ulti-institutional dosimetric delivery assessment of intracranial stereotactic radiosurgery on different treatment platforms

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Radiotherapy and Oncology

Multi-institutional dosimetric delivery assessment of intracranial stereotactic radiosurgery on different treatment platforms

--Manuscript Draft--

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Abstract:	<p>Background and Purpose: Assessment of dosimetric accuracy of radiosurgery on different treatment platforms.</p> <p>Material and Methods: Thirty-three single fraction treatment plans were assessed at thirty centres using an anthropomorphic head phantom with target and brainstem structures. The target being a single irregular shaped target, ~8cc, 10 mm from the brainstem. The phantom was “immobilised”, scanned, planned and treated following the local protocols. EBT-XD films and alanine pellets were used to measure absolute dose, inside both the target and the brainstem, and compared with TPS predicted dose distributions.</p> <p>Results: PTV alanine measurements from gantry-based linacs showed a median percentage difference to the TPS of 0.65%. Cyberknife (CK) had the highest median difference of 2.3% in comparison to the other platforms. Gamma Knife (GK) showed the smallest median of 0.3%. Similar trends were observed in the OAR with alanine measurements showing median percentage differences of 1.1%, 2.0% and 0.4%, for gantry-based linacs, CK and GK respectively. All platforms showed comparable gamma passing rates between axial and sagittal films.</p> <p>Conclusions: This comparison has highlighted the dosimetric variation between measured and TPS calculated dose for each delivery platform. The results suggest that clinically acceptable agreement with the predicted dose distributions is achievable by all treatment delivery systems.</p>

Covering Letter

Dear editor,

This is a resubmission of manuscript RO-D-18-00727 that was previously rejected with major corrections.

We previously received very good comments from all four reviewers on the importance of this work. We believe that with the revisions done, we have addressed the comments of the reviewers and this is now a unique study which addresses a gap in the literature and will generate several citations in the future.

We look forward to receiving your feedback.

Best Regards,

Alexis Dimitriadis

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Highlights:

- A multi-institutional end-to-end assessment of radiosurgery dosimetric delivery was performed for 33 plans in 30 participating centres using a variety of treatment platforms.
- The comparison has highlighted the dosimetric consistency achievable with different delivery platforms.
- The need for standardisation in intracranial stereotactic radiosurgery is highlighted.

Dear Editor,

We would like to thank the reviewers for their detailed and comprehensive reviews. We believe that in addressing the reviewers' concerns we have further improved the paper and hope that it is now suitable for publication.

Reviewer #1: The manuscript is concerned with a dosimetric intercomparison of stereotactic intracranial radiotherapy in UK with particular emphasis on the performance of different technologies. As these procedures are becoming more popular this is a relevant topic of interest to readers of the Green Journal.

Response: We thank the reviewer for this comment and agree that this is a relevant topic of interest to readers of the Green Journal.

It would be important to clarify if cones, tertiary microMLCs or other accessories were used for the linac based deliveries. I also do not think tomotherapy with a fixed ring gantry and no non-coplanar deliveries should be combined in with other linac based deliveries.

Response: The grouping of the technological platforms has been based upon their broadly similar dosimetric and clinical practices (ref 6) and this justification has now been emphasised within the manuscript and reference made to the use of cones, tertiary microMLCs etc.

Maybe it would also be worthwhile to directly compare FFF and flattened delivery systems directly.

Was an attempt made to correlate different metrics from individual centres (eg is a centre that has difficulties getting high gammas in the film comparison also a larger chance to have a larger alanine output measurement difference?

Response: No attempt has been made within this study to directly compare FFF and flattened delivery systems directly. Each centre received a full dosimetric report of their output measurement difference and gamma analysis of their film comparison but no correlation between these parameters has been performed.

It should also be checked if the figures and table are correctly labeled as they refer to 33 centres while the manuscript refers to 30 centres with 33 treatment platforms. As there may be some common features even of different technologies in a single centre it would be better to show which centres utilize more than one technology (unless this would identify the centres in an UK setting but this may already be possible also from other technical details, eg only one tomotherapy unit).

Response: Centres has been replaced by "platform number" in the respective tables and figures. To avoid identifying individual centres those centres which utilise more than one technology have not been identified.

Specific comments:

Highlights: the third highlight appears to be a bit optimistic - would 'centre' 16's

Response: The third highlight has been deleted

Abstract: It would be more informative if range of difference was given as - ... + ... instead of a single number.

Response: the reporting of ranges has been deleted in the abstract

Line 147: please provide manufacturer and location for QAPro.

Response: These details (Ashland ISP Advanced Materials, NJ, USA) are within the text

Line 163: maybe add AAPM to TG

Response: AAPM has been added.

Results, para1: Given the fact that the number of tests for different pieces of equipment was different, the 'spread' is not necessarily a meaningful quantity to compare as more measurements are likely to create a greater spread even if the standard deviation is identical.

Response: the reporting of ranges within each subgroup has been maintained as this provides information on the consistency in dosimetry between centres using these platforms, however the comparison of the range between different subgroups has been deleted.

Line 250: also tomotherapy has single energy

Response: the text has been changed to acknowledge this

Table 1: As the authors rightly point out the prescription details are one of the more interesting features of the manuscript. One of the last two columns could be omitted though as they show identical information.

Response: the last column has been deleted.

Figures: while there is an attempt made to use the same symbols throughout, the formatting of figures 3, 4, 5 and A2 could be more uniform (aspect ratio, location of legend)

Response: the formatting has been edited to create a more uniform appearance.

Reviewer #2: I have previously reviewed this work back in 2018 and found a major revision necessary before publication of the manuscript. After re-reading the work now and my initial review and criticism I find that all points previously raised have been well addressed such that I can now vote this important work for publication as is. I have no major or minor comments left, but, at the authors discretion, to add some more results detailed (e.g., on the film evaluation) in the abstract.

Response: we would like to thank the reviewer for recommending this "important work" for publication.

Reviewer #3: The authors have addressed most of the reviewer's comments from the previous version. The statistical analysis has been performed and this has clearly improved the soundness of the discussion section.

Response: We would like to thank the reviewer for his comments on the improved soundness of the discussion section.

However there are still minor issues that would merit some consideration:

Why didn't the auditors perform a reference dose measurement using alanine pellets?

Response: the reference dose was measured according to the appropriate dosimetry code of practice using the ionisation chamber recommended there. However, alanine were employed to measure absolute dose in the target and brainstem.

It would be of interest to know how many institutions using gantry based linacs used, VMAT arcs or 3DCRT (coplanar or non coplanar)

Response: This information is given in Table 1.

L68 I would suggest to use "assess" instead of "determine"

Response: The wording has been changed as suggested

L98 the collimation systems should be added to table 1. If too busy, it should, at least, be mentioned that CK used cones and not iris collimator.

Response: it has been mentioned that CK used cones.

L111 Was the geometric phantom "water" or was it forced to match the phantom material?

Response: The geometric phantom was water equivalent. This has been clarified in the text

L117 Could you state the dimensions of the alanine pellets?

