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Systematic evaluation and plan quality assessment of the Leksell® gamma knife® lightning dose optimizer

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ABSTRACT

To compare stereotactic radiosurgery (SRS) plan quality metrics of manual forward planning (MFP) and Elekta Fast Inverse Planning™ (FIP)-based inversely optimized plans for patients treated with Gamma Knife®. Clinically treated, MFP SRS plans for 100 consecutive patients (115 lesions; 67 metastatic and 48 benign) were replanned with the FIP dose optimizer based on a convex linear programming formulation. Comparative plans were generated to match or exceed the following metrics in order of importance: Target Coverage (TC), Paddick Conformity Index (PCI), beam-on time (BOT), and Gradient Index (GI). Plan quality metrics and delivery parameters between MFP and FIP were compared for all lesions and stratified into subgroups for further analysis. Additionally, performance of FIP for multiple punctate (<4 mm) metastatic lesions on a subset of cases was investigated. A Wilcoxon signed-rank test for non-normal distributions was used to assess the statistical differences between the MFP and FIP treatment plans. Overall, 76% (87/115) of FIP plans showed a statistically significant improvement in plan quality compared to MFP plans. As compared to MFP, FIP plans demonstrated an increase in the median PCI by 1.1% ($p<0.01$), a decrease in GI by 3.7% ($p< 0.01$), and an increase in median number of shots by 74% ($p< 0.01$). TC and BOT were not statistically significantly different between MFP and FIP plans ($p>0.05$). FIP plans showed a statistically significant increase in use of 16 mm ($p< 0.01$) and blocked shots ($p< 0.01$), with a corresponding decrease in 4 mm shots ($p< 0.01$). Use of multiple shots per coordinate was significantly higher in FIP plans ($p<0.01$). The FIP optimizer failed to generate a clinically acceptable plan in 4/115 (3.5%) lesions despite optimization parameter changes. The mean optimization time for FIP plans was 5.0 min (Range: 1.0 – 10.0 min). In the setting of multiple punctate lesions, PCI for FIP was significantly improved ($p<0.01$) by changing the default low-dose/BOT penalty optimization setting from a default of 50/50 to 75-85/40. FIP offers a significant reduction in manual effort for SRS treatment planning while achieving comparable plan quality to an expert planner—substantially improving overall planning efficiency. FIP plans employ a non-intuitive increased use of blocked sectors and shot-in-shot technique to achieve high quality plans. Several FIP plans failed to achieve clinically acceptable treatments and warrant further investigation.

Introduction

Gamma Knife® (Elekta AB, Stockholm, Sweden) stereotactic radiosurgery (SRS) is a treatment platform commonly used in the treatment of benign and malignant intracranial tumors[1-3], and various nonneoplastic conditions[4-6] such as arteriovenous malformations[7] and trigeminal neuralgia[8]. The latest redesigned systems,

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Perfexion™ and Icon™, consist of 192 cobalt-60 sources fixed on 8 sectors (each sector with 24 sources)[9-11]. Each sector can move independently of the others and can be set to four different positions during treatment, three defining collimator sizes of 4, 8, and 16 mm and an off (blocked) position[9-11], facilitating the efficient delivery of complex shots compared to older platforms.

Historically, manual forward planning (MFP) has been used where the planner manually places shots within the tumor to shape a desired isodose distribution. In this process, multiple parameters need to be determined by the planner, including the number, location, collimator settings, and relative weights of each of the shots. In the simplest of examples, one individual shot has 65,536 possible beam shapes given different selections for sector collimator size. Since most tumors require more than one shot to cover the target volume, the number of possibilities increases exponentially. As a result, the quality of MFP plans is highly dependent on the experience of the planner and time invested into each plan. For large tumors with irregular shapes, the MFP process is tedious and time intensive. Elekta AB introduced an inverse planning (IP) tool in the Leksell GammaPlan (LGP) in 2010 which provides a choice of optimizing the target dose based on predefined planning settings[12]. The IP tool uses well-established metrics such as coverage, selectivity, and Gradient Index (GI) at a predetermined isodose level as well as a Beam-On Time (BOT) penalization to develop a plan solution. Unfortunately, obtaining an optimal plan solution is inherently difficult due to the nonconvex nature of the optimization problem where difficulties arise due to the use of relative isodose lines and the variability in the positions of the shots[13]. Because of this, its clinical use has been limited as it has not been able to consistently outperform manual planners with significant experience and still universally requires manual editing[14,15].

In late 2020, Elekta AB released a new dose optimizer for the Leksell Gamma Plan. The optimizer, called Fast Inverse Planning (FIP) and commercially referred to as Lightning™, optimizes a well formulated linear objective function employing linear programming published in the seminal study by Sjolund et.al[13]. Unlike previous methods of planning Gamma Knife® treatments, Lightning™ was developed to rapidly generate plans that require minimal to no adjustments after optimization to reach target coverage and conformity goals while minimizing maximum doses to surrounding critical structures.

The FIP algorithm addresses inverse planning in three phases: isocenter placement, optimization, and sequencing[9,13]. In the first phase, well-distributed isocenters are generated in the target using two geometrical attributes - skeleton and curvature. The positions of the isocenters are unaltered in the subsequent optimization steps. In the second phase, an optimization problem is formulated as a weighted sum of objectives and constraints resulting in a cost function that penalizes the following parameters: 1) Dose to target: Penalizes if dose is less than prescription dose within the interior and surface voxels of the target; 2) Sparing of organs-at-risk (OARs): High selectivity and high dose gradient is achieved by penalizing dose exceeding the prescription dose in voxels in a ring region close to the target and by penalizing dose exceeding the threshold doses in the low dose region; both the ring and the low dose regions are defined by the optimizer for single and multi-target problems; and 3) BOT penalization: During optimization, times for each sector and collimator are minimized but allowed to vary independently and are then converted to deliverable shots in the sequencing phase[9,13]. The resulting irradiation times of individual collimator in each sector are combined into deliverable composite shots in the sequencing phase. This optimization step could result in multiple shots at the same isocenter position. Shots with BOT less than shutter time (0.1 min) are discarded in this step, and a final optimization is executed with the derived shots.

In light of the development of this new dose optimizer, the motivation for this study is to investigate and evaluate the quality of treatment plans produced using FIP as well as understand any improvements in treatment planning time. Specifically, the key objective of the study is to compare relevant plan quality metrics between MFP and FIP SRS plans.

