Physics

First clinical implementation of GammaTile permanent brain implants after FDA clearance

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ABSTRACT PURPOSE: GammaTile cesium-131 (131Cs) permanent brain implant has received Food and Drug Administration (FDA) clearance as a promising treatment for certain brain tumors. Our center was the first institution in the United States after FDA clearance to offer the clinical use of GammaTile brachytherapy outside of a clinical trial. The purpose of this work is to aid the medical physicist and radiation oncologist in implementing this collagen carrier tile brachytherapy (CTBT) program in their practice.

METHODS: A total of 23 patients have been treated with GammaTile to date at our center. Treatment planning system (TPS) commissioning was performed by configuring the parameters for the 131Cs (IsoRay Model CS-1, Rev2) source, and doses were validated with the consensus data from the American Association of Physicists in Medicine TG-43U1S2. Implant procedures, dosimetry, postimplant planning, and target delineations were established based on our clinical experience. Radiation safety aspects were evaluated based on exposure rate measurements of implanted patients, as well as body and ring badge measurements.

RESULTS: An estimated timeframe of the GammaTile clinical responsibilities for the medical physicist, radiation oncologist, and neurosurgeon is presented. TPS doses were validated with published dose to water for 131Cs. Clinical aspects, including estimation of the number of tiles, treatment planning, dosimetry, and radiation safety considerations, are presented.

CONCLUSION: The implementation of the GammaTile program requires collaboration from multiple specialties, including medical physics, radiation oncology, and neurosurgery. This manuscript provides a roadmap for the implementation of this therapy. © 2020 The Authors. Published by Elsevier Inc. on behalf of American Brachytherapy Society. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Keywords: GammaTile; Collagen carrier tile brachytherapy (CTBT); Brain cancer; Cesium-131

Introduction

External beam radiation therapy (EBRT) after brain tumor resection has been shown to improve local tumor control (1). However, delivering external beam radiation therapy after tumor resection typically requires a waiting period of 3–5 weeks to allow for wound healing and recovery. During this time, patients may experience tumor regrowth (2,3). Permanent brachytherapy brain implants can be performed intraoperatively, immediately after tumor resection, thus allowing irradiation to begin immediately. In 2017, Wernicke et al. presented the safety and efficacy of postoperative stranded 131Cs seeds as permanent implants for brain metastases (4). They described their implant techniques, in which the resection cavity was lined with 131Cs seeds in a pattern similar to barrel staves or parallel tracks and subsequently covered with absorbable fibrin patches and cavity filled with fibrin glue (4). This technique has also been used in previously irradiated brain tumors (5).
Additionally, previous studies have shown that to deliver a more homogeneous dose to the target and to decrease the incidence of brain radionecrosis, a fixed separation between seeds should be used during implant (6).

A permanently implantable collagen carrier tile brachytherapy (CTBT) device consisting of $^{131}$Cs seeds embedded within a biocompatible carrier/spacer (GammaTile, GT Medical Technologies, Tempe AZ) has been introduced for treatment of certain brain tumors (7–9). The University of Minnesota was the first institution in the United States after FDA clearance to offer the clinical use of GammaTile therapy outside of a clinical trial. The new GammaTile design addresses some of the shortcomings of previously available stranded $^{131}$Cs seeds, by eliminating direct contact of the seeds with the adjacent brain tissue and offering consistent fixed spacing due to the structural collagen matrix. The ease of use of the modular structure of the CTBT also provides simpler and faster implantation. This, in turn, reduces exposure to staff and shortens the duration of the anesthesia for patients. Clinical trials of GammaTile showed that this technique can be used to treat recurrent malignant brain neoplasms, including high-grade gliomas, Grades II and III meningiomas, brain metastasis, craniopharyngioma, and dural sarcoma in patients who had been previously irradiated with EBRT (10). The objective of this work was to aid the radiation oncology team in implementing and commissioning the GammaTile brachytherapy program, with the intent of addressing the questions that might arise during the process of implementing this technique. Aspects related specifically to the neurosurgery components of this procedure are beyond the scope of this work.

### Methods

To date, 23 patients have been treated (n = 23) in our institution with GammaTile permanent brain implant brachytherapy. Based on our clinical experience, a thorough investigation of all aspects of the clinical implementation of the GammaTile technique was performed. The responsibility of commissioning the GammaTile program was mainly assigned to the medical physicist; however, it required close collaboration with the radiation oncologist, radiation safety officer and other members of the care team (11). Overall, the commissioning of the program included determining the physical properties of GammaTile and $^{131}$Cs seeds, a protocol development, TPS commissioning using $^{131}$Cs line source brachytherapy parameters, and seed calibration using an accredited dosimetry calibration laboratory (ADCL) calibrated well chamber. Finally, clinical implementation required estimating the number of tiles, determining the implant day procedures, postimplant treatment planning, and development of patient intake and release instructions. Radiation safety considerations were also a fundamental aspect of implementing this new brachytherapy program and included determining absorbed dose using ring and body badges and performing exposure rate measurements.