Response: The pellets were discs each of 5mm diameter and 2.5mm thickness. This has been added to the text.

L144 State that the films were placed inside the phantom

Response: This wording has been added

L177 As in last version, this sentence is confusing. Did the centres performed reference output measurements? There is a need for clarification. Although in methods is not said figure 2 clearly states that measurements are performed by the centres. If so the used detector could be of interest to the readers and also could be used for the discussion on discrepancies.

Response: This sentence has been clarified to read "Reference output measurements were performed independently by both the host centre and the auditors using their respective equipment and these are presented in Figure 3." No analysis has been made based on the host centres' detectors

L197 Does this apply for all platforms, please state.

Response: This has been reworded as: "Individual pellet measurements in the target showed differences of up to 14.1%, 4.2 and 5.9% (for GK, CK, linac respectively) when compared to the TPS-predicted mean dose in their individual contoured pellet structure."

L255 I don't see any problem for gantry based linacs where the reference field is 10x10 cm². Even by using FFF the KQ,Q0 factors in TRS483 correct for this averaging.

Response: This work predates the publication of TRS-483 and was not taken into account at the time the study was conducted.

L274 Not in the accuracy of the delivery but in the dose calculation accuracy.

Response: This has been corrected.

L333 Shouldn't conclusion start here?

Response: The conclusion has been started at this point.

L351 "approach"?

Response: This has been corrected

L379 Although I fully agree, I still don't know how this is demonstrated by your study.

Response: This sentence has been rephrased to read "Future multicentre SRS studies may benefit from some standardisation and consensus of practice."

Reviewer #4: I have major concerns about the way the results have been presented (also relevant to discussion, conclusion, etc). The data is being evaluated as if it was a single-variable dataset with variations attributed solely to the delivery platform. I.e., delivery is from a gammaknife, a cyberknife, or linac-based system (which includes tomotherapy). This ignores the other variables and confounders that exist in the dataset. A large one is the dose calculation platform and algorithm, of which there are numerous - it seems probable to me that this has a bigger impact on the dose accuracy (and range of accuracy) than the delivery platform, but it is essentially ignored in the analysis. I would also expect the immobilization to play a role - dose gradients are steep enough that misalignments will impact the dose agreement with the TPS. Although this issue is raised briefly in the discussion, I think the issue is bigger - the results are not reasonable to presented because the groups are not really groups as they have been lumped by a single common parameter.

Response: Dosimetry intercomparisons have an acknowledged part to play in confirming the consistency in dose delivery for advanced radiotherapy treatments. This is the first reported study investigating intracranial stereotactic radiosurgery and is therefore a valuable addition to the literature. In the sense that all centres were delivering intracranial stereotactic radiosurgery this is a single dataset. The methodologies for grouping within that dataset are multiple. However, for the results to be presented in a meaningful manner it is important that the subsets within this single dataset are grouped such as to enable adequate numbers to enable some statistical calculation of significance. The justification for the groupings considered has been emphasised within the text. It is acknowledged that this audit has come from a wide range of delivery and ancillary systems, however it has the potential to benchmark what can be achieved with intracranial stereotactic surgery systems and therefore contribute data for use in setting tolerances for clinical trials and external audits.

Ln 181-186. If there weren't any statistical differences, then you can't say that the linac group had the largest spread or that the GK had the smallest spread. This is the whole point of statistical analysis and the implications of the results. Although I'm also concerned because your description is focused substantially on which platform has the largest range of values, but your methods only talks about a Kruskal-Wallis test (and associated post hoc analysis) which is not appropriate for comparing ranges or variances, only means. You need a Levene test of Variance or something like that to evaluate the relative spreads.

Response: the reporting of ranges within each subgroup has been maintained as this provides information on the consistency in dosimetry between centres using these platforms, however the comparison of the range between different subgroups has been deleted.

Ln 191-194. Similar problem. The spread for linacs is qualified as being "larger". There is not evaluation to support this. You have observational data here (for the ranges) and no qualification is appropriate without actual evaluation. Simply state that the range was "X", or, better yet, actually evaluate the data to see if there is a difference.

Ultimately, compared to the number of variables that you have in play here, you really have 33 distinct anecdotes rather than data in groups that can be compared. I think there is still substantial value in what was found, but I do not think you can draw the results and conclusions, as presented, are valid.

Response: As in the previous reply the reporting of ranges within each subgroup has been maintained as this provides information on the consistency in dosimetry between centres using these platforms, however the comparison of the range between different subgroups has been deleted.

Minor

Ln 124. I do not understand how comparing the mean TPS and alanine doses allowed you to account for positional uncertainties. Are you implying that you excluded specific results if they didn't agree but the mean did?

Response: Small positional errors in set up of the alanine pellets can result in large differences between measured and calculate dose in areas of large dose gradients. By employing mean doses this takes the dose over a larger area and so effectively smooths out any positional errors. No specific results were excluded.

Ln 126. I can't figure out how you "normalize" a percent difference. Please clarify.

Response: this may be explained as follows:

$$[(DOSE_alanine/12Gy)-(DOSE_tps/12Gy)]*100\%$$

Ln 154. The optimum shift algorithm is relevant for small shifts. This indicates a different approach was used to align to high precision to begin with (at least within 1mm). What was this initial alignment method?

Response: An additional explanation has been added to the text stating:

"The measured dose distributions were matched to TPS dose distributions by aligning the fiducial marker holes in the film with known coordinates in the TPS dose planes and then using the optimum shift algorithm, where small shifts were applied (<1mm and <1°) to optimise the gamma passing rate".

159 "the criteria selected were based on their clinical significance". Yet the authors used 3%/2mm because its common, 2%/2mm because of TG-135, and then include 5%/1mm as being more suitable. None of these appear to be based on clinical significance. Please provide relevant citations indicating the clinical impact in SRS of these (and for 5%/1mm being more suitable), or more easily, just state that you "selected the following criteria for evaluation....."

Response: As suggested we have now stated that the criteria were selected as follows

170 "Kruskai" should be "Kruskal"

Response: This has been corrected

Supplemental figure 1. I don't think this is necessary.

Response: As a supplementary figure we are happy for this to be deleted and leave the final decision with the editor.

Ln 132. "passing rates improved significantly". Please provide magnitude and associated p values (or at least max p value over the cohort).

Response: This has been rephrased to: "passing rates improved substantially".

Ln 245. Why would a smaller number of centres lead to more consistent outputs?

Response: this has been deleted

Ln 308-310. I would think that the steeper gradient of the GK (and to a lesser extent the GK) would be an important factor in elevating the gamma pass rate because dose criteria would be easiest to meet under conditions of steeper gradients.

Response: This sentence has been reworded to emphasise the impact of the steeper GK dose gradients.

Ln 333-366 consider shortening or removing as they are not incorrect, but the first two paragraphs feel substantially unnecessary, the third is dramatically away from the findings of the current study.

Response: The first and second paragraphs have been shortened to clarify and the third paragraph has been removed. The concluding sentence has been rephrased to better reflect the findings of the study.