Materials & Methods

Patient selection

The lesions included in the study were broadly divided into two groups: non-punctate lesions (Group 1) and punctate lesions (Group 2). Group one consisted of 100 patients with 115 non-punctate lesions of which 67 were metastatic lesions and 48 were benign lesions. To study the behavior of FIP in the setting of multiple, small volume punctate lesions (median volume 0.005 cc), a second group of patients, Group two, was investigated. Group two consisted of 4 patients, with 6, 14, 17 and 28 lesions, respectively, for a total of 65 punctate lesions. Clinically treated MFP SRS plans from both groups were replanned with the FIP dose optimizer. Characteristics of all lesions included in Group 1 and Group 2 are presented in Table 1

Manual planning

Clinical plans were generated using MFP with or without the assistance of the previous version of inverse planning tools (GammaPlan v11.0.3 and v11.1.1). For Group one, the clinical treatment plan was generated by manual optimization of the number of shots, isocenter positions in 3D space, relative weight (dose contribution), and collimators to maximize selectivity while ensuring target coverage of 100%. The first step in planning is shot placement in the target. Depending on the size of the lesions, prescription isodose line was selected to be greater than 50% followed by shot placement that was performed either manually or using the Shot Fill tool available in the previous versions of the optimizer. The Shot Fill technique was set to use either single collimator size or composite shots based on the size of the lesions. For plans adjacent to risk structures, the shot placements were often performed manually. The shot sector configuration, weight, and isocenter positions were then optimized either manually, with the inverse planning optimization tool, or a combination of both until target coverage of 1.0 was achieved, and the selectivity value was optimized. The inverse plan-generated parameters were evaluated by the planner and based on the institutional directives and the experience of the planner. The following criteria was used to evaluate the inverse plan (1) Target coverage of 100% per institutional guidelines (2) Assessment if optimal number of shots and collimator sizes were generated (3) Smoothness and conformity of prescription isodose line around the target volume. (4) BOT. The last three evaluation criteria are heavily dependent on the planner expertise.

The punctate lesions in Group two were planned using either a single 4 mm shot, or a composite shot of 4 mm, 8 mm, and blocked sectors, depending on tumor shape. The prescription IDL was chosen in the composite dose mode to maximize selectivity while maintaining target coverage of 100%. The range of prescription IDL for these punctate lesions was limited to a range between 50-94% per institutional practice guidelines.

Inverse planning (FIP)

FIP plans were generated to match or exceed the MFP plan metrics in the following order of importance: 1) Target Coverage (TC); 2) Paddick Conformity Index (PCI)[16]; 3) BOT; and 4) GI[17]. The FIP optimizer design allows for inverse planning on all or select lesions with or without a base plan. The inputs fed into the optimizer for the select targets include prescription dose, maximum target dose, coverage option, low-dose penalty, BOT penalty, and maximum dose to OARs. The coverage option is a checkbox that can be chosen optionally to maximize target coverage.

In Group 1, 101 of the 115 lesions were optimized individually using the FIP optimizer. 7 cases with 2 lesions each were optimized simultaneously. In Group 2, all lesions in each patient were optimized simultaneously. For multiple lesion optimization, all lesions were included in the initial optimization. Select lesions that required adjustment in coverage, conformity, or BOT were then reoptimized. The process was repeated until the composite dose distribution was found optimal. In both groups, FIP plans were generated by providing a prescription dose, and a maximum target dose such that the prescription isodose line was greater than 50% with the coverage option enabled. The initial FIP dose optimization was executed with the default 50/50 (Range 0:100) optimization settings for low dose and BOT penalty on the optimizer. Successive optimization parameters were then adjusted to maximize target coverage and dose conformity, while keeping treatment time comparable to MFP plans. Plans with 99% target coverage were minimally modified by altering shot weight or adding low weighted 4 mm shots at cold spots to achieve to achieve 100% target coverage as per institutional guidelines. Practice guidelines vary across institutions and plans are optimized to achieve a target coverage of 98%-100% and the final step of modification may be skipped for FIP plans with target coverage >98%.

Table 1
Distribution and volume characteristics of the 115 lesions (Group 1) and 65 (Group 2) punctate metastases investigated in this study

	Lesion characteristics	# of Lesions	Mean Volume (cc)	Volume Range (cc)
Group 1	Benign lesions	48	2.756	0.117 - 9.327
	Vestibular Schwannoma (VS)	10	2.715	0.276 - 8.288
	Facial Nerve Schwannoma	1	0.303	0.303
	Pituitary Adenoma (PA)	7	1.257	0.319 - 3.903
	Meningioma	13	2.782	0.151 - 6.128
	AVM	17	3.521	0.117 - 9.327
	Non-punctate Metastatic lesions	67	9.213	0.041 - 33.503
Group 2	Punctate metastatic lesions	65	0.008	0.002 - 0.040

For the multiple, metastatic punctate lesions (Group 2), if the initial FIP optimization with default optimization settings did not produce clinically optimal plan in terms of conformity and target coverage, successive optimization using higher low dose penalty and slightly lower BOT penalty were performed for select targets. Clinically acceptable plans were achieved by setting the low dose penalty to 65-85, while the BOT penalty was set to 40. Targets that had reached convergence were removed from the optimizer list and optimizations were run until all targets reached a clinically acceptable dose distribution.

Evaluation

To compare the plans generated using FIP and MFP, plan quality metrics and delivery parameters were compared for all Group 1 lesions as well as further stratified into subgroups for metastatic and benign lesions. For benign lesions, an additional sub-group analysis was performed for pituitary adenomas, vestibular schwannomas, arteriovenous malformations, and meningiomas. The number of dose optimization iterations with FIP and planning time were recorded for each case.

Plan quality metrics

To quantify plan quality and facilitate comparison, the following plan parameters were noted and evaluated: treatment planning time, BOT, number of isocenters, prescription IDL, TC, and selectivity. Number of iterations and optimization time were noted for all plans grouped by change in PCI, Δ PCI, where Δ PCI = PCI_{FIP} – $PCI_{Clinical}$. The following subgroups were identified: Improved PCI (Δ PCI > 0.01), Minimal Change PCI (Δ PCI = ± 0.01), Worsened PCI (ΔPCI < 0.01). In addition, the following dosimetric planning indices were noted: The Paddick conformity index, PCI,[16] was defined as:

$$PCI = \frac{TV_{PIV}{}^2}{TVxPIV} \quad (1)$$

where TV_{PIV} was the volume of the target covered by the prescription isodose, TV was the Target Volume and PIV was the Prescription Isodose Volume.

The gradient index, GI,[17] was defined as:

$$GI = \frac{PIV_{50\%}}{PIV_{100\%}} \quad (2)$$

where $PIV_{50\%}$ was the absolute volume of 50% of the prescription isodose and $PIV_{100\%}$ was the volume of the prescription isodose

Delivery parameters

Distribution frequency (%) of sector collimator size across all shots was defined as:

$$\eta_c(\%) = \frac{N_c}{Nx8}\ x\ 100 \quad (3)$$

Where N_c was the number of occurrences of collimator size c (mm) across all shots where $c \in \{4,\ 8,\ 16,\ B\}$ and N was the number of shots used. The denominator in Equation (3) is the total number of sectors in a treatment plan, which is the product of N and 8, the scalar quantity denoting the number of sectors per shot.

Frequency of shot-in-shot: Number of shots at the same coordinate location was tabulated for each lesion.

For statistical analysis, data was tested for normality. A Wilcoxon signed-rank test for non-normal distributions was used to assess the statistical differences between the MFP and FIP treatment plans. Statistical significance was established at $p<0.05$.