### Physical properties of GammaTile

The GammaTile is based on a modular structure that allows several tiles to be abutted to cover the resection cavity while offsetting the seeds from the surface of the brain. The GammaTile collagen matrix is rigid when dry and becomes flexible and adherent when hydrated. Each GammaTile contains four titanium-encapsulated $^{131}$Cs (Model CS-1, Rev2) seeds (IsoRay Medical Inc., Richland, WA) secured using VICRYL sutures and embedded in a collagen matrix structure (Saturable DuraGen Matrix, Integra Lifesciences, Plainsboro, NJ). VICRYL is a synthetic flexible bioabsorbable surgical suture commonly used to approximate and ligate soft tissues. DuraGen is a porous collagen material, which has been used in brain surgeries for over 30 years, because it allows for cell ingrowth and conforms easily to complex surfaces of the brain. Each GammaTile device is manufactured with the $^{131}$Cs seeds in a square geometry with a 1 cm interseed distance (measured from the center of each seed). The surface area of each GammaTile is $\times 2 \times 2$ cm$^2$ as shown in Fig. 1a. Hydrated tiles are 4 mm thick: the seeds are 1 mm from the smooth side and 3 mm from the textured side. According to the manufacturer, the 3 mm nominal distance can vary from 2.25 mm to 3.75 mm with a normal distribution having 3 mm mean and $\pm 0.25$ mm standard deviation.

The textured surface of the GammaTile as shown in Fig. 1b should be in contact with the resection cavity as it “sticks” to the cavity surface, allowing each tile to conform to the resection cavity. The tiles are shipped pre-sterilized and are ready to be implanted upon receipt. Sterilization is done by means of electron beam sterilization (E-BEAM) irradiators using standard radiation sterilization doses of 25 kGy (12). Tiles are for single use and cannot be resterilized according to the GammaTile instructions for use (IFU) (13). After tiles are placed in the desired position, a fibrin patch, sealant, and adhesive fibrin glue (Tisseel, Baxter, Westlake Village, CA) are used to fill the resection cavity (14). Hemostatic matrix (FLOSEAL, Baxter, Westlake Village, CA) may also be applied to the cavity to stop bleeding.

### Properties of IsoRay CS-1 Rev2 $^{131}$Cs seed

The IsoRay CS-1 Rev2 seed is currently the only $^{131}$Cs source that meets the Joint AAPM/IROC Houston Registry of Brachytherapy Sources meeting the American Association of Physicists in Medicine (AAPM) dosimetric prerequisites (15). The CS-1 $^{131}$Cs seed has been introduced in the clinical practice for permanent seed implants for cancer since its clearance by the FDA in 2003. In 2006, the production process changed and the CS-1 Rev2 model replaced its predecessor. Each seed consists of an inner 0.25 mm diameter gold (Au) marker wire surrounded by a glass tube coated with ceramic (containing $^{131}$Cs). The seed is encapsulated by an outer titanium tube with
0.056 mm thick wall and 0.1 mm thick laser-welded ends. The final seed dimensions are 0.82 mm outer diameter, 4.5 mm physical length, and consensus value of $C_{ONL} = 4.0$ mm for the source active length (16).

The half-life of $^{131}\text{Cs}$ is $9.689 \pm 0.016$ days (17). The $^{131}\text{Cs}$ source spectrum used as a reference for the determination of consensus values for the IsoRay CS-1 Rev2 was obtained from the National Nuclear Data Center (NNDC) of Brookhaven National Laboratory (16,17). The NNDC website provides the gamma-ray energies vs intensities for various radionuclides, and it is the AAPM and The Groupe Européen de Curiethérapie in conjunction with the European Society for Radiotherapy & Oncology (GEC-ESTRO) recommended data for reference photon spectra (16). The spectrum for $^{131}\text{Cs}$ ranges from 3.760 keV to 34.496 keV with mean energy reported as 30.411 keV (>10 keV photons) (16). Brachytherapy parameters in water for the IsoRay $^{131}\text{Cs}$ (Model CS-1, Rev2) seeds have been previously published (18-22). Consensus values and dose rates per unit source strength for this source were reported in the AAPM TG-43U1S2 and Erratum to TG-43U1S2 (16,23). These parameters will be further discussed in the treatment planning system (TPS) section. The conversion factor from air kerma strength (U) to mCi for $^{131}\text{Cs}$ IsoRay is 0.638 U mCi$^{-1}$ and the consensus value for dose rate constant is $C_{ON} A = 1.056 \pm 0.013$ cGy h$^{-1}$ U$^{-1}$ (16). The exposure rate constant has been reported by the Health Physics Society in 2012 for cesium-131 as 0.679 R cm$^2$ mCi$^{-1}$ h$^{-1}$ and the half-value layer (HVL) as 0.0262 mm Pb (lead attenuation thickness) (24).

A standard value for air kerma strength provided by the manufacturer of $S_K = 3.50$ U per seed on the implant date was ordered for all patients. With this seed strength and given tile design, it was possible to achieve the desired dosimetry in most resection cavities. GammaTile’s manufacturer provides the user with a dose atlas, containing planar dose diagrams for several case scenarios of tile configurations and doses delivered at a depth. The atlas presents doses for 1 to 10 tiles distributed in several two-dimensional configurations, including gaps between tiles and asymmetric shapes. While in theory it would be possible to tailor the seed strength to each treatment area to obtain a tailored dose, a much more complex implant procedure and postimplant treatment plan would be necessary.

**Protocol development**

The protocol to implement a new brachytherapy delivery method was written by the medical physicist, in collaboration with the radiation safety officer, and contained an overview of the procedure and a brief review of the current literature. Center-specific details included: a list of radiation oncologists and neurosurgeons involved, training requirements, procedure to estimate the number of tiles, and written directive specifications. Furthermore, the protocol specified the radiation safety aspects and as low as reasonably achievable (ALARA) principles used during the procedure to ensure the safety of medical staff and members of the general public. It also included a general description of how the postimplant plan is performed and confirmed that the management of the implanted patient was done in compliance with local and national guidelines.