Short title: Multi-institutional audit of dosimetric delivery in radiosurgery

Title: Multi-institutional dosimetric delivery assessment of intracranial stereotactic radiosurgery on different treatment platforms

Keywords: Radiosurgery, Dosimetry, End-to-end, Audit, Anthropomorphic Phantom, Alanine, Radiochromic film

Highlights:

- A multi-institutional end-to-end assessment of radiosurgery dosimetric delivery was performed for 33 plans in 30 participating centres using a variety of treatment platforms.
- The comparison has highlighted the dosimetric ~~variation~~ consistency achievable between with different delivery platforms. ~~The gantry-based linac group showed the greatest dose variation, compared to CK, and GK.~~
- ~~The results showed clinically acceptable accuracy for all participants and illustrate the variation in the dosimetric accuracy achieved by various treatment platforms.~~
- The need for standardisation in intracranial stereotactic radiosurgery is highlighted.

Abstract:

Background and Purpose:

Assessment of dosimetric accuracy of radiosurgery on different treatment platforms.

Material and Methods:

Thirty-three single fraction treatment plans were assessed at thirty centres using an anthropomorphic head phantom with target and brainstem structures. The target being a single irregular shaped target, ~8cc, 10 mm from the brainstem. The phantom was “immobilised”, scanned, planned and treated following the local protocols. EBT-XD films and alanine pellets were used to measure absolute dose, inside both the target and the brainstem, and compared with TPS predicted dose distributions.

Results:

PTV alanine measurements from gantry-based linacs showed ~~the largest range in a~~ median percentage difference to the TPS of ~~5.2% (median=0.65%)~~. Cyberknife (CK) had ~~a range of 2.6% with~~ the highest median difference ~~of (2.3%)~~ in comparison to the other platforms. GammaKnife (GK) showed the smallest ~~range and~~ median of ~~2.4% and 0.3% respectively~~. Similar trends were observed in the OAR with alanine measurements showing ~~ranges and~~ median percentage differences of ~~4.6% and 1.2%, 1.9% and 1.1%, 2.0% and 0.4%~~, for gantry-based linacs, CK and GK respectively. All platforms showed comparable gamma passing rates between axial and sagittal films.

Conclusions:

This comparison has highlighted the dosimetric variation between measured and TPS calculated dose for each delivery platforms, ~~with the gantry-based linac group showing the greatest dose variation, compared to CK, and GK.~~ However, the

results suggest that clinically acceptable agreement with the predicted dose distributions is achievable by all modality treatment delivery systems.

1. Introduction

Stereotactic radiosurgery (SRS), was first developed in the 1950s [1] and has since evolved substantially. There are now several manufacturers that offer commercial solutions for delivering SRS and such treatments may be delivered by ~~either a~~ Gamma Knife (GK) unit, a CyberKnife (CK) or a gantry-based linear accelerator (linac) system with stereotactic capabilities.

All radiotherapy practices should be subjected to appropriate quality assurance procedures, including regular quality control testing and independent external dosimetry audit [2,3], to minimize potential errors in treatment delivery that can lead to clinical complications [4]. This is especially the case for SRS where a very high dose is delivered in only a single fraction, meaning an error cannot be mitigated in a subsequent fraction.

The multiple platforms which can be used for SRS are very different in terms of their technologies and techniques [5]. Furthermore, they have been, and are being, used very differently in terms of their dosimetric and clinical practices [6]. The categorisation of the various systems into Gamma Knife (GK) units, CyberKnife (CK) units or gantry-based linear accelerator (linac) systems with stereotactic capabilities is justified according to their broadly similar dosimetric and clinical practices [6]. The latter category includes systems which use cones or tertiary microMLCs and also includes Tomotherapy units, which use a fixed ring gantry and have no non-coplanar delivery capability.

This national study was undertaken to support an initiative in the UK to regulate the provision of cranial SRS services [7–9]. The participating centres were audited in an end-to-end test, incorporating local clinical procedures for immobilisation devices, CT-scanning, target contouring, treatment planning and treatment delivery. We evaluated the agreement between planned and delivered dose for each of the

audited systems. It is acknowledged that the audited systems cover a wide range of delivery and ancillary systems, however such a study has the potential to benchmark what can be achieved with intracranial stereotactic surgery systems and therefore contribute data for use in setting tolerances for clinical trials and future external audits. Furthermore, the variations in clinical practice observed between these different platforms have been evaluated to ~~determine~~assess the need for standardisation.

2. Materials and Methods

A comprehensive end-to-end test was developed based on an anthropomorphic head phantom, STEEV (Stereotactic End-to-End Verification, CIRS, Norfolk, VI, USA). The phantom was adapted to contain a single irregularly shaped target (~8cc), 10mm anterior to the brainstem, for treatment by the audited centre following their local protocol for brain metastasis to be treated in a single fraction [10]. A Computed Tomography (CT) scan of the phantom was sent in advance to the participating centres in DICOM format for volume contouring and pre-planning. This was followed by a visit to the centre where the phantom was scanned following the local protocol (CT only), with eight dummy alanine pellets and two dummy pieces of EBT-XD Gafchromic film (Ashland ISP Advanced Materials, NJ, USA) placed inside the phantom to mimic the detector positions. These were subsequently replaced with the real detectors prior to phantom treatment irradiation. A graphical representation showing the target (PTV), brainstem (OAR) and detector positions is included in Figure 1. The two CT scans were co-registered, and the pre-plan transferred to the local scan and finalised.

Thirty centres participated in the audit. In three centres two treatment platforms were assessed and hence thirty-three single fraction treatment plans were generated and delivered to the phantom. Table 1 provides details for each platform and plan that participated in the audit. Further details of the auditing protocol followed are given in Figure 2.

2.1. Reference beam output measurements

A calibrated PTW 31010 semiflex ionisation chamber (0.125cc), traceable to a graphite calorimeter primary standard at the National Physical Laboratory (NPL, Teddington, UK) was used in all centres to perform reference beam output measurements. The chamber was placed in an auditor provided water-equivalent plastic material, using the centre's reference conditions, to measure the output in the machine specific reference field [11]. All such auditor measurements were corrected for temperature and pressure. Temperature and pressure were measured using independent auditor equipment. The measurements were performed in machine-specific reference conditions and deviations from agreement were expressed relative to the TPS-calculated value for dose in a geometric [water equivalent](#) phantom.

The reference beam output measurements were used to apply corrections to the alanine measurements of the clinical plan, to compensate for any daily output variation.

2.2. Alanine measurements

Two sets of four alanine pellets, [each a disc of 5mm diameter and 2.5mm thickness](#), were irradiated in each centre: one in the target and one in the brainstem. The phantom temperature before and after each measurement was recorded and used to apply a temperature correction factor. All pellets were returned to NPL and were processed within [one4](#) month of the audit visit, ensuring negligible fading [12]. The measured doses were compared to the mean dose calculated by the TPS for each pellet. Additionally, in order to account for positional uncertainties that can lead to large percentage differences between measured and predicted doses, mean doses for each pellet stack were compared with the TPS prediction for the complete stack.

