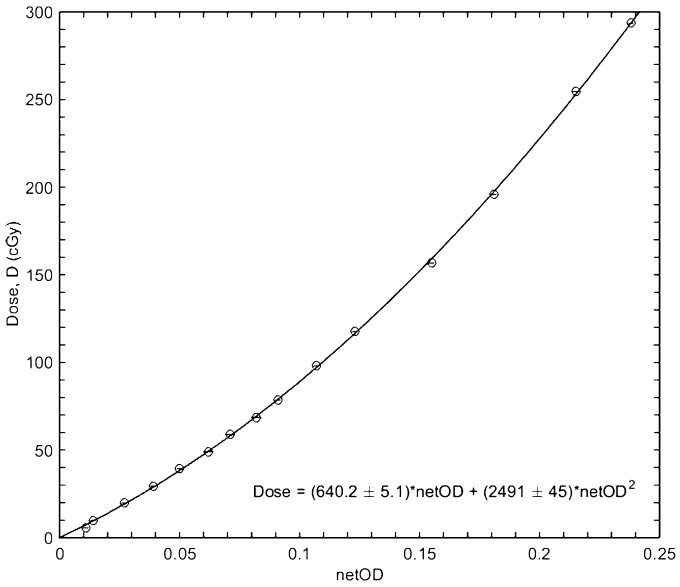

Figure 2. The calibration curve of the GafChromic EBT3 film batch used in this work for the red color channel and the Epson Expression 1680Pro flatbed optical scanner. The fitted polynomial function used to convert the net optical densities to doses is also presented.

the obtained values to corresponding dose results using the calibration curve of the specific film batch.

The head and neck part of the RANDO phantom was CT imaged and imported into the CK database. The TPS dose quality assurance tool was used to overlay the patient's treatment plan on the head of the phantom. Employing this procedure phantom dose measurements were performed for the exact 3D beam configuration, collimator dimensions and MUs of the patient's treatment plan.

In Fig. 2, the calibration curve of the used film batch is presented along with the fitted polynomial function used to convert net optical densities to absorbed dose values. The uncertainty associated with the calibration procedure obtained using error propagation on the uncertainty of the polynomial coefficients was found equal to 2%. The uncertainty associated with the measured film fetal doses was determined using error propagation on the standard deviation of the mean netOD and the uncertainty associated with the calibration procedure. In concordance, ion chamber uncertainty was estimated according to the TRS-398 dosimetric protocol [19].

Results

Treatment details

A conformal treatment plan was prepared consisting of 226 non-isocentric pencil beams of 1 cm (151 beams) and 1.5 cm (75 beams) nominal diameter, respectively (Fig. 3). These beams were created using the corresponding fixed collimators of the CK platform. The volume of the delineated target was equal to 14.9 cm^3. A dose of 1400 cGy was prescribed in a single fraction at the 80% isodose line encompassing 95% of the target volume, resulting in a number of 18,086 MUs (12,085 MUs were delivered with the 1 cm and 6001 MUs with the 1.5 cm field, respectively). It is noted that while the prescription dose of 1400 cGy cannot be considered therapeutic, it was chosen as a means to provide temporary tumor control while allowing a safe full term child delivery with limited fetal exposure to radiation. The maximum dose to the brain stem, optic nerves and optic chiasm was 267 cGy, 110 cGy and 175 cGy, respectively.

Prior to treatment a written consent was obtained from the patient. Treatment was delivered with the patient in the 21st week of pregnancy using the G4 version of the CyberKnife system employing the 800 MU/min linac with the upgraded shielding device [20–22]. Treatment was well tolerated as no side effects were recorded. A number of 170 x-ray images of the patient's head were acquired (with settings of: 120 kV tube voltage and 10 mAs tube load) during treatment and used for image guidance. It is noted that the acquired x-ray images contributed to a total dose of 4.1 cGy and less than 0.1 cGy, to the surface of the patient's head and abdomen, respectively, obtained based on imaging dose measurements performed using a solid state detector (PTW-T60004) and a diagnostic beam electrometer (PTW-DIADOS) calibrated in kV [15]. Since the imaging dose to the patient abdomen was found negligible, it was ignored from further risk assessment considerations.