**TPS commissioning**

Brachytherapy parameters for the IsoRay CS-1 Rev2 $^{131}\text{Cs}$ seeds were configured within the BrachyVision
Brachytherapy Planning Version 11.0.47 (Varian Medical Systems, Palo Alto, CA) TPS. Data entered in the TPS included isotope name, manufacturer, half-life, type of source (line), calculation model (linear source), consensus dose rate constant $\text{CON}A$, kerma to activity conversion factor, consensus source active size $\text{CON}L$, consensus anisotropy function $\text{CON}F(r, \phi)$, and consensus radial dose function $\text{CON}R(r)$. These consensus values for the IsoRay CS-1 Rev2 seeds were extracted directly from the AAPM TG-43U1S2 report (16). Once entered in BrachyVision, the data was used by the TPS to calculate dose rate to water using TG-43U1 linear calculation model formalism (25). Doses from BrachyVision were obtained and compared to independently calculated doses using TG-43U1 formalism, according to the TPS manufacturer and AAPM recommendations (26). TPS doses were obtained using the smallest dose matrix resolution in BrachyVision of 0.05 cm (0.5 mm). Dose rates (cGy h$^{-1}$ U$^{-1}$) per unit source strength for the IsoRay CS-1 Rev2 $^{131}$Cs obtained from BrachyVision TPS were compared to the published dose rates in Table XII in the Erratum to the AAPM/GEC-ESTRO TG-43U1S2 report (23), in accordance with quality assurance recommendations by AAPM TG-56 guidelines (11). Additionally, doses for the entire decay of both a single $^{131}$Cs seed and also for a single GammaTile implant were obtained using the TPS and compared with calculated doses to water using an in-house spreadsheet. The in-house calculation used the TG-43U1 line source equation and TG-43U1S2 parameters for dose rate integrated over the entire decay of $^{131}$Cs for permanent implants. The decayed source strength calculated by the TPS was also verified using an independent hand calculation. Initial investigation of using BrachyCheck (Oncology Data Systems, Inc., Oklahoma City, OK) has been done in our clinic to perform secondary checks. The same consensus brachytherapy parameters for CS-1 Rev2 seed were entered into the BrachyCheck software, and the plan DICOM files containing the seed coordinates were exported from BrachyVision. Point doses were calculated and compared.

**Seed calibration and dosimetric uncertainty analysis**

A single (nonsterile) calibrated seed was ordered with every batch of tiles for strength verification. The measured seed strength at the time of calibration was forward decayed to the time of implant. It was expected that the mean value of the patient specific $S_k$ obtained by the physicist using an ADCL-calibrated well chamber (HDR 1000 Plus, Standard Imaging, Middleton, WI) agreed with the source strength provided by the vendor within tolerance, that is, 3% (27). Dosimetric uncertainties were evaluated, including uncertainties in the brachytherapy dosimetry parameters, air kerma strength at the time of implant, and TPS interpolation uncertainties. Uncertainties in the dosimetry parameters were used to calculate the total uncertainty in the calculated dose and accounted for uncertainties in the $S_k$, $\text{CON}A$, $\text{CON}L$, $\text{CON}F(r, \phi)$, and $\text{CON}R(r)$ parameters. Uncertainties in the consensus brachytherapy parameters originated from Monte Carlo (MC) simulations’ uncertainties and measurements using thermoluminescent dosimeters (TLD) (16,25).

An uncertainty analysis was performed to account for dosimetric uncertainties of the brachytherapy source calibration and dosimetry, following the recommended guidelines in the AAPM Task Group No. 138 (28). An expanded uncertainty was calculated to estimate the propagation of uncertainties in the dose calculations. Dosimetric uncertainties caused by potential changes in the cavity anatomy during treatment delivery were not included in the analysis.

**Estimating the number of tiles**

Target volumes frequently change in the 2–3 week period between the preoperative magnetic resonance imaging (MRI) evaluation and the GammaTile placement. These changes can result from several factors, including preoperative tumor growth or target enlargement, and relief of mass effect intraoperatively or target shrinkage. The relief of mass effect intraoperatively might cause cavity dynamics, that is, change in the resection cavity shape after tumor resection in which the cavity may become smaller. Because of the inherent tumor variability and the cavity dynamics, a pretreatment plan may not be useful.

Currently, there is no nomogram or lookup table available to correlate the planned resection area with the number of GammaTile units needed for the procedure. Therefore, the number of tiles was estimated based on the preoperative T1 MRI with gadolinium. A preoperative gross tumor volume (GTV) was drawn by the radiation oncologist. Guided by this volume and clinical experience, the expected resection cavity area in cm$^2$ containing the brain parenchyma at high risk of disease recurrence was then estimated. The area calculation did not account for the skull side surface that will not be treated. The number of tiles required to line the surgical bed was calculated by dividing the treatment area by the area of each GammaTile surface (4 cm$^2$). This estimate was done by the neurosurgeon, radiation oncologist, and medical physicist. Once the team agreed on the number of tiles for a given patient, the physicist ordered the tiles with sufficient lead time to ensure that their arrival occurred on the day prior to surgery, typically at least five business days in advance. Seeds were manufactured to have 3.5 U per source (14 U per tile) at the prespecified date and time.

