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RESEARCH ARTICLE

Tolerability and Stability of Mask Fixation in Gamma Knife Stereotactic Radiosurgery: Predictors of Treatment Interruptions

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ABSTRACT

Background. Frameless fixation with a thermoplastic mask is an alternative to traditional frame-based immobilization for Gamma-Knife stereotactic radiosurgery (SRS) or fractionated stereotactic radiotherapy (FSRT). However, interruptions during beam-on time can significantly prolong treatment delivery, impacting patient experience and unit workflow.

Aim. We investigated clinical and technical predictors of treatment interruptions, and the phases of treatment during which interruptions are most likely to occur.

Methods. Patients undergoing frameless Gamma Knife SRS or FSRT in 2020 were retrospectively reviewed. Clinical parameters were extracted from electronic medical records. Dosimetric and treatment interruption data were obtained from Gamma Knife treatment reports. Univariate and multivariate analyses analyzed technical and clinical predictors of treatment interruptions.

Results. Our cohort included 84 patients receiving 141 fractions encompassing 255 lesions. 49/84 (58.3%) were female, 79/84 (94.0%) had brain metastases, 49/84 (58.3%) were taking dexamethasone and 30/84 (35.7%) used analgesics. 89/106 (84.0%) courses were single fractions. Mean planned beam-on time was 37.1 minutes (range 7.1-118.8 min) versus a total bed time of 64.9 minutes (range 15-252min) per fraction. 64.5% (91/141) of fractions were interrupted at least once; 12/141 fractions were paused 20 times or more, with a maximum 54 pauses. The mean number of pauses per quartile decreased the further the patient proceeded in beam-on time, and patients receiving first lifetime cranial radiation paused more often than during subsequent fractions. At least one pause occurred in 100% of fractions with a planned beam-on time exceeding 60 minutes. Planned beam-on time, number of gating events and high-definition motion management alarms significantly correlated with total number of pauses on multivariate analysis (all $p<0.0001$); these three factors, along with prep time and number of operator-initiated pauses, predicted total time on the Gamma Knife couch (all $p<0.0001$). Clinical factors, medication use, and prior SRS/FSRT were not predictive of pauses.

Conclusions. Planned beam-on time, number of gating events and high-definition motion management alarms significantly predicted likelihood of interruptions during frameless Gamma Knife SRS/FSRT. These factors should be considered in selection of immobilization method, especially if exceeding 60 minutes.

Introduction

Historically, Gamma Knife (GK) stereotactic radiosurgery (SRS) has been performed using frame-based immobilization .[1] While the frame provides precise and reproducible positioning and a stereotactic coordinate system for treatment localization, it is invasive, can be uncomfortable for the patient, and is less practical for fractionation. [2-4] Frame placement can be stressful, painful, anxiety-provoking or traumatic. [5-8] Possible complications include small risks of bleeding, numbness, persistent pain, pressure headaches, infection, and slippage. [6-10] The care of framed patients requires dedicated nursing and physician support and often extended periods of time in the department, especially after conscious sedation. [8,10-11] Frame use also places time constraints on the clinical team to complete imaging, planning and delivery in the same day. [7-8,10] Imaging with the frame on can result in pin-related artifacts, especially if CT alone is used. [11] Prior craniotomy defects and shunts must be avoided; [11] repeated or recent neurosurgical procedures make frame placement challenging, [5-6] as does intolerance of local anesthetics. [5-6]

The Gamma Knife ICON (Elekta AB, Stockholm, Sweden), FDA-approved in 2015, is the sixth generation GK unit. It allows use of a thermoplastic mask with an infrared high-definition motion management system (HDMM) for non-invasive immobilization. [12] The ICON's integral cone beam CT (CBCT) defines stereotactic coordinates independent from the frame. [3,13] Submillimeter frameless positioning accuracy is achieved by a combination of CBCT imaging, automatic coregistration, online adaptive planning, and monitoring of intrafraction movements with the HDMM. [14]