Fetal dosimetry results

Fetal dosimetry results obtained with the Farmer chamber situated at 8.5 cm depth within the RW3 phantom were as follows: (4.4 ± 0.1) cGy and (4.1 ± 0.1) cGy for the embryo's head and legs, lying 56 cm and 72 cm distance from the isocenter, respectively. Regarding film dosimetry results, a dose of (4.4 ± 0.5) cGy, (3.5 ± 0.7) cGy and (2.0 ± 0.8) cGy was measured for the films positioned at 6.5 cm, 9.5 cm and 14.5 cm depths inside the RW3 slab phantom, respectively. These results were obtained by averaging the optical densities of pixels lying within an area of (5×10) cm^2 formed along the patient's left–right and superior–inferior directions, respectively. An average fetal dose value of (4.2 ± 0.1) cGy was calculated by weighting the above Farmer and film measured fetal dosimetry results according to the corresponding uncertainty values (i.e., the average fetal dose was calculated by summing the measured doses with a normalized weight given by the inverse square of their corresponding uncertainties).

Surface doses of (7.5 ± 0.7) cGy, (7.5 ± 0.5) cGy and (7.4 ± 0.7) cGy, with an average value of (7.5 ± 0.4) cGy, were obtained using the films lying upon the phantom surface at a 56 cm distance with respect to the isocenter. This suggests that the average surface dose was found to be 1.8 times higher than the corresponding average dose to the embryo. Corresponding dosimetry results obtained using the three films situated upon the patient skin were found equal to (6.2 ± 0.6) cGy, (5.7 ± 0.6) cGy and (5.6 ± 0.7) cGy, exhibiting an average of (5.8 ± 0.4) cGy. By combining the patient measured dose data and the observed relation between the surface and fetal dose measurements using the phantom a value of (3.2 ± 0.3) cGy was derived for the dose delivered to the embryo during the radiosurgery treatment.

Discussion

A pregnant woman was treated for a malignant glioma using the CyberKnife stereotactic radiosurgery system. A dose of 1400 cGy was administered to the periphery of the target in a single fraction. While the prescribed dose cannot be considered therapeutic, it was deemed sufficient to achieve tumor control until full term child delivery. Tumor control was successfully achieved, as shown by serial MR follow-up scans and the patient delivered a healthy child at due time (38th week of pregnancy). Further control MR scans carried out three months after delivery showed progressive disease defined by a volumetric increase (lesion volume of 28.3 cm^3, >30%). Tumor progression was accompanied by vasogenic edema. At this time a more aggressive treatment was in order, hence and a second hypo-fractionated CK treatment was performed delivering a prescribed dose of 2400 cGy in three fractions at the 82% isodose line