**Implant day procedures**

The patient’s preparation for surgery, anesthesia, and craniotomy took approximately 3–5 h. After a maximum safe resection of the tumor (29), an intraoperative MRI was performed for verification, which helped determine whether additional resection was warranted (30). Once the neurosurgeon was ready for the implant, the medical
physicist brought a cart to the operating room containing the survey meter, tiles, trays, the patient chart with a signed written directive, and the room survey form. Once the resection cavity was ready to be implanted, the medical physicist retrieved the radioactive package from the metal tray and peeled the outer layer of sterile packaging. The expiration date of each GammaTile package was the scheduled implant date.

Tiles were placed on portions of the surgical bed judged by the neurosurgeon and radiation oncologist to be most at risk for recurrence. In infiltrating lesions, such as gliomas and metastases, the tissue most at risk for recurrence is typically the brain parenchyma. In meningiomas, sites of suspected brain invasion and residual dural or sinus involvement were also treated (31,32). The written directive was signed before administration and accounted for all ordered tiles. However, the actual number of tiles implanted were not known at that time. Therefore, the postimplant part of the prescription described how many tiles were actually implanted. The date, time, and number of tiles were reviewed and signed by both radiation oncologist and medical physicist.

Postimplant treatment planning

To our knowledge, there is currently no consensus on target definition for brain brachytherapy. According to the ICRU report 71 (33), the GTV cannot be defined if the tumor was removed by surgery. Therefore, the following convention was adopted: the resection cavity (also called surgical bed) was determined by the surface/edge of the postoperative implanted bed. The residual GTV (GTVr) included residual (post-op) enhancement on the T1 MRI with gadolinium, thus defining any gross disease that was not resected during the procedure. The residual gross tumor volume was tracked to assess the correlation between GTVr doses and outcomes in future studies. Finally, the high-risk clinical treatment volume (HR-CTV), which contains regions of the resection cavity abutting uninvolved brain parenchyma, was defined as a 5 mm expansion of the resection cavity wall plus the GTVr. In our practice, 60 Gy was prescribed to HR-CTV for all patients treated. This is currently considered to be a safe and adequate clinical dose (34). The coverage was evaluated by calculating the $D_{90}$ and $V_{100}$ for HR-CTV, GTVr, and the resection cavity.

Patient intake and release instructions

During the initial patient consultation, the radiation oncologist discussed the medical aspects of the procedure with the patient. Following the consultation, the medical physicist met with the patient to discuss radiation safety concerns and recommendations for the first few weeks after implant. These recommendations were discussed again with the patient and family members at the time of signing the release consent. In our center, a medical physicist was assigned this duty. However, this task could be performed by health physics staff, radiation oncologist, or anyone knowledgeable and trained for this task. A form containing release instructions was signed by the staff responsible for the release consent and by the patient or family member. A hardcopy was provided to the patient, and the original document was kept in the patient’s medical record.

Patient release instructions were based on exposure rates after the implant and the decay rate of $^{131}$Cs radionuclide (35,36). They included avoiding public transportation and public areas for 2 weeks, maintaining separate sleeping arrangements for 2 weeks, avoiding contact with pregnant women and children under 18 years old for 3 weeks, and carrying a card confirming the implant of a radioactive medical device for 3 months. The card was provided in case the patient’s radioactive levels were detected and the patient was questioned by public safety authorities. The card contained information about the radionuclide implanted, the total source strength contained on the day of the implant, and a number to reach the on-call radiation oncologist who could confirm the radionuclide implanted. Finally, implanted radioactive seeds should not be exposed to extreme environmental conditions. To avoid unwanted release of radioactivity into the environment, instructions regarding cremation were included in the patient consent for treatment.

Absorbed doses determined using body and ring badges

To estimate the doses received by the staff, for the first two patients treated in our hospital, each nurse used a single body badge to care for one implanted patient over several hours per day and several days before the patient’s discharge. Therefore, the body badge readings collected the dose received per nurse caring for one single GammaTile implanted patient for the entire hospital stay. Per our radiation safety guidelines, declared pregnant nurses were not involved in the care of GammaTile patients. Ring badges were worn by the neurosurgeon, medical physicist, and radiation oncologist for all GammaTile procedures. To estimate doses received by medical staff extremities per GammaTile patient, the dose readings were recorded over the first two GammaTile implants and averaged. Ring badges did not include accruing exposure from other procedures. Badges were gas sterilized between implants, as implants did not happen on the same day.

Exposure rate measurement for implanted patients

Exposure rate limits for patient release were calculated based on the NUREG 1556, Vol. 9, Rev.2, Equation U-2 (37), using the exposure rate constant and half-life aforementioned for $^{131}$Cs. The release requirement by the U.S. Nuclear Regulatory Commission (NRC) § 35.75 (Release of individuals containing unsealed byproduct material or
implants containing byproduct material) is that the effective dose equivalent from exposure to the released patient to any other individual is not likely to exceed 5 mSv (500 mrem). Equation U-2 was solved initially for source strength \( Q \), using the recommended 5 mSv as the integral dose limit \( D \) at 1 m and recommended occupancy factor of 0.25. The exposure rate limit at 1 m was calculated by multiplying the calculated source strength by the \(^{131}\text{Cs} \) exposure rate constant and divided by the distance squared. The exposure rates immediately after implant and surgical closure at 1 m from ipsilateral and contralateral sides of the patient’s resection cavity were measured using a calibrated Inovision 451B (Fluke Biomedical, Everett, WA) ionization chamber survey meter.

**Results**

An overview of the GammaTile commissioning and implant procedures is summarized in Fig. 2. The results of dose calculations are presented, followed by the planning considerations and radiation safety aspects and findings.