Results

For all patients in Group 1, with non-punctuate lesions, the FIP dose optimizer was able to generate clinical plans for 111 of 115 (96.5%) lesions that were included for analysis. The coverage option allowed the optimizer to produce target coverage of at least 99%. For 52% (60/115) of the lesions, FIP plans required additional minor manual adjustments after optimization to achieve 100% target coverage. For the multiple target optimization in Group 1, 5 of the 7 cases required multiple iterations before generating plans that match or exceed the MFP plans. After the initial optimization using 50/50 weight for the low dose and BOT penalty, the dose distribution of both targets was evaluated. Successive optimizations for target dose distributions that need adjustments were performed using modified weights for either the low dose penalty, the BOT or both until the desired outcome was achieved. For lesions in close proximity to each other with overlap of the low dose region, the first run of optimization generated a solution with suboptimal Gradient Index and selectivity. Further iterations with higher weights on the low dose constraint yielded plans with improved plan quality metrics. It was further noted that for multiple non-punctate lesions, BOT can be markedly lower when optimized simultaneously as compared to individually.

Plan quality metrics

Table 2 shows the comparison of median plan metrics and delivery parameters for MFP and FIP plans in Group 1 for the 111 lesions included in the analysis. FIP plans showed a statistically significant improvement in the median PCI by 1.1% ($p<$ 0.01) and median GI by 3.7% ($p<$ 0.01) compared to MFP. A substantial increase in median number of shots by 74% ($p<$ 0.01) was observed for FIP plans. There was no significant difference ($p>0.05$) in BOT between the metastatic and benign lesion subgroups. Table 3 shows the comparison of plan quality metrics and delivery parameters for each of the four benign lesion subgroups. Among the subgroups, the FIP plans showed a 4.3% increase in PCI ($p<0.01$) for the AVM subgroup and had comparable PCI relative to the MFP plans for all other subgroups. Significant improvement ($p<0.05$) in GI and comparable BOT was demonstrated across all benign lesion subgroups. A statistically significant increase in median total number of shots was noted for the FIP plans ($p<0.05$).

Figures 1,2, and 3 illustrate sample dose distribution comparisons between the Group 1 MFP and FIP plans for cases with Δ PCI < 0.01, Δ PCI = ± 0.01, and ΔPCI > 0.01, respectively. For cases with Δ PCI < 0.01, 28 plans, corresponding to 24% of FIP plans, either did not match or exceed the PCI metric of the MFP plans largely due to the irregular shape of the target. A subset of this group (4/28) did not converge to a solution that was deemed acceptable for a clinical use. An acceptable solution could not be achieved for various combinations of optimization parameters. The clinically unacceptable plans were characterized by a large decrease in the PCI (mean Δ PCI= -0.16) with prescription isodose line extending more than 5 mm beyond the target volume and a mean increase in treatment time of 190%. Figure 4 displays a sample dose distribution comparison from this subgroup, and specifically for this case, it can be noted in the axial plane for the FIP plan that the prescription isodose exends >5mm outside of the target volume in most directions. Figure 5 shows a sample dose distribution of MFP compared to FIP plan for a vestibular schwannoma case. For this case, the MFP plan shows a higher PCI (0.83 vs 0.79) compared to the FIP plan. Investigating further, the FIP plan revealed a higher use of 16 mm and 8 mm collimators, and the maximum PCI of 0.79 was achieved after exploring a range of low dose penalty and BOT penalty combinations.

Table 4 shows the mean number of iterations and mean optimization time as grouped by Δ PCI, lesion type, and use of OAR constraints in the optimization. As expected, the mean number of iterations and the mean optimization time increases for plans in which the use of OAR constraints are employed in the optimization.

For Group 2 with punctate lesions (median volume = 0.005cc), the FIP plans were initially generated with the default optimization setting of 50/50 for the low dose penalty and BOT penalty, respectively. In doing so, the optimizer produced suboptimal plans for clinical use in 21.5% (14/65) of targets. The number of suboptimal plans had a direct correlation to the total number of targets in the optimization run. This failure was characterized by a poor PCI, high GI, and increased number of shots including the use of 16 mm collimator in the shot sectors. Successive iterations using increased weight of the low dose penalty in the range of 65-85 were able to produce plans comparable to the MFP plans.

Table 5 shows the plan parameters of FIP with the default setting and final optimization setting for the Group 2 lesions. The initial optimization showed an increased use of 16 mm and 8 mm sector collimators while the final optimization plan parameters show an increased use of single 4 mm shot as expected for the lesion size. Figure 6 compares the dose distribution for an MFP plan, a suboptimal FIP plan with default 50/50 optimization setting, and an acceptable FIP plan using the final 85/40 optimization setting. The plan generated using the default setting again

Table 2
Comparison of median plan metrics and delivery parameters for manual forward planned (MFP) and fast inverse planning (FIP) optimized plans for the Group 1 lesions grouped as Benign, Metastatic, and Total. Overall, a statistically significant improvement in the median PCI and GI was noted for comparable beam on treatment times and target coverage for all three groups. Statistical significance was established at $p<0.05$.

	TC (Range in %)		Median PCI		Median GI		Median Beam on Time [mins]		Median # of Shots	
Metastatic	MFP	[99.6 100]	0.88 ± 0.09	$p<0.01$	2.65 ± 0.51	$p=0.01$	48.6 ± 27.1	$p=0.13$	23 ± 13	$p<0.01$
	FIP	[99.1 100]	0.89 ± 0.07		2.63 ± 0.64		52.5 ± 26.8		43 ± 14	
Benign	MFP	[99.4 100]	0.81 ± 0.13	$p<0.01$	2.78 ± 0.32	$p<0.01$	62.1 ± 51.9	$p=0.42$	22 ± 15	$p<0.01$
	FIP	[99.8 100]	0.83 ± 0.14		2.59 ± 0.25		64.7 ± 49.5		32 ± 20	
Total	MFP	[99.5 100]	0.87 ± 0.12	$p<0.01$	2.72 ± 0.44	$p=0.01$	53 ± 41	$p=0.13$	23 ± 13	$p<0.01$
	FIP	[99.8 100]	0.88 ± 0.11		2.62 ± 0.51		55 ± 39		40 ± 17	

Table 3
Comparision of median plan metrics and delivery parameters for manual forward planned (MFP) and fast inverse planning (FIP) optimized plans for benign lesions binned by subgroup. A statistically significant improvement was noted in PCI for AVMs between MFP and FIP plans. The median GI showed signifcant inprovement for all subgroups in the FIP optimized plans. All subgroups showed a significant increase in the number of shots for FIP plans

	TC (Range in %)		Median PCI		Median GI		Median Beam on Time [mins]		Median # of Shots	
PA	MFP	100	0.74 ± 0.16	$p=0.69$	2.93 ± 0.43	$p=0.01$	102 ± 76	$p=0.22$	19 ± 7	$p=0.01$
	FIP	100	0.80 ± 0.17		2.65 ± 0.39		100 ± 70		24 ± 15	
VS	MFP	100	0.90 ± 0.04	$p=0.33$	2.73 ± 0.33	$p<0.01$	46 ± 18	$p=0.51$	25 ± 17	$p=0.04$
	FIP	100	0.89 ± 0.05		2.59 ± 0.13		47 ± 25		32 ± 13	
AVM	MFP	[99 100]	0.69 ± 0.12	$p<0.01$	2.77 ± 0.30	$p<0.01$	113 ± 43	$p=0.19$	25 ± 18	$p<0.01$
	FIP	[99.7 100]	0.72 ± 0.14		2.48 ± 0.24		113 ± 39		52 ± 25	
Meningioma	MFP	[99.7 100]	0.87 ± 0.04	$p=0.08$	2.88 ± 0.30	$p=0.01$	31 ± 22	$p=0.55$	18 ± 9	$p<0.01$
	FIP	[99.7 100]	0.90 ± 0.05		2.69 ± 0.24		28 ± 24		29 ± 14	

Table 4
The mean number of iterations and optimization time for Group 1 FIP plans in various subgroups: Improved PCI (Δ PCI $>$ 0.01), Minimal Change PCI (Δ PCI $=\pm$ 0.01), Worsened PCI (ΔPCI $<$ 0.01), metastatic lesions, benign lesions, total lesions, no risk constraints, and those with risk constraints.

