


Clinical Positioning Accuracy for Multisession Stereotactic Radiotherapy With the Gamma Knife Perfexion

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Abstract

Multisession stereotactic radiation therapy is increasingly being seen as a preferred option for intracranial diseases in close proximity to critical structures and for larger target volumes. The objective of this study is to investigate the reproducibility of the Extend system from Elekta. A retrospective review was conducted for all patients treated with multisession Gamma Knife between July 2010 and June 2015, including both malignant and benign lesions. Eighty-four patients were treated in this 5-year span. The average residual daily setup uncertainty was 0.48 (0.19) mm. We compare measurements of setup uncertainty from the Extend system to measurements performed with a linac-based approach previously used in our center. The Extend system has significantly reduced setup uncertainty for fractionated intracranial treatments at our institution. Positive results were observed in a small population of edentulous patients. The Extend system compares favorably with other approaches to delivering intracranial stereotactic radiotherapy and is a robust, simple-to-use, and precise method for treating multisession intracranial lesions.

Keywords

Gamma Knife Perfexion, Extend, SRS, SRT

Abbreviations

CT, computed tomography, Gy, gray; IMRT, intensity-modulated radiation therapy; MRI, magnetic resonance imaging; OGP, Optical Guidance Platform; RCT, reposition check tool; SRS, stereotactic radiosurgery; SRT, stereotactic radiotherapy.

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Introduction

Single-fraction stereotactic radiosurgery (SRS) for intracranial lesions is a well-established technique that has been implemented in a variety of ways using different radiation sources and geometries. Many stereotactic localization methods have also been applied, in some cases intimately associated with a particular radiation source. Decades of experience have served to establish certain constraints on normal tissue doses for single-fraction delivery. These constraints can limit the patients and types of disease that are eligible for radiosurgery. In the last decade or so, explorations in the use of hypofractionated external beam regimens have led to a better understanding of the benefits and pitfalls of using highly localized dose distributions and shortened fractionation.

The convergence of these 2 trends has led to increased interest in multifraction stereotactic radiotherapy (SRT) for certain diseases depending on the locations of the target volume. In particular, when the target is larger than that normally treated with SRS or in close proximity to critical

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structures, SRT is increasingly seen as the preferred option.¹ However, this is not simple to accomplish since the very steep dose gradients in this technique require accurate (and in the case of SRT, precise) positioning of the patient in the radiation field. In other words, how does one make use of improved dose localization when the position of the target is subject to uncertainty?

This article describes 1 solution to that problem that has been developed by Elekta (Elekta AB, Stockholm, Sweden) for use with the Gamma Knife, known as the *Extend System for Leksell Gamma Knife Perfexion*. We describe our experience using this system at the University of Washington Medical Center's Gamma Knife at Harborview Medical Center. This covers our measurements of the reproducibility of the system and comparisons with other approaches to delivering SRT. Although previous reports of setup uncertainty with the Extend system²⁻⁴ have included a small number (10-12) of patients, we seek to expand this published experience with a substantially larger cohort. In addition, we describe a method by which we have been able to treat a small cohort of edentulous patients.

Materials and Methods

Eighty-four patients were treated on an Elekta Perfexion Gamma Knife with the Extend system. The Perfexion consists of 192 cobalt-60 sources isocentrically mounted yielding a dose rate of at least 3.0 Gy/min at isocenter at acceptance testing, corresponding to approximately 5000 Ci of activity when first installed. The sources are arranged in 8 sectors; each sector is individually chosen to be open or blocked for each control point, and every source in each open sector is open to a collimator of 4, 8, or 16 mm diameter.

Extend Multisession Technique

The Elekta Extend patient positioning system has 3 basic components: (1) a patient-specific bite block held in place by a vacuum, (2) an external fiducial frame for imaging similar to the Gamma Knife frames for SRS, and (3) a skull-based measurement system to match daily setup to the benchmark treatment planning position.

Vacuum-Assisted Bite Block

At our institution, patients are sent to a dentist to fabricate a dental mold that resides on a patient unique mouth piece. The dental mold is fixed to the patient's hard palate, and therefore to the patient's skull, establishing a rigid coordinate system. At simulation, the patient is set up on the head plate of the Extend frame using a patient unique pillow (Civco AccuForm Cushion, Coralville, Iowa). The Extend frame is rigidly attached to the Gamma Knife patient positioning couch. The bite block is inserted into the patient's mouth, and a suction is applied with a vacuum pump that seals the mouthpiece to the hard palate. The pump meters the strength of the suction; if

suction is interrupted for any reason, an interlock is enabled and the treatment is automatically paused until suction can be reestablished.