**Dose calculation**

The average percent difference between the TPS dose rates and the data published in table XII in the Erratum to the AAPM/GEC-ESTRO TG-43U1S2 report was within 0.3%. There was a difference in coordinate systems used in TG-43 (polar coordinates) and BrachyVision (Cartesian coordinates), and this can cause rounding errors that may increase the dose differences at points close to the source at angles other than 0° and 90°, unless values are interpolated. BrachyVision uses a maximum of two decimal places for the units used for resolution in distance (cm); therefore, \( p (0.0866 \text{ cm}, 0 \text{ cm}, 0.05 \text{ cm}) \) becomes \( p (0.09 \text{ cm}, 0 \text{ cm}, 0.05 \text{ cm}) \) corresponding to the point \( p \) at \( r = 0.1 \text{ cm} \) and \( \theta = 60° \) in polar coordinates. For example, dose rate per unit of air kerma strength calculated in BrachyVision at \( p (0.08 \text{ cm}, 0 \text{ cm}, 0.05 \text{ cm}) \) was 75.315 cGy h\(^{-1}\) U\(^{-1}\) and at \( p (0.09 \text{ cm}, 0 \text{ cm}, 0.05 \text{ cm}) \) was 64.400 cGy h\(^{-1}\) U\(^{-1}\), which are +10.9% and −5.15%, respectively, from the reported value of 67.9 cGy h\(^{-1}\) U\(^{-1}\) in the Erratum to the TG-43U1S2 (23). Interpolation of these two values resulted in 68.111 cGy h\(^{-1}\) U\(^{-1}\) per unit of air kerma strength or 0.3% from Erratum to the TG-43U1S2. Therefore, for points where spatial resolution was an issue, values were further interpolated for comparison.

Dose comparison between the BrachyVision TPS and the in-house calculated doses was within 0.15% for a single permanent tile (14 U). Source strengths decayed by the TPS presented no differences when compared with independent calculations. Fig. 3 shows a rendering of one GammaTile (or 4 \(^{131}\text{Cs} \) seeds) in BrachyVision and doses obtained from the TPS on both surfaces of the tile for a permanent implant containing a total of 14.0 U. Fig. 4 shows the isodose lines for a single \(^{131}\text{Cs} \) seed (3.5 U) and a single GammaTile (14.0 U), respectively. For secondary checks for patient plans containing several seeds and points BrachyCheck

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**Fig. 2.** An estimated time frame and workflow of the GammaTile implementation and procedure. On the top, from left to right is the timeline of the events, including commissioning of the program, and pre-, post-, and during implant tasks. Next, the personnel involved in each task are listed and a line links them to the tasks performed. For tasks involving more than one specialty, the personnel involved are listed side by side. The personnel involvement with any particular task, however, may not be universal, and this does not imply equal time commitment of individuals to a particular task.
showed an agreement within 1% of BrachyVision doses. A secondary plan check by means of an in-house spreadsheet based on the TG-43U1S2 formalism is possible. However, due to the number of seeds and points, this might be an impractical task.

Seed calibration and dosimetric uncertainty analysis

The average source strength received for all patients treated (n = 23) to date measured to be 3.50 ± 0.03 U, with values ranging from 3.44 U to 3.56 U. The air kerma strengths for all calibration seeds were measured with an ADCL-calibrated well chamber. All cases were within the 3% tolerance. The strength received for each case was used in the postimplant planning. The exact implant time varied from the planned implant time, causing the actual seed strength to differ slightly from the reported strength. For instance, a variation of ±3 h on implant time would result in ±0.9% source strength variation. However, a 24 h variation on the implant time can cause approximately 6.9% source strength variation.

Table 1 presents the dosimetric uncertainty components and their estimated relative propagated uncertainty. Estimated uncertainty in the clinical measurement of $S_K$ was 1.3% (28), and the estimated uncertainty in $S_K$ at the time of the implant was at 0.9%. Uncertainties in the dose calculation included the combined uncertainty for $CON_1$ (1.2%) (23), $CON_g(r)$ (2.2%), and $CON_F(r,\theta)$ (2.6%) parameters (25). The calibration uncertainty for the ADCL-calibrated well chamber was stated as 2.4% at 95% confidence level ($k = 2$). The estimated TPS interpolation uncertainties for low-dose, low-energy sources were also included (28). The expanded uncertainty in the determination of dose to water was estimated at 6.0% ($k = 2$).
Implant considerations

The estimated time that the physicist held and peeled the sterile packaging was 40 s per package. Using sterile long tweezers, the scrubbed radiation oncologist lifted the plastic insert with tiles and placed them on a sterile stainless-steel shielded tray. The radiation oncologist readied the tiles by irrigating them with sterile water. The estimated time for the radiation oncologist to place the tiles in a sterile tray and irrigate them was approximately 1–2 min. The neurosurgeon then placed the tiles onto the surface of the resection cavity and reviewed placement of tiles with the radiation oncologist. The time needed to implant all the tiles by the neurosurgeon ranged from 3 to 6 min. DuraGen collagen pieces were also available for spacing the tiles, if needed.

Fig. 5 shows a photo of a resection cavity implanted with 11 tiles (44 seeds). In this case, no tiles were positioned on the exterior bone flap prior to surgical closure. Several tiles were cut into two pieces, using sterile scissors by the neurosurgeon to conform to the resection cavity. When hydrated, the implanted collagen tile acts as a tissue compensator and helps maintain intersource spacing after closure. The exact distributions, however, are dependent on the number and geometry of tile placement and unique intraoperative clinical circumstances encountered. A video component of a GammaTile implant is available and accompanies the online version of this publication. To access the video component, click on Video 1 (online version only).