	Improved PCI	Minimal Change PCI	Decreased PCI	Metastatic lesions	Benign lesions	Total lesions	No Risk Constraints	Risk Constraints
Mean # of Iterations	2.7 ± 1.0	3.4 ± 1.3	3.8 ± 1.1	2.6 ± 1.1	3.8 ± 1.2	3.1 ± 1.2	2.7 ± 1.0	4.3 ± 2.1
Mean Opt Time [min]	4.0 ± 1.9	5.4 ± 2.3	6.5 ± 2.5	4.7 ± 2.6	5.2 ± 1.9	4.9 ± 2.3	4.5 ± 1.2	6.8 ± 2.3

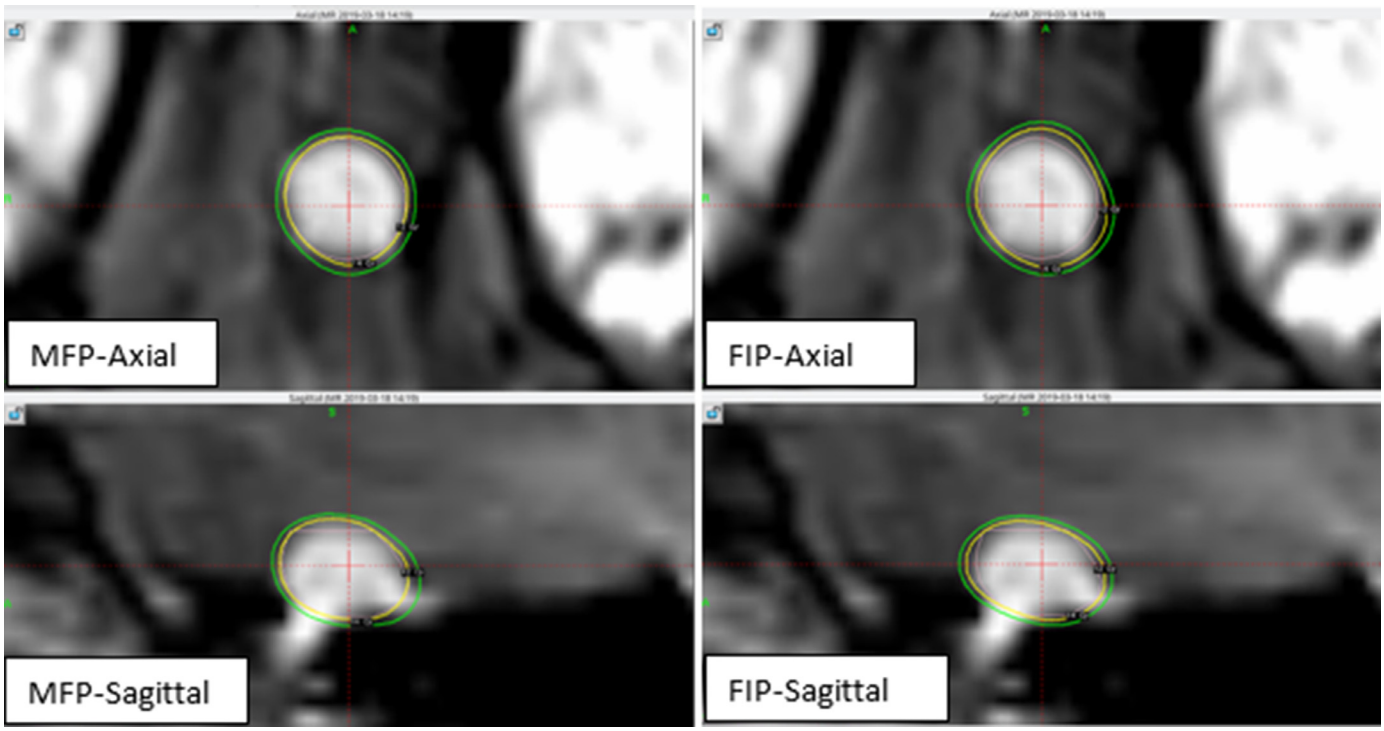

Fig. 1. Axial and sagittal T1-post contrast treatment planning MRIs demonstrating the comparison of the dose distribution of a representative case in the decreased (ΔPCI $<$ 0.01) group. The left column images show the MFP plan with a PCI=0.83, and the right column images show FIP optimized plan with a PCI=0.77. (Color version of figure is available online.)