The HDMM consists of an infrared stereoscopic camera which monitors the position of a reflective marker on the tip of the patient's nose, relative to immobile reflectors fixed to the GK head support. [3,15] The resolution of detection is 0.1mm in space and about 1 second in time. [11] If the HDMM system detects movement beyond a prespecified threshold (eg 1.5mm), the cobalt sources are retracted to the blocked position. [3,14] This pause during beam-on, called a gating event, ends once the total displacement drops below threshold. [14] If the deviation exceeds threshold for >30 seconds continuously or occurs >5 times during delivery of the same isocentre, the couch automatically moves to the home position, and the shielding doors close. [11,16] The operator then waits until the deviation falls below threshold and irradiation can resume, or a new CBCT is required. Beam pauses and repeat CBCT scans prolong a patient's time on the GK couch and disrupt overall unit workflow. [17-18]

Frameless techniques are generally more comfortable for the patient, [6,16,19] and provide more flexibility in the treatment planning process. Mask construction and treatment planning imaging can be performed in advance. [2,5,7,11,20] This helps overcome inherent limitations in available frames and MRI slots on treatment days. [21] The mask allows for fractionated or distributed treatment schedules. [2,5,21] Unlike the frame, there is no post-treatment recovery period. [6] However, the largest drawback is exacerbation of anxiety and claustrophobia, especially when worn for long periods. [6]

Tolerability and stability are challenging for some patients who repeatedly exceed motion constraints. There are limited available data on patient or treatment related factors which predict the occurrence of treatment interruptions. [14,17] The purpose of our study was to evaluate clinical and technical predictors of interruptions during frameless GK SRS, and the phases of treatment in which interruptions are most likely to occur.

Methods

Patient Population

Consecutive adult patients treated with frameless GK SRS or FSRT in 2020 were retrospectively reviewed. Mask-based immobilization, similar to other series, was chosen by the treatment team based on: lesion proximity to clinical structures; expected fractionated or distributed schedule; anticipated beam-on time; physician discretion; anticipated tolerance (eg claustrophobia); and patient preference. [5,19,22-23] Demographics, comorbidities, and medication use were extracted from institutional electronic medical records. Both benign and malignant tumors were included. Treatment details including beam-on time, characteristics of lesions treated, and number and timing of interruptions were obtained from GK treatment reports. One patient treated with FSRT was framed for the first fraction but subsequent fractions were frameless; data were included from the frameless fractions.

Treatment Workflow

A thin-cut 3-Tesla MRI with double-dose contrast is obtained within five days of planned treatment, although typically occurs on the same day. A custom headrest and an ICON-specific three-point thermoplastic mask is formed to the patient's face. [15,21] A bite block is not used. The nose is allowed to protrude from the mask which allows for placement of the reflective marker. [18] The mask cools and forms for 15 minutes, after which an initial CBCT is completed which serves as the stereotactic reference. [3] The treatment planning MRI is then rigidly coregistered to this reference CBCT and a treatment plan created using Leksell Gamma Plan version 11.1.1 (Elekta Instruments AB).

A setup CBCT prior to treatment is used to zero the HDMM system. [14] The setup CBCT is coregistered to the reference CBCT. The shot coordinates are automatically updated then manually edited as necessary to achieve target volume coverage and planning constraints. [3] The threshold for allowed intra-fractional nose marker movement is set, typically 1.5mm (range 0.5-3mm).

Should beam-on be interrupted requiring a new CBCT, the updated images are again co-registered to the original stereotactic reference CBCT, resulting in a new set of corrected shot coordinates and a new re-zeroing of the HDMM system. [3,21] Each new CBCT typically takes approximately 10-15 minutes to obtain, co-register, and verify before treatment restarts. [11,24]

Statistical Endpoints and Analysis

"Prep time" was defined as the time required to bring the patient into the vault, positioning on the couch, application of the headrest and thermoplastic mask, completion of the setup CBCT and any required manual adjustment, until the start of beam-on. A gating event is a pause in beam-on due to detection of movement of the nose marker above the prespecified threshold, which may or may not lead to an HDMM alarm and CBCT, depending on duration. Treatment interruptions include these gating events, HDMM alarms, as well as patient- or operator-initiated pauses. A gating event, HDMM alarm, or operator pause must precede a CBCT. However, an operator pause can occur without a gating event, for example where the patient rings the call bell to request a break. The total number of pauses = the total number of gating events + the total number of operator-initiated pauses. The total time encompassed by all accumulated types of interruptions is called "beam pause time". The planned beam-on time (determined by the approved treatment plan) + beam pause time = "total treatment time". Finally, the total treatment time + prep time = "total bed time", which is the total time the patient occupies the GK treatment couch.