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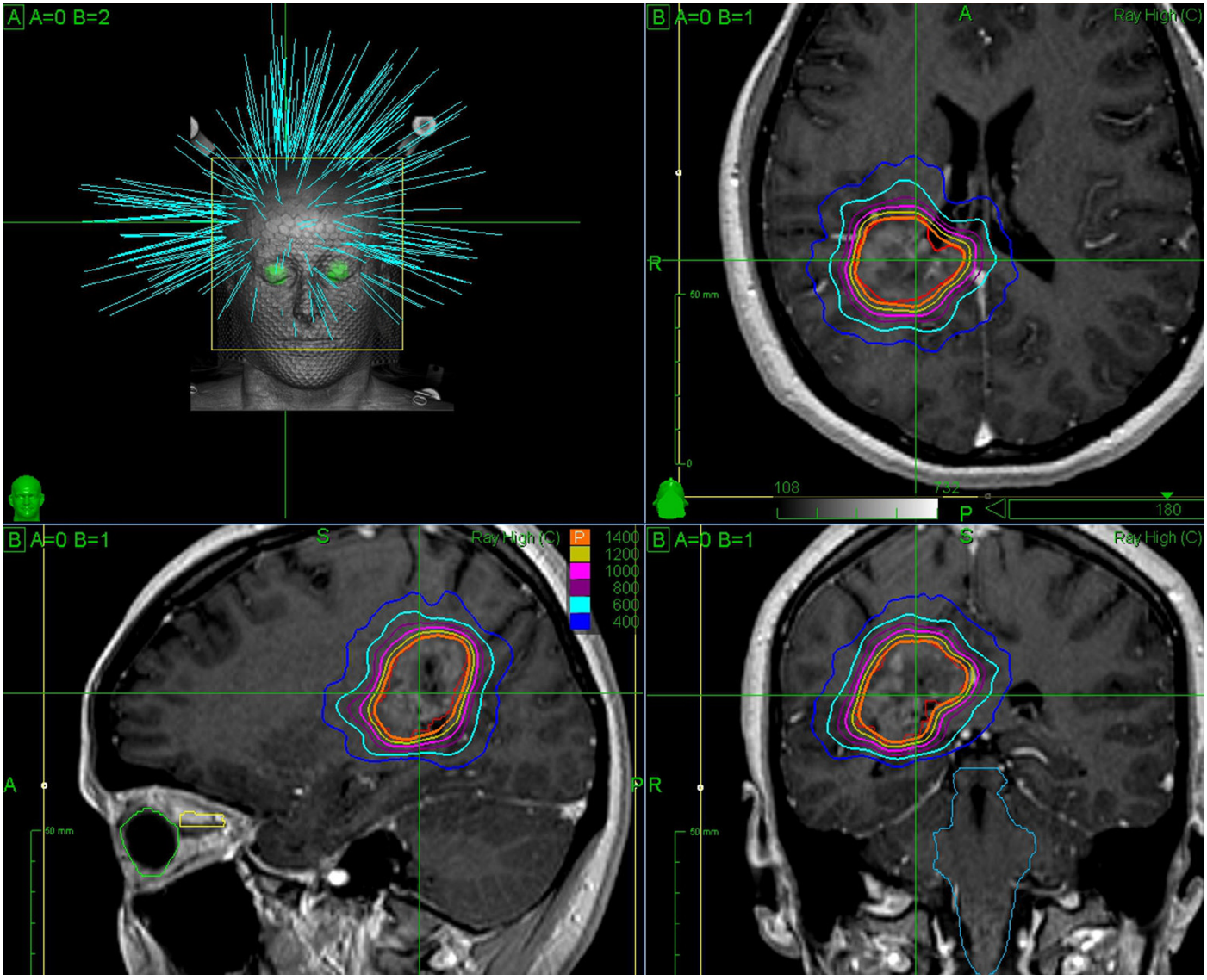

Figure 3. A print screen of the CyberKnife treatment plan delivered to the pregnant patient. The delivered dose distribution is presented in the central axial (upper right), coronal (lower right) and sagittal (lower left) T1 weighted MRI planes in the form of isodose lines. The 3D configuration of the used pencil beams is represented in the upper left panel.

encompassing 97% of the lesion volume. Following the second treatment, long-term growth control was achieved as shown by a control MR scan performed 12 months post treatment.