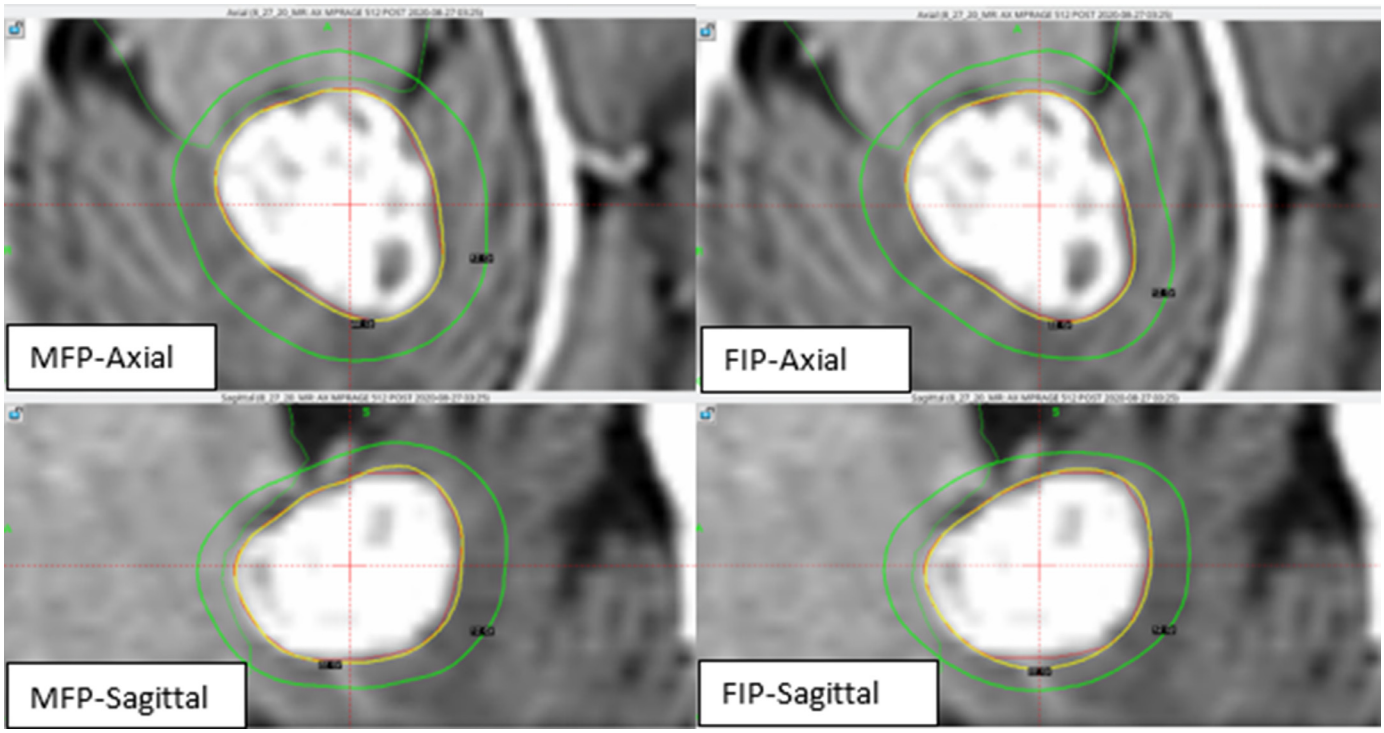

Fig. 2. Axial and sagittal T1-post contrast treatment planning MRIs demonstrating the comparison of the dose distribution of a representative case in the minimal change (ΔPCI = $\pm$0.01) group. The left column images show the MFP plan with a PCI=0.93 and the right column images show FIP optimized plan with a PCI=0.93. (Color version of figure is available online.)

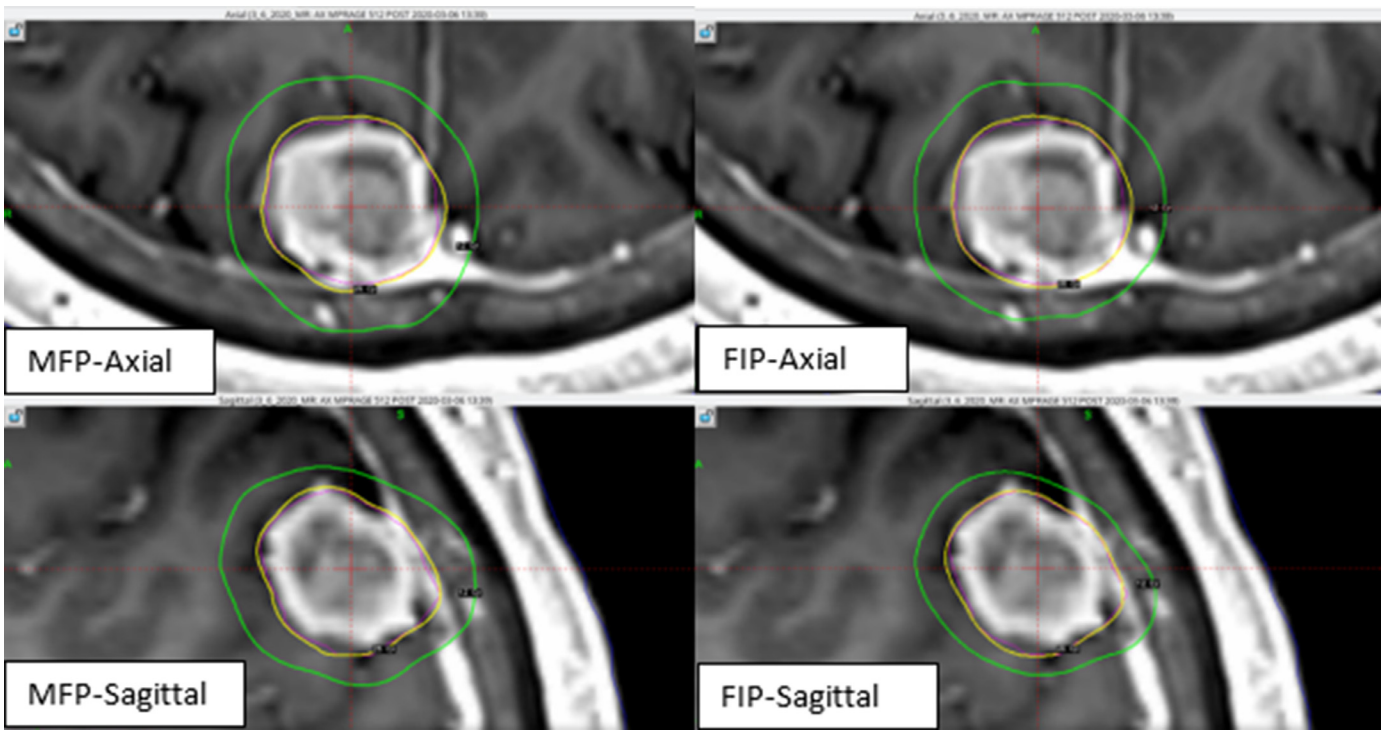

Fig. 3. Axial and sagittal T1-post contrast treatment planning MRIs demonstrating the comparison of the the dose distribution of a representative case in the increased (ΔPCI = >0.01) group. The left column images show the MFP plan with a PCI=0.88 and the right column images show FIP optimized plan with a PCI=0.94. (Color version of figure is available online.)