Total treatment times were divided into four equal time periods (quartiles) to evaluate incidence of treatment interruptions by phase of delivery. Descriptive statistics were reported as means with standard deviations for continuous variables and proportions with ranges for categorical variables. Logistic regression analysis was used to identify factors associated with total number of pauses in beam-on, and total bed time. Factors significant at the $p<0.10$ level on univariate analysis (UVA) were selected for multivariate analysis (MVA). A p value of $\leq$ 0.05 was considered statistically significant. Data were analyzed using SPSS software version 25 (IBM Corp, Armonk, NY, 2017).

Ethics approval was obtained from the institutional research ethics board.

Results

Demographics and Treatment History

84 unique patients (Table 1) received 106 GK courses and 141 total fractions targeting 255 total lesions. The median age was 64 years (range 33-88 years) and the majority were female (58.3%). 96.4% (81/84) had a malignant tumour, with primary histology of non-small cell lung cancer (NSCLC) in almost half. Almost 80% were Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1. Body mass index (BMI) could be calculated for 66 patients, of whom 54.5% (36/66) were either overweight or obese, while 4.5% (3/66) were underweight. Comorbidities included: cardiovascular disease (51.2%), respiratory disease (22.6%), psychiatric disorders (15.5%), diabetes (11.9%), previous seizures (11.9%), bowel disorders (9.5%), or cerebrovascular accident/transient ischemic attack (3.6%). 58.3% of patients were taking dexamethasone as of the treatment day, while 35.7% were using analgesics. Only one patient was documented as claustrophobic prior to GK.

Table 1. Demographics. *ECOG was inferred from clinical notes in 42.9%. Abbreviations: BMI – body mass index; CNS – central nervous system; N/A – not applicable.

Characteristic	N=84 (%)
Median Age, years (Range)	64 (33-88)
Gender	
Male	35 (41.7%)
Female	49 (58.3%)
ECOG Performance Status*	
0	22 (26.2%)
1	45 (53.6%)
2	9 (10.7%)
3	2 (2.4%)
Unknown	6 (7.1%)
BMI Classification	
Underweight (<18.5)	3 (3.6%)
Normal (18.5-24.9)	27 (32.1%)
Overweight (25-29.9)	21 (25.0%)
Obese (≥30)	15 (17.9%)
Unknown	18 (21.4%)
Primary Tumor Histology	
Non-small cell lung	40 (47.6%)
Breast	9 (10.7%)
Melanoma	8 (9.5%)
Genitourinary	7 (8.3%)
Gastrointestinal	5 (6.0%)
Gynecological	3 (3.6%)
Small cell lung	3 (3.6%)
Primary CNS	2 (2.4%)
Other	4 (4.8%)
N/A	3 (3.6%)
Medication Use	
Dexamethasone	49 (58.3%)
Analgesics	30 (35.7%)

No patient with a benign tumour was documented as having previous conventional external beam radiotherapy (EBRT) or SRS. One patient with a benign tumour had previous neurosurgical resection >3 months prior to GK. Previous neurosurgical and RT history for patients with malignant tumours are shown in Table 2. 21/81 patients with malignancy had had previous SRS: 4/21 underwent previous linac-based treatment; 15/21 had previous GK; and 2/21 had both. Mean number of lesions treated per fraction was 1.9 (± SD 2.0) and a mean of 16.2 isocentres were utilized per fraction (±13.7 SD) (Table 2).

Table 2. Previous therapy received by patients with malignancy. ^Including conventional or stereotactic radiation courses. #Including gamma knife or linac-based. Abbreviation: FSRT – fractionated stereotactic radiation therapy; GK – gamma knife; RT – radiation therapy; SRS – stereotactic radiosurgery.

Characteristic	N=84 (%)
Previous RT	
External beam RT to any site	47 (58.0%)
Whole-brain RT	2 (2.5%)
SRS - GK or linac-based	21 (25.9%)
Previous Experience with Immobilization^	
Mask-based	18 (22.2%)
Frame-based	7 (8.6%)
Total Previous Stereotactic Fractions#	
0	60 (74.1%)
1	11 (13.6%)
2	5 (6.2%)
>=3	5 (6.2%)
Previous Neurosurgery	
≤3 months prior to GK	18 (22.2%)
>3 months prior to GK	5 (6.2%)
Never	58 (71.6%)

<u>Dosimetric Parameters, Workflow and Interruptions</u>
Most patients (77.4%) had one course of GK in the study period, while 19.0% and 3.6% of patients had 2 or 3 courses, respectively. 84.0% (89/106) of courses were single fraction, 15.1% (16/106) consisted of 3 fractions, and 0.9% (1/106) of courses consisted of 5 fractions. No patient required unplanned conversion from mask to frame. Planned beam-on time ranged from 7.1 minutes to 118.8 minutes (mean 37.1 min).