Fiducial Frame

A key element in the Elekta system is a reference frame that is visible on the treatment planning images (computed tomography [CT] or magnetic resonance [MR]) that is rigidly attached to the skull. In SRS, this is accomplished by means of a neurosurgical stereotactic frame fixed to the skull by means of sharp pins that penetrate the outer table of the skull. In the Extend system, the bite block provides the registration between skull and external frame, and for imaging, a box is attached to the bite block system which is characterized by the canonical "N-shaped" fiducial markers. The key difference is that the bite block and attendant plastic attachment do not guarantee the same rigidity as the SRS frame. In addition, the bite block is not guaranteed to be reapplied identically from fraction to fraction, which leads to the need for a daily skull-based measurement system.

Skull-Based Measurements

A patient positioning box—the reposition check tool (RCT)—has been designed to allow measurements of the position of the skull within the frame of reference of the patient positioning system. This 3D rectangular box is attached to the Extend frame. The distance between the patient's head and the RCT is measured by means of a mechanical indicator probe in the anterior, superior, right, and left directions, and the values are recorded as the benchmark of the patient's position. The patient is then removed from the system, the head frame is equipped with an adapter for a CT bed, and the vacuum pump, head frame, and RCT are transported to CT where the patient is repositioned on the CT table. A flat table top is ideal, although a standard CT curved table top may be used with a bolus of sheets to simulate the Leksell table. The patient is repositioned using the RCT.

Daily Repositioning

On each day of treatment, the bite block is inserted into the patient's mouth, and the patient is situated on the table in an initial position with the bite block locked to the Extend frame. The RCT is attached to the frame, and initial measurements with the probe are made of the patient's head with respect to the RCT and compared to the benchmark. Once the position is deemed satisfactory, the entire series of measurements collected during simulation are remeasured for that day's setup and captured electronically, and the repositioning vector is computed by the Elekta system. The overall positioning vector is not user configurable and is calculated as,

$$V = \sqrt{\left[\frac{\bar{X}_{\text{left}} - \bar{X}_{\text{right}}}{2}\right]^2 + \bar{Y}^2 + \bar{Z}^2} \quad (1)$$

Table 1. Patient Characteristics.^a

Characteristics	Observed Distribution	
Sex		
Male	34	40%
Female	50	60%
Age, median (years)	57	
<20	3	4%
20-39	15	18%
40-59	33	39%
60-79	30	35%
80+	3	4%
Diseases		
Meningioma	36	43%
Metastasis	21	25%
Pituitary adenoma	10	12%
Craniopharyngioma	8	10%
Schwannoma	2	2%
Recurrent head and neck	2	2%
Glomus	2	2%
Glioma	2	2%
Neurocytoma	1	1%

^aPercentages are rounded and may not total 100%.

where the bar denotes the average of the deviations between the measured value in simulation and the measured value at the time of treatment. Ideally, \bar{X}_{left} and \bar{X}_{right} both gauge the patient's side to side deviation. If the patient has moved to one side, then the \bar{X} term represents the average of the left and right side measurements; if the patient has gained or lost weight equally on both sides, then the \bar{X} average movement will be 0. The individual measurements that constitute the averages are taken along various positions in the superior–inferior direction along the skull and are used to establish and correct for the possibility of a head rotation. The RCT provides 12 possible measurement positions on the patient's anterior, superior, left, and right sides of the patient's skull. Our practice is to use 3 measurements per plane. Points are avoided which measure less stable anatomy such as the ear, or highly sloping regions of the forehead, or a wound that would change over the course of the treatment.

Patient Characteristics

A retrospective chart review was approved by the internal review board at the University of Washington, and all patients treated with SRT using the Extend system between July 2010 and June 2015 were identified. The demographic, clinicopathologic, treatment, and outcomes data from these patients were analyzed and reported in Table 1. Eighty-four patients were consecutively treated during this 5-year span; in comparison, 1040 patients were treated with the single-fraction frame system over this same time period at our institution.

Both malignant and benign lesions were included in our analysis. The vast majority of patients were treated to 20 to 24 Gy in 4 and 5 fractions, prescribed to the 45% to 60% isodose line. Treatment courses were completed within 5 to 9

calendar days. Patients were selected for multisession SRT over frame-based SRS either due to the proximity of nearby critical structures or due to the total volume of healthy brain tissue irradiated, as determined by a board-certified radiation oncologist.