The percentage difference between alanine and TPS for the OAR was normalised to the 12 Gy dose level, being the nominal brainstem tolerance dose used by many

centres. This enabled a dosimetric comparison whilst assessing the plan quality in terms of overdose to the OAR.

Uncertainty on the alanine readout was taken to be 1.4% ($k=2$) [12]. The deviations from agreement were expressed relative to the TPS-calculated value.

Alanine was considered as the primary detector for the audit measurements, as it has proven its efficacy in small fields and is provided by an established dosimetry service based at NPL [12].

2.3. Film measurements

The film response was calibrated in a conventional manner with ten EBT-XD film pieces exposed in the range of 0-40 Gy. The films were irradiated in a 10 cm × 10 cm field at 5 cm depth in water-equivalent plastic, with a nominal 6 MV beam. The scanned pixel value as a function of dose was determined as the average pixel value in a 4 × 4 cm region centred on the beam axis. Images were converted to dose maps using FilmQAPro® software (Ashland ISP Advanced Materials, NJ, USA) using the red-green-blue triple-channel dosimetry algorithm [13].

Two films (one sagittal and one axial) were placed inside the phantom and simultaneously irradiated at each centre. All films were returned to NPL and scanned at least 72 hours after exposure following an established film dosimetry protocol [14,15] and good film dosimetry practice [16,17] with the analysis performed on FilmQAPro. Film-dose linear scaling was applied using reference films at zero dose and 80% of the maximum anticipated dose from the treatment plan, which were scanned simultaneously with the test films. This approach mitigates the effects of post-exposure darkening and variations of the scanner response, and stabilizes the calibration (forced into agreement) at the reference dose levels [18]. The regions of interest used for the analysis were a 6 x 5 cm rectangle for the axial films and a 7 x 4 cm rectangle for the sagittal films. The measured dose distributions were matched to TPS dose distributions by aligning the fiducial marker holes in the film with known coordinates in the TPS dose planes and then using the optimum shift algorithm, where small shifts were applied (<1mm and <1°) to optimise the gamma passing rate. was achieved.

Gamma passing rates [19] were collected for a range of criteria (global and local) using the red colour channel with triple-channel-correction and with film-dose linear scaling corrections applied. The criteria selected were based ~~on their clinical significance for radiosurgery and the typical dose gradients observed~~ on the following:- Data for 3% dose difference and 2mm distance (3%/2mm) were collected as this criterion was commonly used by the participating linac users and 5%/1mm as ~~it this is~~ more suitable for plans with steep gradients. Data for 2%/2mm was also analysed as recommended by AAPM TG 135 [20]. A minimum cut-off threshold of 2 Gy was applied to remove low dose areas of higher uncertainty from the analysis. This absolute value was used as an alternative to a relative value, due to the large variation of prescription doses and maximum doses delivered by the audit participants.

2.4 Statistical analysis

A Kruskal-Wallis test was performed to detect ~~if there were~~ any significant differences in median values between the three platforms, followed by the Bonferroni-type multiple comparison to establish the hierarchy/significant differences between different pairs.

3. Results

~~The R~~reference output measurements were performed independently by both the host centres and the auditors using their respective equipment and these are presented in Figure 3. All measurements from the auditors and the centres were within $\pm 2.4\%$ of the dose calculated by the TPS, ranging from -1.0% to +2.4%. The mean difference between auditor measurement and host centre measurement (audit/host) was +0.5%, with a maximum difference of +1.2%. The gantry based linac group ~~had the largest~~ spread in the output measurements ~~of was~~ 3.2%, ranging from -0.8% to +2.4%, with a median of 0.35%. CKs had a ~~smaller~~ spread of, 1.8%, ranging from -1.0% to +0.8%, with a median of 0.85% and GKs had ~~the smallest a~~ of spread, 1.6%, ranging from -0.9% to +0.7%, with a median of 0.0%. No statistical differences were seen between the platforms.

The differences between the measured and calculated (measured/calculated) doses for the stack of 4 alanine pellets ranged from -1.3% to +4.0% for the PTV (Figure 4A). The gantry based linacs showed ~~the largest~~ spread in percentage difference of 5.2% (from -1.3% to +3.9%) with a median of 0.65%. GKs showed ~~the smallest~~ spread ~~at~~ of 2.4% (from -0.8% to +1.5%), with ~~the smallest~~ median percentage difference of (+0.3%). CK measurements had a spread of 2.6% (from +1.4% to +4%), with ~~the highest~~ median ~~in comparison to the other platforms of~~ (+2.3%), which in comparison with the gantry based linac and GK groups were statistically higher with p values of 0.045 and 0.039 respectively. Individual pellet measurements in the target showed differences of up to 14.1%, 4.2% and 5.9% (for GK, CK and linac respectively) when compared to the TPS-predicted mean dose in their individual contoured pellet structure.

Similar trends were observed in the comparison of OAR alanine pellet measurements to those observed in target alanine pellet measurements, ranging from -1.1% to +4.3% (Figure 4B). Gantry-based linac measurements showed ~~the largest~~ spread at 4.6% ranging from -1% to +3.6% with a median of +1.2%. CK measurements ranged between 0.0% to +1.9% with a median of +1.1%. GKs had a ~~similar spread to CKs of~~ ~~(2.0%)~~ ranging from -1.1% to +0.9% ~~but with a lower and a~~ median of +0.4%. Here the only significance was in the gantry-based linac group being higher than the GK group with a p value of 0.047.

TPS-predicted doses for the alanine pellets in the OAR ranged from 0.3 Gy up to 7.5 Gy. Figure 4 shows the percentage difference between the mean dose measured by OAR alanine pellets with the TPS-predicted mean dose, normalised to 12.0 Gy.

The results for axial and sagittal films (example shown in Supplementary Figure 1) showed consistency in the gamma passing rates achieved. The gamma passing rates for 3% / 2mm local gamma and 5% / 1mm global gamma are shown in Figure 5.

Higher passing rates for all films were observed for global than for local gamma criteria. For the 3% / 2 mm local gamma criterion, all but two films showed passing

rates above 75%. The CK, GK and gantry-based linac groups had median passing rates of 88.7, 92.8 and 85.5 respectively, showing no statistical differences between them. For the 5% / 1 mm global gamma criterion, all but 3 films showed passing rates above 90% (see Figure 5). Here the CK, GK and gantry-based linac groups had median passing rates of 99.3, 98.4, 98.3 respectively, again showing no statistical differences between them. For the 2% / 2 mm global gamma criterion, all but 3 films showed passing rates above 90% (see Supplementary Figure 2). Here the CK, GK and gantry-based linac groups had median passing rates of 99.3, 99.0, 96.6 respectively, with a p value of 0.028 between the GK and the gantry-based linac groups, all other comparisons being non-significant.