Planning considerations

Fig. 6 shows the postimplant scans and isodose lines for the implant shown in Fig. 5. Postimplant computed tomography (CT) and MRI scans were acquired within 24–48 h after implant and imported into BrachyVision, as shown in Figs. 6a and 6b. Postimplant MRI T1 sequence with gadolinium was used for target delineation. However, the true edge of the resection cavity was not clearly distinguished from the surface of the tile on the MRI image. Therefore, in regions close to the tiles, the seeds were used as a surrogate to help identify the resection cavity edge, assumed to be located approximately 3 mm from the center of the seeds. The seeds were not well defined in the MRI images; therefore, the postimplant CT scan was used for the seed delineation. It is important to note that 1 mm scan slices were acquired for both CT and MR imaging. CT and MRI are coregistered as shown in Fig. 6c. The 1 mm slice thickness of the CT scan provided good resolution for tracking each seed position and orientation during the postimplant planning process. Once all seeds were defined, the isodose lines were obtained from the TPS, as shown in Fig. 6d.

It was particularly challenging to account for the seed orientation. Therefore, we developed a simple method for tracking seed orientation. We first selected the IsoRay CS-1 Rev2 131Cs line source seed commissioned in BrachyVision. Then the window/level was adjusted on the CT scan to maximize the contrast between seeds and brain tissue, while minimizing any visible CT artifacts. Starting from the superior (cranial) aspect of the skull, the first seed was visualized by scrolling inferiorly through each axial slice of the CT scan. The crosshair was placed on top of the first seed in a way that the seed was seen in the axial, coronal, and sagittal views simultaneously. The plane providing the best visualization of the longest aspect of the seed was selected. The cursor was dragged along the seed’s axis to digitize it (Fig. 7). The digitized seed orientation was adjusted if needed to better represent the actual implanted seed. The same process was repeated for each seed, until all seeds were accounted for. Table 2 summarizes this process. Seeds in a given GammaTile generally presented similar orientations in the CT scan image, but there were tile-to-tile orientation differences.

After a plan was completed, a physics plan check was done by a second medical physicist. The second check included making sure the seed calibration was within tolerance, accuracy of registered images, number of tiles/seeds and strength implanted, and plan review. After completion of implant, plan documentation was imported into the record and verify system and an end-of-treatment chart check was performed. Checks included plan and patient release.

<table>
<thead>
<tr>
<th>Uncertainty component</th>
<th>Relative propagated uncertainty (%)</th>
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<tbody>
<tr>
<td>SK measurements</td>
<td>1.3%</td>
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<tr>
<td>SK uncertainties at the time of implant</td>
<td>0.9%</td>
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<tr>
<td>Dose calculation uncertainties</td>
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<tr>
<td>ADCL calibration uncertainties</td>
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<tr>
<td>TPS interpolation uncertainties</td>
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<tr>
<td>Expanded uncertainty (k = 2)</td>
<td>6.0%</td>
</tr>
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Table 1 Uncertainty analysis in dose for CS-1 Rev2 131Cs source at 1 cm on the transverse plane associated with air-kerma-strength measurements at the clinic, ADCL-calibration uncertainties, and TPS interpolation uncertainties.
documentation, patient and room survey documentation, treatment recorded on the record and verify system, and billing. Table 3 presents a summary of the second checks and chart checks performed for each patient.

**Radiation safety considerations**

The calculated source strength using the NUREG-1556 Equation U-2 was 88 mCi. This value was used to calculate...
the exposure rate limit in Roentgen per hour at 1 m by multiplying the source strength in U (converted to mCi) times the exposure rate constant (0.679 R cm² mCi⁻¹h⁻¹) and dividing by the distance squared (100 cm)². The exposure rate limit at 1 m was calculated to be 6 mR h⁻¹. For all patients, the exposure rates at 1 m from patient’s skin surface near the resection cavity were within tolerance (< 6 mR h⁻¹) for patient release. The maximum reading after closure at 1 m was 3.2 mR h⁻¹ from ipsilateral implant side on the day of implant. Measurements for one patient at 1 cm from the skin surface were between 95 and 100 mR h⁻¹ after 12 h of implant. The brain and skull attenuate considerably the exposure rate outside of the patient. A fourfold decrease in exposure rate at 1 m from the implant was observed after surgical closure. At distances less than 1 m, the exposure rates can be considerably high, for example, 100 mR h⁻¹ at 1 cm from the surface.

Exposure rates were measured in the operating room at the surface of the closed shielded stainless-steel tray containing six tiles (total strength of 84 U). These values ranged from 0.50 to 0.90 mR h⁻¹, depending on the angle from the tray. Readings from the top of the tray were lower than side readings due to gaps between the top and bottom sliding pieces of the tray. At 1 m from the closed tray, the reading was 0.02 mR h⁻¹. With the open tray, the exposure rate measured at the package surface for the aforementioned six tiles ranged from 900 to 1200 mR h⁻¹.

Ring badge readings per procedure (based on two implants) were 0.39, 0.29, and 0.18 mSv for the neurosurgeon, medical physicist, and radiation oncologist, respectively. The first and second procedures for these measurements consisted of handling and implanting 6 (84 U) and 9 (126 U) tiles, respectively. Whole-body badge readings for nurses caring for a single GammaTile patient during the entire hospital stay ranged from 0.01 to 0.05 mSv for deep, eye, and shallow readings, with corresponding average values of 0.027, 0.028, and 0.028 mSv.