"Prep time" averaged 15.4 minutes (range 7-39 min; Table 3) and was considered 'long' (>=15 min) in 43.3% (61/141) of fractions. In just over 1/3 of fractions, there were no pauses (50/141), and in an additional 12 fractions, there was only 1 pause. In another 12 fractions there were 20 pauses or greater, with a maximum number of 54 pauses in beam-on delivery during a single fraction. At least one gating event took place in 87/141 fractions, and at least one HDMM alarm occurred in 46/141. The mean number of operator pauses per fraction was 0.5; in 2/3 of fractions, there were no operator-initiated pauses (Table 3). The mean number of pauses decreased the further the patient proceeded in beam-on time: there was a mean of 2.1 pauses in the first quartile, 1.7 in the second, 1.4 in the third and 1.2 in the fourth. Pauses in beam-on time by quartile are shown in Figure 1, with stratification based on lifetime fraction received in Figure 2. At least one pause occurred in 100% of fractions once planned beam-on time exceeded 60 minutes. Total treatment time (= planned beam-on time + total beam pause time) ranged from 7.1 minutes to 228 minutes. Total treatment time was within 15% of planned beam-on time in 78/141 (55.3%) fractions, took an additional >15% to 50% of planned beam-on time in 39/141 (27.7%) fractions, and was greater than twice the planned beam-on time in 9/141 (6.4%) fractions. Total bed time averaged 64.9 minutes (Table 3) with a range of 15-252 minutes.

Table 3. Interruption data by fraction. *Includes first setup CBCT prior to initial beam-on. Abbreviations: SD – standard deviation.

Characteristic (mean±SD)	N (%)
Prep time	15.4 ±6.2 min
Beam-on time	37.1 ±22.0 min
Total pauses	6.4 ±9.6
Operator pauses	0.5 ±0.9
Gating events	5.9 ±9.1
HDMM alarms	0.6 ±1.2
Total beam-pause time	12.4 ±21.6 min
Total treatment time	49.6 ±36.5 min
Total treatment time / beam-on time ratio	1.29 ±0.45
CBCTs performed*	1.9 ±1.4
Total bed time	64.9 ±37.7 min

Figure 1. Pauses in beam-on time by planned beam-on time split into quartiles. Data for 140 fractions shown (data missing for one fraction).