When the regions of interest used for the gamma analysis were reduced to smaller areas to include the target region only, passing rates improved substantially for all centres, showing very good agreement (>95%) between TPS-predicted and delivered dose distributions. The majority of failed pixels for all films analysed were found to be outside the target, between the 2 Gy (threshold level) and the 12 Gy isodose line.

4. Discussion

The reference output measurements performed in the standard conditions for each platform at all centres were within $\pm 2.4\%$ of the expected dose, well within the $\pm 3\%$ recommendation of IPEM report 81 [21]. Moreover, the results seen in this study are consistent with the results reported by the NPL over 20 years of reference audits [22]. The differences from expected dose seen in the GK and CK groups were comparable, and much smaller than those seen in gantry-based linacs. This could be related to ~~the smaller number of centres in these groups in comparison to the larger gantry-based linac group, but also due to~~ these platforms having more predictable output in reference conditions, due to having a simpler more straight forward design. The ^{60}Co sources in the GK have a predictable decay, which is reflected in the good agreement seen in these measurements and the tighter tolerances of 1.0 - 1.5% deviation used by GK centres. The compact single energy linear accelerator of the CK may be the reason for the reduced fluctuations observed in output measurements, compared to

multi-energy and multi-modality conventional gantry-based linacs which comprise the majority of units within this category. The systematic difference between the auditor and the centres (+0.5%) may be partly explained by the instruments used. While the auditors used a 0.125cc ionisation chamber for all measurements, the centres used a range of different detectors, which in most cases had a larger sensitive volume. Therefore, a small degree of volume averaging can be attributed to the difference observed, especially since 15 out of 33 participating platforms used Flattening Filter Free (FFF) type beams. However, further investigation-measurements needs to be performed to fully explain this difference.

Overall, good agreement was observed between alanine and TPS, with three centres falling outside (greater than) two standard deviations of the mean (two centres in the target dose measurements and one in the OAR measurements). Although there were some statistical differences between the groups these had p values which were only just less than 0.05 and were not consistent across the measurement methods and PTV/OAR, hence no strong statistical conclusions can be drawn about each platform. The gantry-based linac group was seen to have the largest spread in percentage differences compared to CK and GK, but with a relatively good overall agreement to with the TPS. The reasons behind this spread are most likely attributed to the diversity of techniques, platforms, beam energies, TPSs, calculation algorithms, clinician preferences and influences from the local radiotherapy practices. In comparison, the CK and GK groups had almost identical settings and practices within their subgroups. It is also possible that the variations in the commissioning methodologies used for gantry-based linacs, especially with regards to the dosimeters used for the measurement of small radiation fields, has an impact on the accuracy of deliverydose calculation. Although numerous studies have been conducted on appropriate detectors for small field applications [23–28], there has been a lack of international guidelines until the recently published IAEA TRS 483 [29]. It is expected that these new guidelines will improve the standardisation of commissioning methodologies.

CK measurements in the target, showed that the TPS with Raytracing calculation algorithm under-estimated the dose in all four centres visited. This finding is in agreement with another study utilising the same alanine service for target dose measurements in CK plans [30].

All GK centres used a TMR10 algorithm that does not account for density inhomogeneities and assumes water density within a CT-generated or depth-helmet measured skull contour. A recent study investigating the GK convolution algorithm (employs density corrections) in comparison to the TMR10, showed a 6% difference between the two where 1.5% of this was attributed to depth helmet measurements [31]. Our alanine measurements showed good agreement with the TPS and suggest that these sources of error do not contribute significantly to dosimetric inaccuracies. Further work investigating this convolution algorithm may be required to evaluate its accuracy before it is used clinically.

Alanine measurements in the OAR were performed along a steep dose gradient where [any](#) positional uncertainties may be expressed as large dose differences. Doses to the OAR pellets ranged by up to an order of magnitude, caused by individual planning priorities and protocols used by participating centres. As some centres delivered very low doses to this region the reported doses were normalised to 12 Gy (a nominal brainstem tolerance dose value used by many centres) in order to provide a useful measure of relative accuracy to the centres with different approaches. There was also a higher uncertainty in the lower dose measurements due to lower signal to noise ratios in the alanine readout.

The gamma passing rates showed clinically acceptable agreement between the film-measured dose and the treatment planning system calculated dose distributions for both sagittal and axial films [32]. All treatment modalities showed comparable variations in passing rates between the centres assessed and the passing rates alone do not suggest significant differences between the different platforms. Other studies have suggested that gamma index analysis is non-ideal for direct comparison in multi-institution assessments due to inherent differences in the dose distributions, particularly in dose gradient and maximum doses [32–34]. Local Gamma criteria may favour linac centres in which the dose gradient could be less steep than GK and CK, and Global Gamma criteria may favour GK centres in which the maximum (normalisation) dose is higher [and the dose gradients are steeper](#). Whilst the methodology for film analysis employed in this study was designed to diminish sensitivities to different dose distributions it is impossible to achieve this with gamma index analysis. Gamma passing rates are also sensitive to the position of the film

relative to the dose plan, the position of the region of interest used for the analysis and the 2 Gy threshold levels applied. An analysis method that is less sensitive to these dose distribution differences could be preferable, enabling a more reliable direct comparison between competing plans. Future studies of this nature must develop novel methodologies to enable more meaningful and clinically relevant comparisons, such as 3D dosimetry and improvements in the analysis of dose distributions moving towards a DVH-based assessment. The use of dose-plane-histograms (analogous to dose-volume histograms (DVH) in a single plane) may provide a more clinically relevant analysis [35,36]. Despite its pitfalls, the gamma analysis method used, enabled quantification of the dose shaping abilities of all SRS platforms active in the UK. The results showed clinically acceptable dosimetric performance by all platforms, although noticeable dosimetric differences were apparent outside the target volume, which are unlikely to be clinically relevant. These dosimetric inaccuracies, seen in most centres, are related to the TPS's limitations in simulating out of field doses and typically resulted in underestimation of doses to the OAR, as found by other studies [37]. Another study conducting film-based end-to-end tests in CK plans recorded higher gamma passing rates (>90%) for the criterion of 2%-2mm local gamma [38], compared to the median passing rates seen in this study of 76.8, 81.0 and 75.1% for CK, GK and gantry-based linacs respectively. The differences seen are explained by the higher 50% dose threshold used in that study that excludes the low doses included in our film analysis.

While other multi-platform assessments have been conducted on stereotactic applications [30,39,40] only a few have been performed specifically for SRS [41]. This study is novel in the diversity of treatment platforms included and the advanced dosimetry methods employed. During-In this study, thirty-three treatment plans with differing planning approaches were generated, all for the same realistic patient scenario of a single metastatic lesion located anterior to the brainstem. ~~The approaches adopted by the participants to treat the presented indication differed in many aspects (see Table 1). Some of these differences, with respect to the equipment, software and delivery techniques used, were previously identified [6].~~ Aside from these planning differences, some subtle differences were observed in the accuracy of the measured dose distributions. However, the most influential and clinically relevant

variation observed in the protocols assessed, was found in prescription practices (Table 1), highlighting the potential need for standardisation.