After completion of SRT, all patients were assessed at follow-up visits with repeat history and physical examination, magnetic resonance imaging (MRI) brain studies, and laboratory tests as indicated. Patients typically returned for reevaluation every 3 to 12 months, with their follow-up regimen determined by physician discretion with consideration for patient tolerance to treatment, specific disease histology, overall disease burden, and patient convenience. All patients had at least 1 posttreatment MRI brain study performed, and all MRI studies were evaluated for treatment response by a board-certified neuroradiologist. Radiographic stability was assessed by the neuroradiologist using measurements of the treated lesion with comparisons with prior MRI examinations.

There were a small number of edentulous patients for whom a fractionated SRT approach was deemed best. In order to account for these, we developed a test–retest procedure to determine whether the Extend system was appropriate. Edentulous patients have generally been considered a relative contraindication for use with relocatable bite block systems. This patient population is included in the aggregate in Table 1. There were 4 patients, 57 to 74 years of age, treated in 4 or 5 fractions to 20 to 22 Gy. Three patients had pituitary adenoma (2 nonsecreting pituitary tumors and 1 prolactinoma) and 1 meningioma.

The CT simulation was performed with the normal Extend setup and imaging with the fiducial frame in place. The T1 spoiled gradient recalled acquisition in steady state brain MRIs as well as T2 sequences were coregistered to the standard planning CT acquired with 1.25 mm slices. Given the concern about the robustness of setup, patients underwent 2 treatment planning CT scans. After the first CT scan, the immobilization device was completely removed. For the second CT scan, the patient was placed back in treatment position with the immobilization device as we normally do for treatment. Both treatment planning CT scans were then imported into GammaPlan and separately defined using the attached fiducial frame. Alignment was manually verified by a board-certified radiation oncologist with bony landmarks to confirm positional reproducibility. In all 4 cases, the coordinates of the tumor were the same in both scans within the normal standards of contouring anatomy as determined by a board-certified radiation oncologist. With this process, the patients underwent 2 separate CT scans that resulted in identical treatment coordinates, which results in treating the same anatomy for both separate setups.

Results

Daily Setup Variation

Figure 1 is a histogram of the 352 daily setup vectors after repositioning calculated by Equation 1. The average and

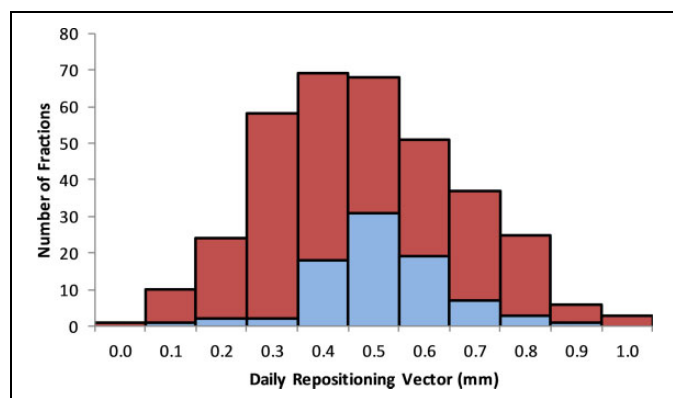


Figure 1. A histogram of daily setup vectors after repositioning for each patient (red) with a mean of 0.48 mm. The per patient means are overlaid in blue.

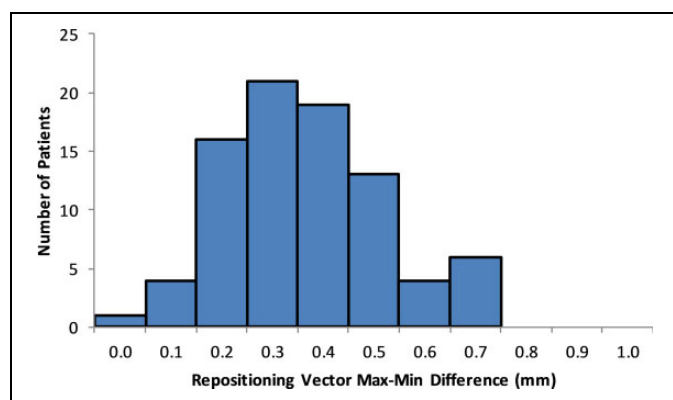


Figure 2. A histogram of max-min measurement spreads for each patient.

standard deviation of the measurements are 0.48 (0.19) mm. Extreme values were 1 measurement at 0.0 mm and 3 measurements at 1.0 mm. Sixty-five percent of the measurements were 0.6 mm or less. Eighty percent of the measurements were between 0.3 and 0.8 mm. Figure 2 is a histogram of the maximum-minimum measurements spreads over the course of treatment for each patient. One patient had the same setup vector daily, 50% of the patients varied by 0.3 mm or less over the course of treatment.