**Discussion**

As the first center to implement the GammaTile brain implants, outside of clinical trials and after FDA clearance in the United States, this manuscript was written with the intent of aiding the clinicians in implementing this technique. This work reflects our experience and includes answers to frequently asked questions we received from other institutions starting their own GammaTile programs.

GammaTile can be implanted directly after tumor resection, immediately delivering radiation therapy. Increasing the duration gap between resection and radiation therapy can significantly decrease the recurrence-free survival (RFS) (3). Therefore, being able to start radiation therapy at the time of tumor resection can potentially improve patient’s RFS. In addition, due to the 3 mm separation of

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Table 2

<table>
<thead>
<tr>
<th>Step</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Insert a new virtual radionuclide seed collection (already commissioned in the TPS).</td>
</tr>
<tr>
<td>2.</td>
<td>Adjust the window/level of the CT scan images to increase the contrast between seeds and brain as much as possible.</td>
</tr>
<tr>
<td>3.</td>
<td>Starting from the superior (cranial) aspect of the skull, scroll inferiorly through each axial slice of the CT scan until the first seed can be visualized.</td>
</tr>
<tr>
<td>4.</td>
<td>Place the crosshair on top of the first seed in a way that the same seed can be seen in all three aspects, axial, coronal, and sagittal.</td>
</tr>
<tr>
<td>5.</td>
<td>Choose which one of the three views allows for the best visualization of the longest aspect of the seed.</td>
</tr>
<tr>
<td>6.</td>
<td>Drag the cursor along the axis of the seed in the chosen image view (axial, coronal, or sagittal) to digitize that seed. Adjust the seed orientation if needed.</td>
</tr>
<tr>
<td>7.</td>
<td>Repeat steps 3–6 for all seeds in that axial slice, then repeat for subsequent inferior slices until all seeds are accounted for.</td>
</tr>
</tbody>
</table>
the seeds from brain tissue and radionuclide as well as the low dose rate delivered by $^{131}\text{Cs}$, this treatment potentially presents a lower risk of radiation injury (6). Radionecrosis has been a major concern in the past, especially for patients who have undergone multiple treatments for recurrent brain tumors (34). The manufacturer recommends a prescription dose ranging from 60 to 80 GY to the target volume. In our practice, a 60 Gy prescription was used with seeds having the same strength for all cases (3.5 U per seed).

The collagen structures hold their shape and position after implant, but are eventually absorbed by the brain tissue, usually within 3–4 months after implant (39). The tiles therefore hold their shape and position within the brain while radiation is being delivered, since 88.3% of the dose from $^{131}\text{Cs}$ is delivered within the first month. However, after the collagen tiles are absorbed, it is possible that loose $^{131}\text{Cs}$ seeds can migrate to the spinal canal (40). Three months after the implant, the strength of a single 3.5 U seed is reduced to 0.0056 U, delivering a dose rate estimated as $0.3186 \text{ cGy h}^{-1}$ at 0.1 cm and $0.0059 \text{ cGy h}^{-1}$ at 1 cm on the transverse plane. These dose rates integrated over the entire life of the radionuclide would result in a dose of approximately $106.8 \text{ cGy at 0.1 cm and 2.0 \text{ cGy at 1 cm}}$ on the transverse plane.

Wernicke et al. assessed the resection cavity dynamics and decrease in brain edema subsequent to $^{131}\text{Cs}$ brain implants visible on MRI fluid-attenuated inversion recovery (FLAIR) images (6). In the aforementioned study, the cavity shrinkage was significantly less for $^{131}\text{Cs}$ implants than that observed for stereotactic radiosurgery (SRS) patients during the first critical month in which 88% of the dose is delivered for $^{131}\text{Cs}$. Han et al. modeled the effects of resection cavity contraction for $^{125}\text{I}$ and $^{131}\text{Cs}$ brain implants on the cumulative doses delivered and concluded that cavity contractions affect $^{131}\text{Cs}$ dose distributions significantly less than that of $^{125}\text{I}$ (41). The relatively short half-life of $^{131}\text{Cs}$ (9.7 days) results in a higher biological effective dose (assuming the same physical dose value is used for prescription) compared to other commonly used low-dose-rate (LDR) isotopes, such as $^{125}\text{I}$ (59.4 day half-life) as previously reported in the literature (42). Further investigation is needed to establish the radiobiological differences between $^{131}\text{Cs}$ permanent implants and EBRT delivered 4–6 weeks after surgery.

Further studies are necessary to determine the optimal timing for postoperative MRI and CT scans for implanted GammaTile patients as the implant localization may vary with changes in resection cavity, which can subsequently affect the accuracy of the dose distribution delivered to the target. Although these titanium-encapsulated seed implants are safe to be used with MRI imaging (43), they may be difficult to visualize due to imaging artifacts caused by the seeds, depending on the image sequence used (44). Furthermore, axial scanning in the T1 MRI sequence may present artifacts resulting from commonality with the $B_0$ field, therefore sagittal scanning with multiplanar reconstruction into axial slices may be preferable. To improve CT seed localization, high-resolution CT scans with slice thicknesses of 1 mm or finer can be used.