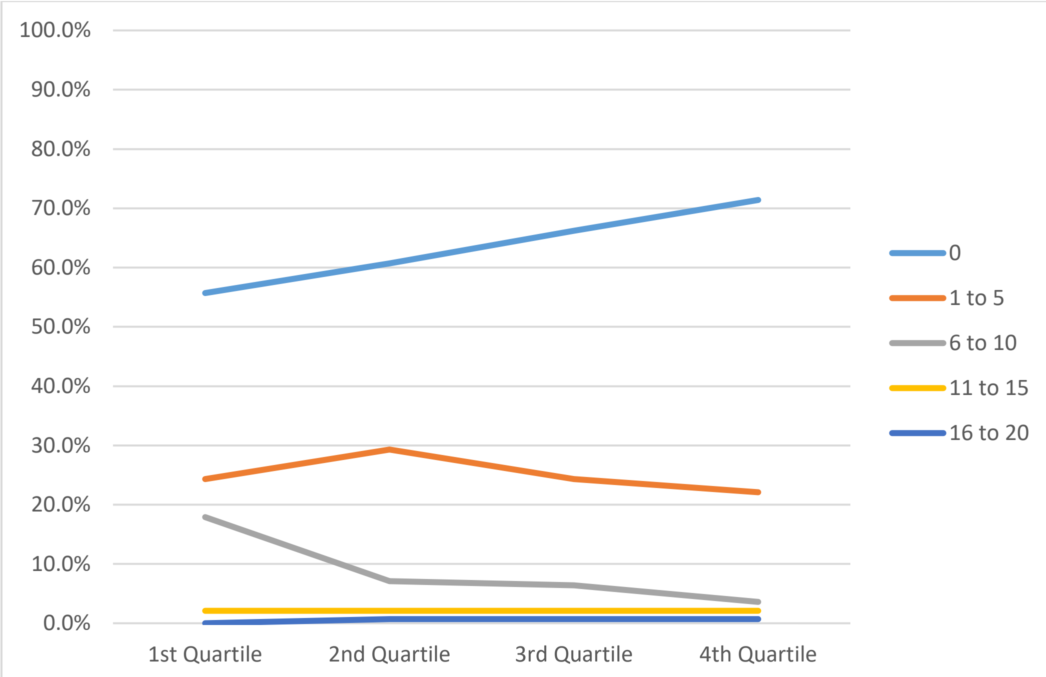
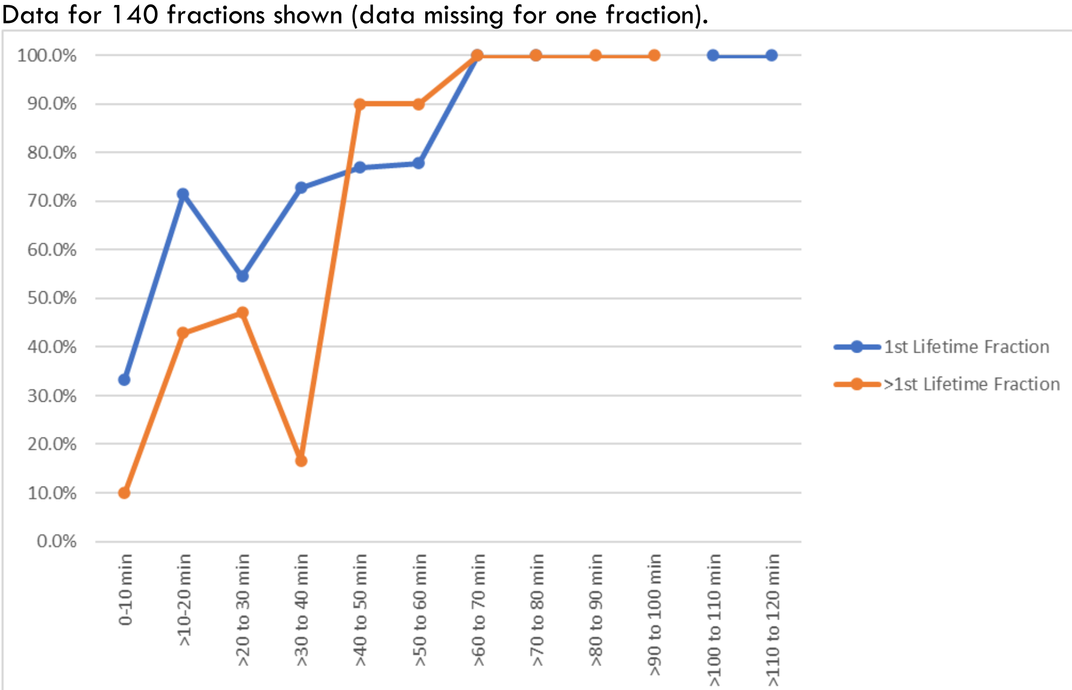


Figure 2. Percentage of fractions requiring at least one pause in treatment versus planned beam-on time. Data for 140 fractions shown (data missing for one fraction).



Predictors of Treatment Interruptions

On UVA, use of dexamethasone and analgesics correlated with increased number of pauses. An association between number of pauses and increased bed time was observed for planned beam-on time, number of lesions, total first quartile pauses, total number of operator pauses, total number of gating events and HDMM alarms. Age, gender, primary tumour, BMI and ECOG were not associated with either outcome. Treatment team was not associated with either outcome. Neither course fraction number nor previous treatment received (lifetime fraction number, previous EBRT, prior GK or linac SRS, or experience with mask immobilization) was associated with either outcome. On MVA, planned beam-on time, number of gating events and number of HDMM alarms significantly correlated with total number of pauses. These factors, along with prep time and total number of operator pauses, were significantly correlated with total bed time (all p<0.001).