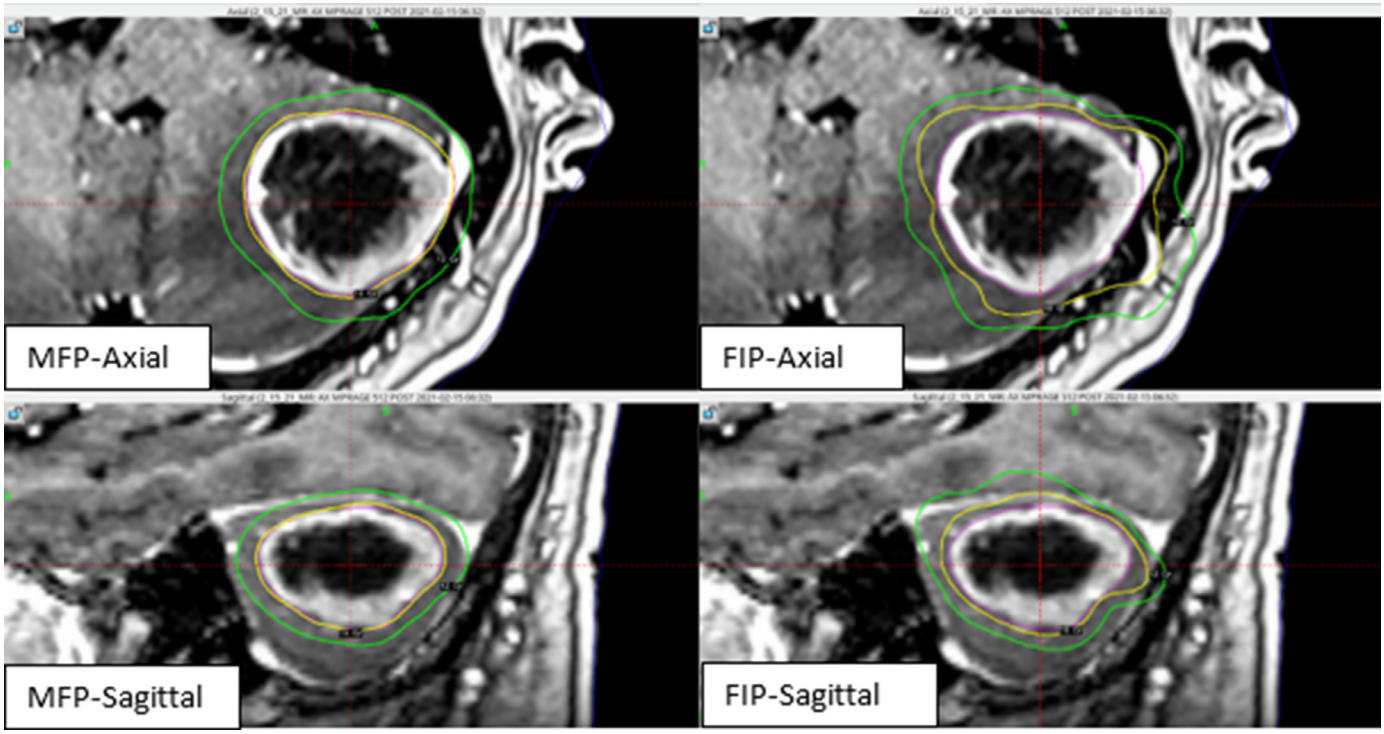

Fig. 4. Axial and sagittal T1-post contrast treatment planning MRIs demonstrating the comparison of the dose distribution of a clinically unacceptable FIP optimized plan with the MFP plan—note the lack of prescription dose conformity. The left column images show the MFP plan with a PCI=0.94 and beam on treatment time of 78.41 minutes. The right column images show the FIP optimized plan with a PCI=0.69 and beam on treatment time of 281.47 minutes. (Color version of figure is available online.)

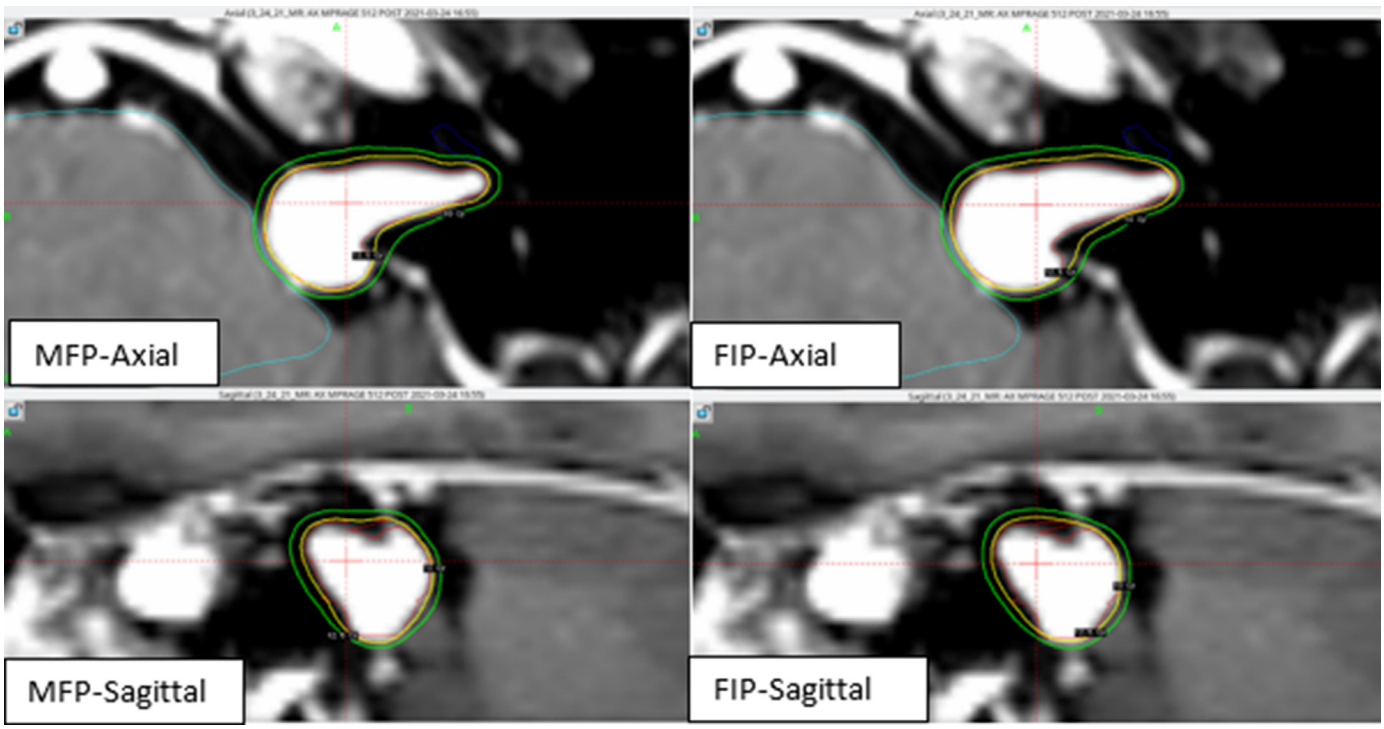

Fig. 5. Axial and sagittal T1-post contrast treatment planning MRIs demonstrating the comparison of MFP plan (left column images) as compared to FIP plan (right column images) for a representative vestibular schwannoma case. MFP shows increased PCI=0.83 as compared to PCI=0.79 for the FIP plan. (Color version of figure is available online.)

Table 5
Comparison of the plan characteristics for the subset of small/punctate Group 2 lesions that produced suboptimal plans in the FIP baseline optimization using the 50/50 optimization setting as compared to the final optimization plan with varying optimization settings. The dose distribution and plan quality metrics of the final optimization plans for these lesions were comparable to the single shot MFP plans

	Baseline Optimization				Final Optimization		
	# of Failed Targets	Opt Setting	Median # of shots	Sector Collimator size	Opt Setting	Median # of shots	Sector Collimator Size
6 Targets	1	50/50	3	16mm-42% 8mm-58%	85/50	1	4mm-100%
14 Targets	1	50/50	2	16mm-44% 8mm-56%	75/40	1	4mm-100%
17 Targets	5	50/50	2	16mm-30.4% 8mm-70.6%	85/40	1	4mm-97.9% Blocked-2.1%
28 Targets	7	50/50	2	16mm-43.3% 8mm-50.9% 4mm-5.8%	85/40	2	8mm-5% 4mm-90% Blocked-5%

Table 6
Comparison of median plan metrics and delivery parameters for manual forward planned (MFP) and fast inverse planning (FIP) optimized plans for Group 2 small lesions (median volume = 0.005cc, Range: 0.002-0.04 cc). Statistically significant improvements in the median PCI and median GI for the FIP plans were noted