~~This study assessed the dosimetric accuracy achieved using the thirty-three participating platforms.~~ Although a statistical analysis was performed, there ~~were~~ small numbers in each group ~~and a more robust analysis can be performed with~~ means a larger population would be needed for a more robust analysis. However, this was a national study and a larger study ~~can~~ could only be realised at a multi-national level. A Such a larger study may also reveal more subtle differences in the individual approaches ~~sd~~ followed in each centre. Another limitation of this work is the lack of incorporation of MRI in the end-to-end assessment, which is an integral step in intracranial SRS. ~~As mentioned previously, there are also limitations with the use of gamma analysis in this setting. Future studies of this nature must develop novel methodologies to enable more meaningful and clinically relevant comparisons, such as 3D dosimetry and improvements in the analysis of dose distributions moving towards a DVH based assessment.~~

~~With the recent rise of gantry based linac SRS [6] it is essential to incorporate all SRS platforms in dosimetric studies and clinical trials, in order to reach consensus in several matters. SRS treatments have been traditionally split between neurosurgery-led single session SRS and multisession oncology-led practices. However, the promising outcomes seen in hypofractionated SRS [42] and staged SRS [43] has brought the two faculties closer. In the future stereotactic trials should consider the diversity of platforms that may be used, in particular for issues such as prescription dose, prescription isodose, delivery capability, and how dosimetric differences may be assessed [44].~~

Currently, the assessment of dosimetric deliveries in a multi-platform, multi-centre SRS setting with individual planning priorities remains a challenge. However, independent dosimetric assessments as presented in this study are important interventions which have a crucial role in ensuring accurate dose delivery to patients. Moreover, when data from multiple centres is pooled together, it enables participants to benchmark their services against the rest of their community, assess their safety, evaluate their practices and consider improvements to their service. As stated the

basis of this audit was to support an initiative in the UK to regulate the provision of cranial SRS services. Consistent dosimetry has been recognised as essential in the evaluation of outcomes from those centres commissioned to provide such clinical services. Overall, there was a smaller spread of data seen in the CK and GK groups, however each had some statistically significant differences with the other platforms. ~~This suggests that~~ future multicentre SRS studies may benefit from some standardisation and consensus of practice.

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Figure 1: Schematic representation of a sagittal view through the centre of the phantom, showing the positions of the detectors in relation to the target and brainstem structures.

Short title: Multi-institutional audit of dosimetric delivery in radiosurgery

Centre Platform m No.	Platform	Energy	Technique	Coplanar / Non- coplanar	TPS	Dose Calculation Algorithm	Density Heterog. Correction	Peripheral Prescr. Dose (Gy)	Max Dose (Gy)	Pr Iso. Relative to Dmax (%)
1	VRN TrueBeam STx	10MV FFF	4DCA	NC	BL iPlan	Pencil Beam	Yes	21.0	26.4	80%
2	BL Novalis Tx	6MV	9FF	NC	BL iPlan	Pencil Beam	Yes	17.5	22.7	77%
3	VRN 2100x	6MV	4CCA	NC	BL iPlan	Circular Cone	Yes	18.0	23.6	76%
4	ELK Synergy	6MV	5VMAT	NC	Pinnacle	Convolution	Yes	18.0	22.9	79%
5	ACC Tomotherapy	6MV FFF	Tomo Therapy	C	Tomo Therapy	Non-Voxel Broad Beam	Yes	18.0	20.7	87%
6	BL Novalis Tx	6MV SRS	8FF	NC	Pinnacle	Convolution	Yes	18.0	22.4	80%
7	ELK Agility	6MV	3DCA	NC	Monaco	MC Photon	Yes	18.0	19.9	90%
8	BL Novalis Tx	6MV SRS	4DCA	NC	BL iPlan	Pencil Beam	Yes	18.0	23.1	78%
9	VRN TrueBeam	6MV	4DCA	NC	BL iPlan	Pencil Beam	Yes	18.0	22.8	79%
10	ELK VersaHD	6MV	5VMAT	NC	Monaco	MC Photon	Yes	21.0	26.3	80%
11	VRN TrueBeam	10MV FFF	2VMAT	C	Eclipse	AAA	Yes	20.0	23.3	86%
12	BL Novalis Tx	6MV SRS	4DCA	NC	BL iPlan	Pencil Beam	Yes	18.0	23.2	78%
13	VRN TrueBeam	6MV FFF	1VMAT	C	Eclipse	AAA	Yes	16.0	19.9	80%
14	VRN TrueBeam	10MV FFF	1VMAT	C	Eclipse	AAA	Yes	16.0	20.3	79%
15	ELK BeamMod	6MV	8 FF	NC	Pinnacle	Convolution	Yes	21.0	23.5	89%
16	VRN TrueBeam STx	6MV	5DCA	NC	BL iPlan	Pencil Beam	Yes	18.0	22.7	79%
17	ELK VersaHD	6MV FFF	3VMAT	NC	Monaco	MC Photon	Yes	18.0	34.8	52%
18	VRN TrueBeam	10MV FFF	4VMAT	NC	Eclipse	Acuros	Yes	20.0	30.0	67%
19	ELK BeamMod	6MV	7DCA	NC	Pinnacle	Convolution	Yes	18.0	24.1	75%
20	VRN TrueBeam STx	6MV	5DCA	NC	BL iPlan	Pencil Beam	Yes	21.0	27.1	77%
21	VRN ix2100	6MV	7VMAT	NC	Eclipse	AAA	Yes	21.0	30.5	69%
22	VRN TrueBeam STx	6MV FFF	5DCA	NC	BL iPlan	Pencil Beam	Yes	18.0	22.2	81%
23	ELK GK Perflexion	⁶⁰ Co	17 shots	NC	Gamma Plan	TMR10	No	18.0	40.9	44%
24	ELK GK Perflexion	⁶⁰ Co	19 shots	NC	Gamma Plan	TMR10	No	20.0	40.0	50%
25	ELK GK Icon	⁶⁰ Co	20 shots	NC	Gamma Plan	TMR10	No	18.0	36.7	49%
26	ELK GK Icon	⁶⁰ Co	22 shots	NC	Gamma Plan	TMR10	No	18.0	36.0	50%
27	ELK GK Perflexion	⁶⁰ Co	11 shots	NC	Gamma Plan	TMR10	No	18.0	39.1	46%
28	ELK GK Perflexion	⁶⁰ Co	22 shots	NC	Gamma Plan	TMR10	No	18.0	40.9	44%
29	ELK GK Perflexion	⁶⁰ Co	22 shots	NC	Gamma Plan	TMR10	No	18.0	41.4	43%
30	ACC CK VSI	6MV FFF	138 beams	NC	Multi Plan	Ray Tracing	Yes	21.0	32.3	65%
31	ACC CK VSI	6MV FFF	123 beams	NC	Multi Plan	Ray Tracing	Yes	18.0	25.7	70%
32	ACC CK VSI	6MV FFF	139 beams	NC	Multi Plan	Ray Tracing	Yes	18.0	34.0	53%
33	ACC CK VSI	6MV FFF	109 beams	NC	Multi Plan	Ray Tracing	Yes	20.0	30.8	65%