The GammaTile IFU recommends placing the textured side of the collagen against the tissue in the resected cavity to offset the seeds from the surface of the brain. The thicker radial separation between the seeds and the brain tissue provided by the textured side of the tiles is likely to deliver a more homogeneous dose. The textured, or “bumpy,” side of the tile also serves as a visual indicator of the orientation of the implant. A picture can be taken to document the implant orientation if the implanted tiles are visible. However, for deep-seated brain lesions, taking a picture may not be trivial. As a way to keep track of the tile orientations, some clinicians put an additional mark on the smooth surface of the tiles intraoperatively as seen in the video supplemental information, published by Brachman et al. (31). Our preferred method to record the GammaTile orientation is to have the scrubbed radiation oncologist visually confirm that the textured side is placed toward the brain (“bumps to brain”), and we include this information as part of our documented standard operating procedures.

Cavity dynamics after tumor resection can be somewhat unpredictable, that is, a tumor cavity may collapse due to brain pressure for deeply ingrained tumors, and therefore, the cavity may become smaller than anticipated. Another unpredictable situation can occur when a larger volume is found for resection on the MRI done on the day of the surgery. In either case, the exact number of tiles may be

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**Table 3**

**Physics plan check and end-of-treatment chart check**

1. Plan check (performed by a medical physicist not involved in the implant procedure)

<p>| | |</p>
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>a.</td>
<td>Confirm seed calibration documentation within tolerance of 3%.</td>
</tr>
<tr>
<td>b.</td>
<td>Confirm CT and MRI images registration accuracy.</td>
</tr>
<tr>
<td>c.</td>
<td>Confirm the number of tiles used in the plan and accuracy with the written directive information.</td>
</tr>
<tr>
<td>d.</td>
<td>Confirm the number of seeds and source strength at the date of implant.</td>
</tr>
<tr>
<td>e.</td>
<td>Confirm the dose volume histograms and target volume coverages.</td>
</tr>
</tbody>
</table>

2. End-of-treatment chart check  
(performed by second medical physicist after treatment was completed and plan documentation was imported into the record and verify system)

<p>| | |</p>
<table>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>a.</td>
<td>Confirm proper documentation of the plan and the patient release consent.</td>
</tr>
<tr>
<td>b.</td>
<td>Confirm proper documentation of the patient and room radiation surveys.</td>
</tr>
<tr>
<td>c.</td>
<td>Confirm manual treatment properly recorded in the record and verify system.</td>
</tr>
<tr>
<td>d.</td>
<td>Confirm accurate billing codes captured.</td>
</tr>
</tbody>
</table>
unknown until the time of implant. Therefore, the best estimate is used for ordering tiles based on the preoperative MRI done not earlier than 3 weeks before the implant. In situations where the cavity is bigger than initially planned and the number of tiles cannot fully cover the cavity, tiles should be placed to provide the best dosimetric coverage to the target using the available tiles. This can be done by distributing the source strength among the periphery of the implant and the implanted area itself considering the size of the implant. In addition to spacing the tiles, the tiles can be purposely flipped to have the smooth side toward the brain to increase penetration of the dose and therefore improve dosimetric coverage to the treated volume.

In infiltrating lesions, such as gliomas and metastases, rates of recurrence are very low at the skull (31,32); therefore, no tiles are used on the skull side of the cavity. Furthermore, due to the low energy of $^{131}$Cs photons and high Z presented by the bone, a higher dose deposition is expected to occur at the skull when compared to dose to water (45). AAPM TG-186 report discusses dosimetric impacts when heterogeneity effects are taken into consideration by model-based dose calculation algorithms (MBDCAs) (46). Dose deposited may be substantial for tissues other than water due to the differences in mass-energy absorption coefficients, specially for low-energy (LE) radionuclides, that is, for energies below 50 keV.

The Cesium Advisory Group (CAG) has published recommendations for prostate seed implants using $^{131}$Cs (47), which agree with our release criterion of exposure rates below 6 mR h$^{-1}$ at 1 m. According to the U.S. Nuclear Regulatory Commission Regulation NUREG-1556 appendix N, in case of either cremation, or autopsy, or medical donation of a body with detectable radioactive materials, it is required that the authorized user (AU) and the radiation safety officer (RSO) be notified of the death of an implanted radiation therapy patient. At that time, there should be a consult and direct permission from RSO for autopsy. The RSO will make the pathologist aware that seeds might have migrated to a different location and the pathologist should consult the RSO about the possibility of slicing through a seed. According to the NRC code of regulations CFR 10 §39.35 Leak testing of sealed sources, levels above 185 Bq (5 nCi) are considered a radioactive contamination. After 25 half-lives, an average implant containing six tiles (84 U, or 132 mCi) will be reduced to levels below 185 Bq. While this situation would be ideal, it may not always be practical. Current recommendations for the seeds to decay for 10 half-lives (97 days, or approximately 3 months) may be more practical and still provide radiation levels low enough to pose acceptable risks to nonradiation workers and the general public.

Conclusion

Commissioning and clinical implementation of a new procedure can be complex and may require collaboration from multiple specialties. A roadmap for implementing the GammaTile program was presented in this work with the purpose of aiding the commissioning of this technique in other centers. This work was based on our experience implementing GammaTile and treating 23 patients to date in our clinic. The items discussed in this manuscript included: the physical properties of the collagen tiles as well as CS-1 Rev2 $^{131}$Cs seeds; protocol development; TPS commissioning and dose calculations; description of the process of estimating the number of tiles; timelines for the estimated duration of each aspect of the program as well as responsibilities of radiation oncologists and medical physicists; and radiation safety and management of implanted patients in compliance with NRC guidelines.

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Supplementary data

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References