Fetal dosimetry measurements performed using the RANDO phantom, the Farmer ion chamber and EBT3 films showed that the average dose delivered to the embryo during radiosurgery treatment was equal to (4.2 ± 0.1) cGy which is equal to 0.3% of the prescribed dose. An in-vivo dose of (3.2 ± 0.3) cGy (or 0.2% of the prescribed dose) delivered to the embryo was also estimated by combining phantom and patient dosimetry data, in relevant agreement to the corresponding phantom fetal dosimetry results. The small differences between the in-vivo and the phantom fetal dosimetry results could be attributed to corresponding differences between the patient and phantom geometrical characteristics. The obtained fetal dose results are lower than the threshold of 10 cGy for congenital malformations and mental and growth retardation [6,7,9]. The childhood cancer risk, attributable to radiation in utero, has been estimated to be 0.06% per cGy (or ~1/1700 per cGy) above the natural background level for childhood cancer [4,6,7]. Therefore the higher measured fetal dose of 4.2 cGy corresponds to an increase in cancer risk by 0.3% over the relatively low natural baseline of childhood cancer risk [9]. Heritable disease caused by radiation exposure has lower risk than cancer, about 1 in 42,000 per cGy, and therefore is not accounted for [8]. At the age of 18 months the child enjoys excellent health with no signs of growth retardation or cognitive impairment.

During radiotherapy, there is always a small unavoidable fraction of radiation that is absorbed by radiosensitive organs outside the irradiated volume. This dose is due to radiation leakage from the linac, the scattered radiation from the beam collimation systems, the flattening filter and wedges (if applicable), as well as the scattered radiation from the patient itself [11]. Therefore, in the case of radiotherapy delivered to pregnant patients, additional care must be taken due to the significant potential for small doses of radiation to cause severe toxicity to the developing fetus. Excluding radiotherapy of the cervix, fetal doses ranging from 3.9 cGy to 18 cGy for breast tumors, from 1.4 cGy to 50 cGy for Hodgkin's disease and from 0.15 cGy to 6 cGy for brain tumors, respectively, have been reported [4]. It should be noted, however, that these dosimetry data correspond to measurements performed using standard radiotherapy

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techniques. In a recent work, an IMRT technique was used to irradiate a brain tumor with three right-side coplanar 6 MV beams and a dose of 2.1 cGy was measured without the use of shielding devices [23]. In our case, higher fetal doses of 3.2 cGy and 4.2 cGy were measured for the patient and the phantom, respectively, which are less than the maximum dose of 6 cGy reported in the literature for brain radiotherapy [4]. These higher measured fetal doses are attributed to the non-coplanar configuration of the pencil beams used by the CK system, which includes beams passing the nasal cavities and beams that lay close to the cranio-caudal axis of the patient (Fig. 3). The beams passing through the nasal cavities increase the leakage and scattered radiation reaching the fetus since they correspond to smaller distances between the linac and the patient's abdomen.

On the other hand, the beams lying close to the cranio-caudal axis increase the scattered radiation within the patient's body. The primary radiation from the latter oblique beams has minimal contribution to the fetal dose due to the increased distance between the source and the fetus and the corresponding large attenuation depths. Nevertheless, a contribution of primary radiation to the peripheral dose received by organs of the neck (e.g., thyroid gland) has been reported for CK intracranial treatments [20,21]. It should be noted that, while during treatment planning the aforementioned set of oblique beams could be excluded to reduce fetal dose this was not exploited herein to avoid decreasing treatment plan quality, and effort was performed to reduce the total MUs of the treatment plan affecting the contribution of radiation leakage.

Conclusion

A pregnant woman suffering from a malignant brain glioma was treated using the CyberKnife stereotactic radiosurgery system. A fetal dose of (4.2 ± 0.1) cGy was measured using the RANDO phantom. A corresponding dose of (3.2 ± 0.3) cGy was also calculated based on results obtained using EBT3 films situated upon the patient's skin. The fetal dose results lie safely below the threshold value of 10 cGy for congenital malformations and mental and growth retardation. An increase of the childhood cancer risk by 0.3% was estimated using the higher fetal dose value. The treatment was administered successfully, allowing the patient to deliver a healthy child. At the age of 18 months the child enjoys excellent health with no signs of growth retardation or cognitive impairment.

Conflict of interest

None.

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