Table 1: Summary of equipment, techniques and prescription practices of the audit participants. The centres are grouped by platform and in random order, different to the order shown in the results, to avoid identification of individual centres. On-board imaging for positioning the phantom was used by all participants except centres 3, 23, 24, 27, 28 and 29. (VRN=Varian, BL=Brainlab, ELK=Elekta, ACC=Accuray, GK=Gamma Knife, CK=Cyberknife (with cones), DCA=Dynamic Conformal Arcs, FF=Fixed Fields, CCA=Circular Collimator Arcs, VMAT=Volumetric Modulated Arc Therapy)

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Pre- assessment

1. A high resolution DICOM image set of the phantom was send to the host centre with instructions for contouring the target and the brainstem.
2. The host centre outlined the structures and reported back to auditors.
3. After approval from the auditors, the host centre practised on the planning scenario available and prepared a plan prior to the day of the audit.

On day of assessment

1. The phantom was presented to the host centre with dummy film and alanine pellets in place.
2. The immobilisation device (frame/mask) was applied to the phantom followed by a CT-scan in stereotactic conditions following the local SRS protocol.
3. The acquired scan was fused/co-registered with the previously sent image set and the alanine pellets were delineated.
4. The plan was recalculated on the CT scan acquired on the day and exported to the treatment platform for delivery.
5. Output measurements in reference conditions were performed by both the auditor and auditee.
6. The dummy film and alanine pellets were replaced with real film and alanine pellets.
7. The audit phantom was accurately positioned on the treatment platform, with/without the use of on-board imaging, and the plan was delivered.

Post- assessment

1. The participating centre provided the auditors with RTDOSE DICOM files and dose-volume histograms from the delivered treatment plan for comparison to the measured alanine and films.
2. Alanine pellets and films were returned to the responsible laboratories for analysis
3. Alanine and film measured doses were compared to the TPS predicted doses.
4. The results were checked by a second person and a provisional report with the results was prepared and sent to the participating centre.

Figure 2: Flowchart diagram showing the main steps of the procedure followed in performing the end-to-end assessments.

Figure 3: Output measurements in local reference conditions for the 33 platforms that participated in the audit. An uncertainty of $\pm 0.7\%$ ($k=1$) is indicated by the error bars as a standard protocol based on the calibration certificate of the detector. The “acceptable” tolerances of $\pm 2\%$ are indicated.

Figure 4: Alanine pellet measurements performed in the target (4A) and organ at risk (4B). Platform groups are indicated in the legends. The mean for all centres is represented by the solid blue line, the dotted lines represent one standard deviation of the mean and the dashed lines represent two standard deviations of the mean.

Figure 5: Axial (5A&5B) and Sagittal (5C&5D) film passing rates of the local gamma criterion of 3% - 2mm and the global gamma criterion of 5% - 1mm for the 33 platforms that were assessed.

Supplementary Figure 1: Example of dose distribution comparisons between the film-measured doses (thin lines) and the treatment planning system- calculated doses (thick lines) for the axial and the sagittal films used.

Supplementary Figure 2: Axial (A&B) and Sagittal (C&D) film passing rates of the local gamma and the global gamma criteria of 2% - 2mm the 33 platforms that were assessed.

Short title: Multi-institutional audit of dosimetric delivery in radiosurgery

Title: Multi-institutional dosimetric delivery assessment of intracranial stereotactic radiosurgery on different treatment platforms

Keywords: Radiosurgery, Dosimetry, End-to-end, Audit, Anthropomorphic Phantom, Alanine, Radiochromic film

Highlights:

- A multi-institutional end-to-end assessment of radiosurgery dosimetric delivery was performed for 33 plans in 30 participating centres using a variety of treatment platforms.
- The comparison has highlighted the dosimetric consistency achievable with different delivery platforms.
- The need for standardisation in intracranial stereotactic radiosurgery is highlighted.

Abstract:

Background and Purpose:

Assessment of dosimetric accuracy of radiosurgery on different treatment platforms.

Material and Methods:

Thirty-three single fraction treatment plans were assessed at thirty centres using an anthropomorphic head phantom with target and brainstem structures. The target being a single irregular shaped target, ~8cc, 10 mm from the brainstem. The phantom was “immobilised”, scanned, planned and treated following the local protocols. EBT-XD films and alanine pellets were used to measure absolute dose, inside both the target and the brainstem, and compared with TPS predicted dose distributions.

Results:

PTV alanine measurements from gantry-based linacs showed a median percentage difference to the TPS of 0.65%. Cyberknife (CK) had the highest median difference of 2.3% in comparison to the other platforms. GammaKnife (GK) showed the smallest median of 0.3%. Similar trends were observed in the OAR with alanine measurements showing median percentage differences of 1.1%, 2.0% and 0.4%, for gantry-based linacs, CK and GK respectively. All platforms showed comparable gamma passing rates between axial and sagittal films.

Conclusions:

This comparison has highlighted the dosimetric variation between measured and TPS calculated dose for each delivery platforms.. The results suggest that clinically acceptable agreement with the predicted dose distributions is achievable by all treatment delivery systems.

1. Introduction

Stereotactic radiosurgery (SRS), was first developed in the 1950s [1] and has since evolved substantially. There are now several manufacturers that offer commercial solutions for delivering SRS and such treatments may be delivered by a Gamma Knife (GK) unit, a CyberKnife (CK) or a gantry-based linear accelerator (linac) system with stereotactic capabilities.

All radiotherapy practices should be subjected to appropriate quality assurance procedures, including regular quality control testing and independent external dosimetry audit [2,3], to minimize potential errors in treatment delivery that can lead to clinical complications [4]. This is especially the case for SRS where a very high dose is delivered in only a single fraction, meaning an error cannot be mitigated in a subsequent fraction.

The multiple platforms which can be used for SRS are very different in terms of their technologies and techniques [5]. Furthermore, they have been, and are being, used very differently in terms of their dosimetric and clinical practices [6]. The categorisation of the various systems into Gamma Knife (GK) units, CyberKnife (CK) units or gantry-based linear accelerator (linac) systems with stereotactic capabilities is justified according to their broadly similar dosimetric and clinical practices [6]. The latter category includes systems which use cones or tertiary microMLCs and also includes Tomotherapy units, which use a fixed ring gantry and have no non-coplanar delivery capability.

This national study was undertaken to support an initiative in the UK to regulate the provision of cranial SRS services [7–9]. The participating centres were audited in an end-to-end test, incorporating local clinical procedures for immobilisation devices, CT-scanning, target contouring, treatment planning and treatment delivery. We evaluated the agreement between planned and delivered dose for each of the audited systems. It is acknowledged that the audited systems cover a wide range of delivery and ancillary systems, however such a study has the potential to benchmark what can be achieved with intracranial stereotactic surgery systems and therefore contribute data for use in setting tolerances for clinical trials and future external

audits. Furthermore, the variations in clinical practice observed between these different platforms have been evaluated to assess the need for standardisation.