Figure 3 shows the treatment planning MRI study with isodoses overlaid (left) and a representative follow-up MRI brain study performed at 12 months (right) with original isodoses overlaid for an edentulous patient who was treated for prolactinoma. This patient had radiographic stability of her tumor on MRI brain performed at 1 month follow-up followed by consecutive reduction in the size of her tumor on MRI examinations at 9-, 12-, and 24-month follow-ups.

A nonsecreting pituitary patient demonstrated radiographic stability on follow-up MRI studies performed at 5, 19, and 37 months and remained asymptomatic from his nonsecreting pituitary tumor at his last follow-up visit at 56 months post-treatment. Another nonsecreting pituitary patient had stable findings on MRI brain studies performed at 3-, 8-, 15-, 21-,

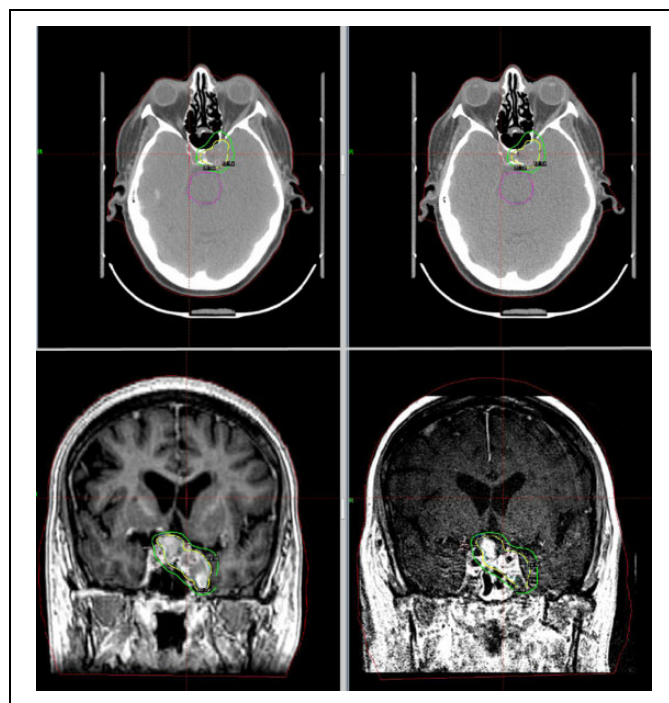


Figure 3. Test/retest (top) and treatment planning magnetic resonance imaging (MRI) study with isodoses overlaid (bottom left) for an edentulous patient treated for prolactinoma and a representative MRI study performed at 12-month follow-up with original isodoses overlaid (bottom right) for geometric reference.

36-, and 53-month follow-ups. The patient treated for meningioma demonstrated radiographic stability on follow-up MRI studies at 1, 10, 19, and 33 months. All 4 edentulous patients had stable visual fields on physical examination performed at their respective follow-up visits.

A subset analysis of the 18 initial setup vectors recorded for these 4 edentulous patients finds an average and standard deviation of 0.51 (0.21) mm. The range of setup vectors was 0.30 to 0.90 mm, with a per patient min-max variation of 0.20 to 0.60 mm. This small subset of measurements is comparable to those measured for the overall group of patients treated with the Extend system.

Radiocamera System for Linac

Our institution had previously implemented a linac-based radiocamera system for treating patients with steep dose gradients.⁵ The system was originally designed and manufactured by Sofamor Danek and was later acquired by Varian Medical Systems and known as the Optical Guidance Platform (OGP). This system was comprised of a Polaris infrared camera system fixed to the ceiling of the linac vault. The cameras were used to detect the position and orientation of an array of passive reflecting spheres attached to the patient's bite block. The system was in use largely before integrated imaging became a standard feature of linear accelerators, and was used to treat hypofractionated brain lesions (4-5 fractions) with tertiary collimated arcs, and for intensity-modulated radiation