	TC (%)		Median PCI		Median GI		Median Beam On Time [mins]		Median # of Shots
Small Lesions	MFP	100	0.36 ± 0.11	$p<0.001$	8.35 ± 3.04	$p<0.001$	11.27 ± 1.74	$p=0.81$	1 ± 0
	FIP	100	0.39 ± 0.11		8.81± 3.93		11.37 ± 1.68		1 ± 1

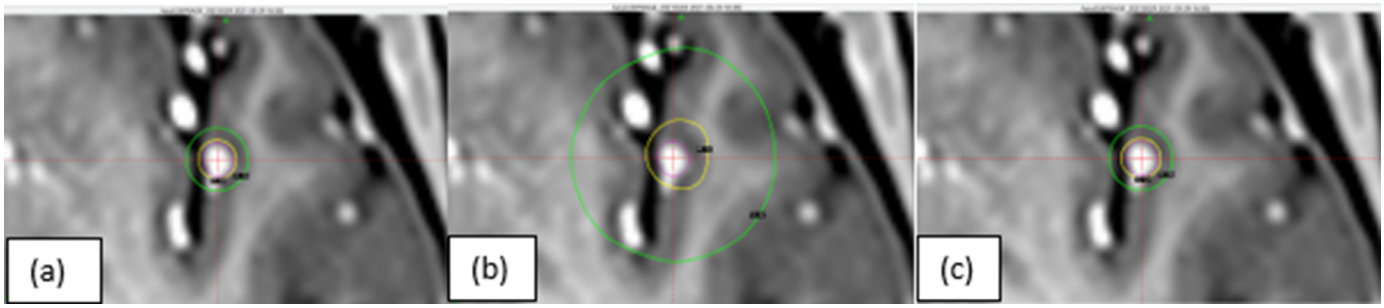

Fig. 6. Axial T1-post contrast treatment planning MRIs demonstrating the dose distributions of a metastatic punctate lesion for the MFP plan (A), FIP plan with default 50/50 optimization setting (B), and FIP plan with 85/40 optimization setting (C). Using appropriate optimization settings, FIP optimizer can generate a plan comparable to MFP plans. (Color version of figure is available online.)

had poor PCI and high GI. Table 6 shows an improvement in median PCI ($p<0.01$) for FIP plans with final optimization settings while the MFP plans demonstrated an improved median GI ($p<0.01$). BOT was comparable between MFP and FIP plans for all punctate lesions.

Delivery parameters

Compared to MFP plans, the FIP plans from Group 1 showed a significant increase in use of 16 mm collimators ($p<0.01$) and blocked sectors ($p<0.01$) and a significant decrease in 4 mm ($p<0.01$) sectors as shown in Figure 7. This decrease in the use of the 4 mm collimator size can lead to the difficulty of achieving higher PCI for highly irregularly shaped targets as explained above in the case of Vesibular Schwannoma and shown in Figure 5. Unlike MFP, where it is unlikely to find multiple shots located on the same coordinate, the FIP optimizer favors using multiple shots on the same coordinate more frequently. Figure 8 shows that FIP had as many as 7 shots in the same coordinate in a single plan.

Planning time for MFP plans were not recorded, due to the retrospective nature of this study, but estimated to vary from 45 to 120 minutes based on clinical experience of the planner. When compared to FIP, optimization time is comparatively reduced with the use of the FIP optimizer. Overall, the optimizer was shown to take an average of 3 iterations with a mean optimization time of 5 minutes for FIP plans (Range: 1.0 – 10.0 min) (Table 4).

Discussion

Gamma Knife® SRS treatment planning historically used an MFP technique, where the plan quality was heavily dependent on planner experience and the planning time available between simulation and treatment. In principle, an ideal plan is efficiently generated and aims to maximize target coverage and selectivity while minimizing GI and BOT. Developing a software solution to accomplish this is challenging as the problem of inverse optimization is essentially non-convex if all available parameters—i.e., shot position, shot collimation, and shot weight—are varied during the optimization phase. The first commercially available inverse planning tool, LGP v5.34, became available in 2000. This software was shown to produce inferior plans relative to expert planners; it often resulted in shot coordinates too far outside the target and failed to limit dose to the adjacent OARs due to limitations in the optimizer[14]. The latter limitation was addressed by the introduction of the gradient index[16] to limit dose outside the target volume, which was added in the LGP v10.0, released in 2010. Although this resulted in a significant improvement over the previous optimizer, manual planning still outperformed inversely optimized plans, especially in plans with multiple target[15]. Inverse optimization tool v11.0.1 was used in combination with manual planning for the lesions optimized using MFP in this study. The objective used in this optimization is based on relative isodose values and hence has two main drawbacks, i.e., (1) the inverse optimizer requires an isodose line to be selected prior to optimization which directly impacts the final optimized solution and (2) optimization using relative isodoses limits the optimization of multiple lesions and constraining maximum dose to adjacent OARs. Furthermore, the optimizer allows for isocenter positions to be varied in the optimizer resulting in a non-convex optimization problem. The new FIP optimizer evaluated in this study is a novel complete inverse optimization planning solution on GammaPlan v.11.3.1, which optimizes collimator configuration and weighting in parallel for a set of well-positioned isocenters[9]. The software solution has been designed to maximize target coverage and selectivity while minimizing BOT, GI, and maximum dose to OARs. The FIP optimizer offers

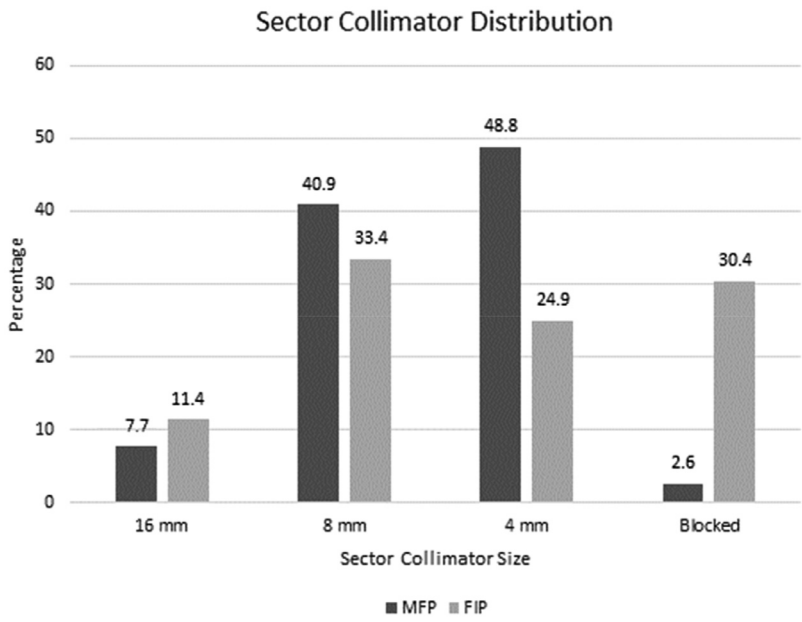

Fig. 7. Distribution frequency of sector collimator sizes and blocking for MFP and FIP plans of all lesions. A significant increase in the use of blocked sectors as well as a decrease in the use of 4 mm sector collimators is noted for FIP plans as compared to MFP. (Color version of figure is available online.)