Discussion

In this retrospective study, we report that longer planned beam-on time significantly increased the total number of treatment interruptions and total time the patient occupies the GK couch. The number of gating events and HDMM alarms were also associated with both endpoints, while the total number of operator-initiated pauses and time required for patient setup and acquisition of the reference CBCT ("prep time") predicts for longer total time on the bed. These findings are clinically important because frequent pauses and unanticipated protracted time in the vault both prolong treatment times for specific patients and disrupt the overall day's workflow. [18] Additionally, treatment interruptions related to motion can result in variations of target coverage and normal tissue dose from what has been planned and approved. [25]

Protracted workflow related to fixation method has been recently reported in a phase III randomized trial. [16] 58 NSCLC patients with <5 unresected brain metastases were randomized 1:1 between frame or frameless fixation (02/2016-01/2017). The primary endpoint was patient comfort, which was rated more highly by patients in a mask compared to the frame. In addition, while all 29 assigned to the frame were treated as such, 2/29 randomized to the mask could not tolerate it and were converted to a frame, and another two had to be treated over two sessions. Beam-on time was not significantly different between arms, but total treatment time and overall time in the vault were significantly longer in the mask group due to interruptions. In the mask arm, the median number of interruptions due to exceeding their 1mm movement threshold was 9. The maximum number of interruptions per patient was 54, identical to our cohort. The median number of repeat CBCT scans was 3 (range 2-14), corresponding to 7.5mGy of extra dose. Treatment duration was the main factor associated with discomfort, which becomes "unbearable", according to the authors, after one hour in the mask. [16]

Our results are consistent with other recent publications regarding treatment interruptions (Table 4). Bush et al treated 124 patients with 358 intracranial tumours in a mask (01/2018-12/2019). [20] Each mask was constructed with a bite block and a 1.5mm motion threshold was used. The average treatment time was 25.6 minutes and withdrawal occurred in 16.5% of fractions. [20] Vulpe et al reported on their first 100 mask patients (04/2017-02/2018). [2] 42% had metastases (N=96 lesions) and median treatment time was 17.7 minutes (range 5.8-61.7 minutes). Despite commonly setting the HDMM movement threshold at 3mm, 31% required more than 1 localization CBCT (excluding the reference scan).[2] Wegner reviewed 150 frameless GK patients (2019-2020). [18] Median planned beam-on time was 23 minutes (range 4-108 minutes). 69/150 (46%) patients experienced at least one interruption. For patients with an interruption, the median increase in treatment time was 11 minutes (range 2-110 min). The interruption rate was 13% for plans under 10 minutes, 50% for times exceeding 20 minutes, and 92% for treatments exceeding one hour. This is consistent with our data, in which fractions with a planned beam-on time of greater than 60 minutes were paused 100% of the time. [18] Published factors associated with treatment interruptions are shown in Table 4.

Table 4. Published factors significantly predicting increased treatment interruptions.

	Parameter	References
Body Habitus	Increased BMI	14
Planned beam-on time	>19 minutes Longer treatment time	18 17,22,26
Performance status	ECOG >1	22
Gender	Male	22
Age	<65 years	22
Medications	No anxiolytics	22

The ultimate goals of identifying patient-specific motion characteristics would be to both implement personalized target margins and take steps to mitigate deviations before they occur. Investigators from Toronto are using AI neural networks to try to predict, from the HDMM motion tracing over the first five minutes of a patient's treatment, the likelihood of a subsequent interruption. [17] For the 1446 cases reviewed, the mean treatment time was 46.4±35.1 minutes. 29% had at least one interruption with the threshold set at 1.5mm. [17] In our cohort, the total number of pauses in the first

quartile of the fraction was associated with both total number of pauses overall, and total bed time on univariate analysis, but not MVA. However, "prep time" was predictive of total time on the GK couch, suggesting that the more difficulty a patient had tolerating the initial mask application, positioning and setup CBCT, the more protracted the actual treatment delivery was going to be.
At times, estimating tolerability is more an art than a science (Table 5). [21] Even patients with good performance status who appear cooperative in clinic can have significant difficulty minimizing motion in the mask. [26] Ways to proactively increase patient tolerance include: intentional coaching during the mask-making process; [14] scheduling breaks; [12] regular time calls; and frequent encouragement. [10,18] Fractionation or distributed schedules, [21] linac SRS, [17] or frame placement, may ultimately be required. [12,17-18]
Whether anxiolytics or sedation should be used to improve mask tolerability is under debate. In semi-structured interviews of patients receiving GK via frameless fixation, many reported taking lorazepam to help relax. [6] In the cohort of Seneviratne et al, just over 2/3 of patients received anxiolytics, with significantly less motion associated. [22] Wegner et al suggested consideration of premedication with anxiolytics if planned beam-on time was >19 minutes. [18] However, other authors caution against routine sedation; patients who fall asleep or become confused can no longer purposefully cooperate, often resulting in increasing motion. [11,21]

Table 5. Published guidelines regarding patient selection for mask immobilization.