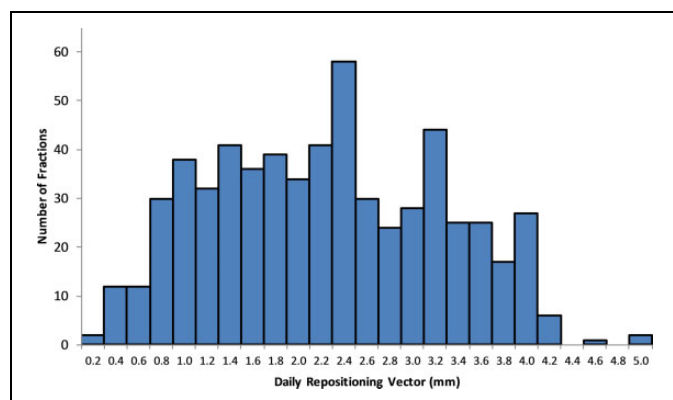


Figure 4. A histogram of daily setup vectors for the Sofamor Danek radiocamera system.

therapy (IMRT). The bite block was created by the simulation therapist and was placed in the mouth and did not utilize a vacuum system for fixation. The primary advantage of the OGP system is that it monitors patient motion during the entire time of treatment.

Figure 4 depicts the daily setup histograms for 28 patients treated between June 2002 and February 2009. The average and standard deviation of the recorded setup errors was 2.1 (1.0) mm. The majority of these treatments were IMRT treatments of ≥ 25 fractions. There was a procedure to verify that the bite block was registered to the patient's anatomy correctly, but it was based on surface marks. This measurement was subject to considerable uncertainty and it was used in a binary fashion; if the bite block registration was below a given value, it was considered to be correctly seated in the patient's anatomy. The vector displacement between position of an array mounted on the bite block and its expected position was recorded daily by the treating therapists and is described in Figure 4 and the surrounding text of.⁵

Discussion

Calculation of the overall uncertainty can be broken into several separate values that depend on the different components of the system. Four different reference frames can be defined: (a) the anatomical reference frame including the absolute position of the target volume within the skull, (b) the imaging reference frame that relates the anatomy to an external reference frame, (c) the reference frame of the patient positioning system, and (d) the radiation reference frame. Ideally, the origins and/or offsets of these reference frames are accurately superimposed. Table 2 describes the uncertainties in these processes. *Planning image* is the uncertainty in alignment between the reference frames of (a) and (b); *target positioning* refers to the match between (b) and (c); and *isocenter* refers to the match between (c) and (d). In addition, we include the motion of the patient within the radiation reference frame, as measured by differences in measurements in target positioning before and after treatment. Linac-based radiosurgery is an option for many patients, and we include a comparison of uncertainties with 1

common system. The ExacTrac system from BrainLAB (BrainLAB AG, Feldkirchen, Germany) combines stereoscopic X-ray imaging with real-time infrared tracking for frameless or frame-based linac-based SRS and is typically used in conjunction with a robotic 6-degree of freedom couch.

Table 2 lists uncertainties associated with several systems. The values for the Perfexion come from our own experience, including this publication, with the exception of the value for intrafraction motion which is an average of 2 values reported in the literature^{2,4} on 10 and 12 patients, respectively. The manufacturer's specification for positional accuracy of the radiological focus point—similar to isocenter on a linac—for the Perfexion is 0.4 mm, our own value from acceptance testing—which is also performed at every source exchange—is 0.12 mm. We have included 0.2 mm in the table as a representative value as our experience is that the accuracy drifts slightly over the lifetime of the sources. Target positioning for the Perfexion includes our institutional average stereotactic definition error of 0.5 mm, and in the case of the Extend system, the daily positioning uncertainty of 0.48 mm, summed in quadrature. The values for uncertainties for ExacTrac come from the literature.^{6,7} One group has developed a vacuum mouth piece system to be used on conjunction with the ExacTrac system which they have shown to reduce the setup uncertainties with the system,⁸ but this approach is not in general use. The isocenter uncertainty of ≤ 1.0 mm is typically achieved by a linear accelerator utilized for radiosurgery.^{9,10} The values for non-SRS image-guided radiotherapy are from our own institutional experience with patients in mask-based immobilization and are provided as a comparison for non-SRS treatments. Our own radiocamera experience is included, as described in⁵ and Figure 4, to highlight important advances in the arena of patient positioning.

Published experience with the Extend system has been limited to a handful of studies with small patient populations. In this work, we report on a substantially larger patient cohort than has been published thus far and focus on the ability of the system to reproducibly set up patients on a daily basis. Reports that have focused on clinical outcomes (as opposed to patient positioning uncertainty) have shown that Extend treatments are an effective and safe option that offers reasonable controls and toxicity rates on the patient populations studied,^{4,11-13} albeit with relatively small numbers (12-34) of patients. Commissioning and quality assurance has been presented,¹⁴ and the dosimetric impact of inter- and intrafractional uncertainties has been studied.¹⁵ Three reports of patient setup uncertainty with small patient numbers, 10² and 12,^{3,4} have produced results that are consistent with our measurement of 0.48 (0.19) mm, taken on 352 consecutive treatments from 84 patients, which is a larger cohort than the combined previously published experiences.