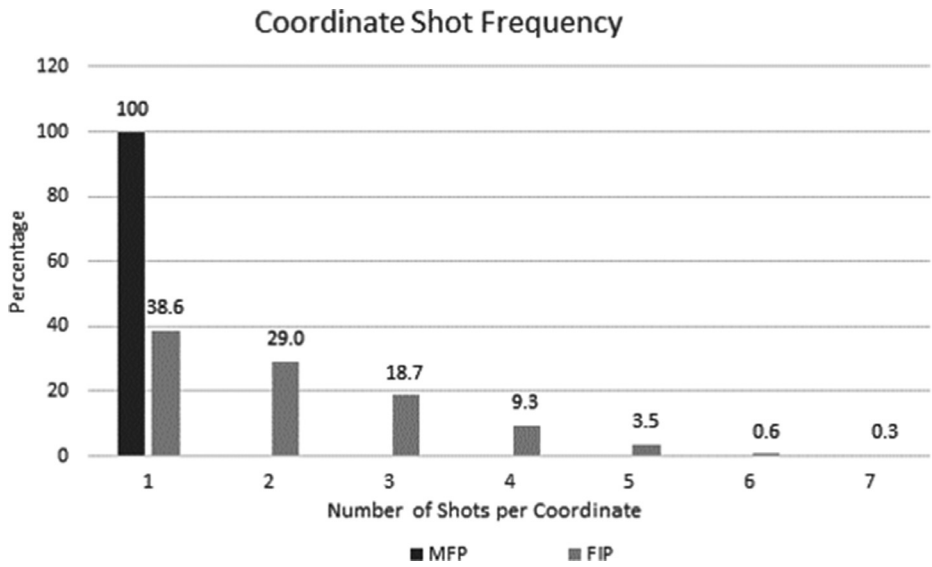

Fig. 8. The frequency of number of shots per coordinate between MFP and FIP plans for all lesions is shown. As noted, a significant increase in the number of shots per coordinate is noted for FIP plans as compared to MFP. (Color version of figure is available online.)

a fast and fully automated way of planning Gamma Knife cases, with minimal user input, for those requiring >99% target coverage. To the authors' knowledge, this is the first manuscript extensively assessing the clinical plan quality metrics of FIP for SRS treatment plans.

In testing the clinical performance of FIP as evaluated in this study, 115 clinically treated lesions were re-optimized to match target coverage metrics with the default optimization weighting setting of 50/50 for Low-dose and BOT penalty. Further improvement was sought to match the target coverage of the FIP plans in 52% of cases. In this study, FIP converged to a solution with a median time of 5 minutes, which significantly shortened the time needed to generate a plan. FIP-generated treatment plans employ a significantly higher number of shots, and many with low shot times, a strategy not typically employed by expert planners. FIP also showed an increased use of a higher number of shot-in-shot isocenter positions. This appears to be driven by the design of the optimizer since the isocenter positions are well distributed and fixed during the optimization process. Because of this, the isocenter positions are recycled/reused to achieve an optimal dose distribution. Furthermore, the sequencing phase following the sector-based optimization results in multiple shots at the same isocenter. Finally, FIP-generated treatment plans employ increased use of the 16 mm collimator compared to MFP plans, which likely derives from efforts to minimize BOT. This increased use of 16 mm collimators, as was observed in the vestibular schwannoma sample case shown in Fig. 5, may result in a clinically inferior plan in select cases.

FIP does not provide an option to select the prescription IDL, however, the optimizer can be driven to not fall below a minmum IDL by providing a maximum dose constraint on the target volume. In the current study, the maximum dose was limited to ensure a prescription IDL $\geq$ 50%. This decision is driven by the precedent that this provides the steepest dose fall-off outside the tar-

get, which is correlated with clinical outcomes. However, previous studies show that dose fall-off is affected by multiple factors, such as %IDL, composite shots, and variable shot-in-shot weighting[17,18]. Additionally, there is little to no evidence of the clinical impact of maximum dose on the efficacy or safety of SRS treatments[19,20]. Without maximum dose to target specified, the prescription IDL is chosen by the optimizer to maximize the gradient index, which was not utilized in the current study.

Overall, the selectivity and gradient indices were significantly improved in 76% of the cases compared to the expertly planned MFP cases. The BOT with FIP is comparable to MFP cases for all the lesions included in the study. In some clinical scenarios similar to the case demonstrated in Fig. 4, FIP failed to converge to a solution and generated clinically inferior plans. Initial investigation by the manufacturer indicates limitations in the algorithm in the case of certain non-punctate lesions, which will be addressed in future releases. PCI was comparable for all subgroups of benign lesions except in the case of AVMs, where the PCI of FIP plans was significantly better than MFP plans. Despite the increased use of 16 mm shots, FIP plans for benign lesions showed an improvement in GI ($p<0.05$) relative to MFP plans overall. In the case of multiple non-punctate lesions, it was noted that multiple iterations of optimization was required for improved gradient index especially for the lesions in close proximity to each other. Furthermore, it was noted that the BOT for individual optimization was markedly longer than BOT for simultaneous optimization of multiple non-punctate lesions. This warrants further investigation of the optimizer and is outside the scope of this study.

For multiple punctate lesions, using the default optimizer setting of 50/50 may result in suboptimal plans due to increased use of multiple shots with 8 mm and 16 mm sector collimation. However, using an increased low-dose penalty setting of 65-85/40 results in a plan comparable to a plan with a single 4 mm shot. Multiple iterations of optimization may be required for convergence of all lesions while excluding targets that have reached clinical goals in subsequent iterations. Due to the retrospective nature of this study, the time required for optimization of MFP was not recorded and is a limitation of this study. However, planning time using FIP is estimated to be substantially lower while achieving similar/higher plan quality metrics. Although FIP can produce plans with similar or better plan quality metrics as compared to MFP with default optimization settings, complex plans in the setting of multiple lesions or adjacent OARs would still need an expert planner to assess plan deliverability metrics and optimize planning parameters to achieve an optimal solution.

Conclusion

The goal of this study was to clinically assess the use of the recently released FIP optimizer by comparing plan quality and delivery parameters for 115 non-punctate and 65 punctate lesions manually planned by an experienced Gamma Knife planner. FIP was shown to generate a high-quality treatment plan with comparable or better plan quality metrics as compared to an MFP plan by an expert planner. Implementation of FIP may substantially improve overall planning efficiency in an SRS practice. In particular, FIP plans were observed to employ a non-intuitive increased use of 16 mm collimation, blocked sector collimation, and shot-in-shot technique to achieve high quality metrics and reduce BOT. FIP failed to achieve an inversely optimized solution in 3.5% of the plans in this study.

Declaration of interests

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M.P. Mehta: Consulting for Karyopharm, Tocagen, Astra-Zeneca, Blue Earth Diagnostics, Celgene, Abbvie. Board of Directors: Onco-ceutics.

M.C. Tom: Research funding from Blue Earth Diagnostics

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None

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