Parameter	Mask	Frame	References
Target size	≥5-10mm	<5-10mm	2,8
Target number and shape	Limited number of simple geometric targets	Functional, multiple or more complex eg AVM, trigeminal neuralgia	2,11,16,21,24
Target location	Relatively central	Extremes of location in cranial vault (far inferior, anterior, posterior; skull base)	11
Multiple previous or recent craniotomies	Preferred	Can be challenging (location dependent)	11
Critical structures	>2-3mm from a critical structure	<2-3mm to brainstem, optic structures	2,8,11,21
Planned beam-on	<60 min <45 min <30 min	>60 min >45 min >30 min	21 24 11
Patient mental status	Calm, cooperative, composed	Anxious, claustrophobic, restless, confused, agitated, uncooperative, very tired	2,11,16,21,23
Facial shape/structure	Minimal subcutaneous fat; angular	Beards, long bushy hair Facial dysmorphism Relatively round face	3,11,14,15,16
Body habitus	Nose marker can be visualized	Large chest/abdomen precluding visualization of nose marker	11
Change in Gamma Angle required	Not possible within the same fraction	Possible	11,21
Comorbidities	No respiratory compromise No significant pain	Psychiatric or respiratory comorbidities Need for oxygen	16,22
Level of sedation	None to light	Range possible from none to general anesthetic	11

A patient-centered approach should be used regarding selection of mask versus frame (Table 5). [21] It is important to recall that the mask construction process, including shaping, hardening, reference and setup CBCTs, imaging and verification takes 20-30 minutes, before radiation delivery has even started. [11] Additionally, as the cobalt-60 sources decay, treatment times naturally increase, requiring more attention to planned beam-on time. [18,21,25] While there are dosimetric methods within Gamma Plan to decrease beam-on time, it is suboptimal to accept a lower quality treatment plan in order to reduce mask-on time. [11,16] From published literature including our data, mask-based immobilization appears most likely to be tolerable when planned beam-on time is less than 60 minutes. Interestingly, in our patients with interruptions, the frequency of pauses decreased over the course of the fraction. This suggests decreases in anxiety, which has been previously reported with linac SRS. [26]

Even as recently as 2020, limited data were available on optimal thresholds for gating. [17] While an extensive discussion of the factors to be considered in determining the optimal HDMM motion threshold is beyond the scope of this work, [3,13,22-23] it should be noted that very tight thresholds (0.5mm) allow less motion but will result in multiple pauses in treatment. [3,15,21,23,25] Conversely, a threshold of 3mm will reduce pauses, but theoretically could result in geographic miss. [17-18] Some centres vary the threshold depending on whether the patient is undergoing SRS or a fractionated course, [24] whether the target is unresected or a postoperative cavity, and based on location. [3] Overall, an HDMM threshold of 1.5mm has a reasonable trade-off between patient immobilization and treatment efficiency. [23]

Our study has some limitations. This is a retrospective single centre analysis of a cohort treated in 2020, which largely coincided with the COVID-19 pandemic. As a result of prioritizing malignant tumors during this period, nearly all of our patients had brain metastases. As only patients immobilized via a mask were reviewed, inherent selection bias exists: patients for whom a mask was not felt to be tolerable were not offered that fixation option. We did not compare outcomes to frame-based systems. While information regarding prior use of steroids and analgesics was available, records of patients who received supplemental premedication (anxiolytics, analgesics) on the treatment day were not.

Conclusions

Longer planned beam-on time, amongst other factors, significantly predicted likelihood of interruptions during frameless GK SRS/FSRT, especially when exceeding 60 minutes. Our data contributes to the body of literature on tolerability and stability of mask fixation, supporting evolution of recommendations for selection of immobilization method as they become more evidence based.

Conflict of Interest statement. The authors have no conflicts of interest to declare.

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