When the program began, we took intrafraction measurements of each patient treated. At that time, the accept/reject criteria for continuing the treatment was 0.8 mm; none of the patients exceeded that threshold even after the treatment completed, leading to an estimate of less than 0.3 mm on average. This is similar to the 0.16 mm average measured on 12 patients.⁴

Table 2. Comparison of Overall Setup Uncertainties in Several Common Intracranial Treatment Techniques, Include Gamma Knife, Our Radiocamera System, ExacTrac, and Standard Fractionated Radiotherapy on an IGRT Equipped Linac.^a

	Isocenter	Target Positioning	Intrafraction Motion	Planning Image	Total	Total w/o Imaging
Perfixion frame	0.2	0.5	<0.1	1.6	1.7	0.5
Perfixion Extend	0.2	0.7	0.2	1.6	1.8	0.8
Linac radiocamera	1.0	2.1	1.0	1.6	3.0	2.5
ExacTrac	1.0	0.8	0.5	1.6	2.1	1.4
IGRT (non-SRS)	1.0	3.0	2.0	3.2	4.9	3.7

Abbreviations: IGRT, image-guided radiotherapy; SRS, stereotactic radiosurgery.

^aWe present totals with and without the effects of imaging, which are the same for every system. Totals by quadrature. All values are in mm.

The Elekta Extend system has reduced the spatial uncertainty for fractionated intracranial treatments at our institution for several reasons. First, the dental molds manufactured by a dentist contain more of the anatomy of the palate and consequently they are vastly superior in their ability to reproducibly situate within the patient's oral cavity, which leads to more easily reproducible daily positioning. Also, the vacuum system stabilizes the bite block to the hard palate, which provides for a more reproducible daily setup, in addition to pausing treatment if the suction is lost. Another advantage is that the tumor to cranial anatomy to bite block to head frame to the table is a system of rigid mechanical objects fixed to one another, whereas with the radiocamera system the location and orientation of the positioning array was measured and served as a surrogate for the patient's position. With modern imaging-based alignment systems, the alignment of 2 images still has the limitations of a voxel size.

While the majority of patients were treated with 4 and 5 fractions, a small number of patients were treated with 3 fractions. This typically occurs when a patient receives a standard frame-based single-fraction treatment for a large number of small lesions followed by a multisession treatment for a large volume lesion. Some patients have also had adaptive therapy with this system in which 2 treatments are given, an MR is obtained a week later, and the treatment of the remaining fractions adapted if needed based on the changes in the target volume.

Daily doses of 4 to 5 Gy require short times (typically 8–20 minutes for sources at a strength of 3.0 Gy/min) to deliver which is useful since the bite block is often fairly uncomfortable. Given that, it is also useful to reduce the overall treatment time. Our experience has been that there is a steep but short learning curve. Originally, it could take us 30 to 45 minutes to get the patient in treatment position. With experience, however, that has been shortened to approximately 10 minutes on average.

The comparison of uncertainties in Table 2 displays a comparison of rigid fixation over imaging-based modalities. The independent uncertainties sum in quadrature. The treatment planning imaging component—which refers to the process of localizing the tumor on an image—is limited by the voxel size and is the dominant form of positioning uncertainty even in a system of rigid body fixation such as the Perfixion systems. For a typical linac-based system, the commonly reported target

positioning uncertainties come from phantom-based measurements, such as the value of 0.8 mm has been reported⁶ for a rigid phantom using the ExacTrac system, and are likely an underestimate of what is achievable for a live patient setup. The arenas where this difference is clinically important are an open question and revolve around the trade-offs inherent in increasing the margin size in order to compensate for the uncertainty.

Conclusion

The Elekta Extend system has proven to be an effective method of repositioning patients for hypofractionated treatments of intracranial lesions. The use of this approach may allow for the treatment of larger lesions and those that lie uncomfortably close to sensitive structures. Although the sample size was small, the system also has the technical capability of treating edentulous patients with acceptable positioning uncertainty; however, additional follow-up and clinical experience are needed to fully evaluate the safety and efficacy of this technique in this subgroup of patients.

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Declaration of Conflicting Interests

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