2. Materials and Methods

A comprehensive end-to-end test was developed based on an anthropomorphic head phantom, STEEV (Stereotactic End-to-End Verification, CIRS, Norfolk, VI, USA). The phantom was adapted to contain a single irregularly shaped target (~8cc), 10mm anterior to the brainstem, for treatment by the audited centre following their local protocol for brain metastasis to be treated in a single fraction [10]. A Computed Tomography (CT) scan of the phantom was sent in advance to the participating centres in DICOM format for volume contouring and pre-planning. This was followed by a visit to the centre where the phantom was scanned following the local protocol (CT only), with eight dummy alanine pellets and two dummy pieces of EBT-XD Gafchromic film (Ashland ISP Advanced Materials, NJ, USA) placed inside the phantom to mimic the detector positions. These were subsequently replaced with the real detectors prior to phantom treatment irradiation. A graphical representation showing the target (PTV), brainstem (OAR) and detector positions is included in Figure 1. The two CT scans were co-registered, and the pre-plan transferred to the local scan and finalised.

Thirty centres participated in the audit. In three centres two treatment platforms were assessed and hence thirty-three single fraction treatment plans were generated and delivered to the phantom. Table 1 provides details for each platform and plan that participated in the audit. Further details of the auditing protocol followed are given in Figure 2.

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2.1. Reference beam output measurements

A calibrated PTW 31010 semiflex ionisation chamber (0.125cc), traceable to a graphite calorimeter primary standard at the National Physical Laboratory (NPL, Teddington, UK) was used in all centres to perform reference beam output measurements. The chamber was placed in an auditor provided water-equivalent plastic material, using the centre's reference conditions, to measure the output in the machine specific reference field [11]. All such auditor measurements were corrected for temperature and pressure. Temperature and pressure were measured using independent auditor equipment. The measurements were performed in machine-specific reference conditions and deviations from agreement were expressed relative to the TPS-calculated value for dose in a geometric water equivalent phantom. The reference beam output measurements were used to apply corrections to the alanine measurements of the clinical plan, to compensate for any daily output variation.

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2.2. Alanine measurements

Two sets of four alanine pellets, each a disc of 5mm diameter and 2.5mm thickness, were irradiated in each centre: one in the target and one in the brainstem. The phantom temperature before and after each measurement was recorded and used to apply a temperature correction factor. All pellets were returned to NPL and were processed within one month of the audit visit, ensuring negligible fading [12]. The measured doses were compared to the mean dose calculated by the TPS for each pellet. Additionally, in order to account for positional uncertainties that can lead to large percentage differences between measured and predicted doses, mean doses for each pellet stack were compared with the TPS prediction for the complete stack.

The percentage difference between alanine and TPS for the OAR was normalised to the 12 Gy dose level, being the nominal brainstem tolerance dose used by many centres. This enabled a dosimetric comparison whilst assessing the plan quality in terms of overdose to the OAR.

Uncertainty on the alanine readout was taken to be 1.4% ($k=2$) [12]. The deviations from agreement were expressed relative to the TPS-calculated value.

Alanine was considered as the primary detector for the audit measurements, as it has proven its efficacy in small fields and is provided by an established dosimetry service based at NPL [12].

2.3. Film measurements

The film response was calibrated in a conventional manner with ten EBT-XD film pieces exposed in the range of 0-40 Gy. The films were irradiated in a 10 cm × 10 cm field at 5 cm depth in water-equivalent plastic, with a nominal 6 MV beam. The scanned pixel value as a function of dose was determined as the average pixel value in a 4 × 4 cm region centred on the beam axis. Images were converted to dose maps using FilmQAPro® software (Ashland ISP Advanced Materials, NJ, USA) using the red-green-blue triple-channel dosimetry algorithm [13].

Two films (one sagittal and one axial) were placed inside the phantom and simultaneously irradiated at each centre. All films were returned to NPL and scanned at least 72 hours after exposure following an established film dosimetry protocol [14,15] and good film dosimetry practice [16,17] with the analysis performed on FilmQAPro. Film-dose linear scaling was applied using reference films at zero dose and 80% of the maximum anticipated dose from the treatment plan, which were scanned simultaneously with the test films. This approach mitigates the effects of post-exposure darkening and variations of the scanner response, and stabilizes the calibration (forced into agreement) at the reference dose levels [18]. The regions of interest used for the analysis were a 6 x 5 cm rectangle for the axial films and a 7 x 4 cm rectangle for the sagittal films. The measured dose distributions were matched to TPS dose distributions by aligning the fiducial marker holes in the film with known coordinates in the TPS dose planes and then using the optimum shift algorithm, where small shifts were applied (<1mm and <1°) to optimise the gamma passing rate..

Gamma passing rates [19] were collected for a range of criteria (global and local) using the red colour channel with triple-channel-correction and with film-dose linear scaling corrections applied. The criteria selected were based on the following: data for 3% dose difference and 2mm distance (3%/2mm) were collected as this criterion was commonly used by the participating linac users and 5%/1mm as this is more suitable for plans with steep gradients. Data for 2%/2mm was also analysed as recommended

by AAPM TG 135 [20]. A minimum cut-off threshold of 2 Gy was applied to remove low dose areas of higher uncertainty from the analysis. This absolute value was used as an alternative to a relative value, due to the large variation of prescription doses and maximum doses delivered by the audit participants.

2.4 Statistical analysis

A Kruskal-Wallis test was performed to detect any significant differences in median values between the three platforms, followed by the Bonferroni-type multiple comparison to establish the hierarchy/significant differences between different pairs.

3. Results

Reference output measurements were performed independently by both the host centre and the auditors using their respective equipment and these are presented in Figure 3. All measurements from the auditors and the centres were within $\pm 2.4\%$ of the dose calculated by the TPS, ranging from -1.0% to $+2.4\%$. The mean difference between auditor measurement and host centre measurement (audit/host) was $+0.5\%$, with a maximum difference of $+1.2\%$. The gantry based linac group spread in the output measurements was 3.2% , ranging from -0.8% to $+2.4\%$, with a median of 0.35% . CKs had a spread of 1.8% , ranging from -1.0% to $+0.8\%$, with a median of 0.85% and GKs had a spread of 1.6% , ranging from -0.9% to $+0.7\%$, with a median of 0.0% . No statistical differences were seen between the platforms.

The differences between the measured and calculated (measured/calculated) doses for the stack of 4 alanine pellets ranged from -1.3% to $+4.0\%$ for the PTV (Figure 4A). The gantry based linacs showed a spread in percentage difference of 5.2% (from -1.3% to $+3.9\%$) with a median of 0.65% . GKs showed a spread of 2.4% (from -0.8% to $+1.5\%$), with a median percentage difference of $+0.3\%$. CK measurements had a spread of 2.6% (from $+1.4\%$ to $+4\%$), with a median of $+2.3\%$, which in comparison with the gantry based linac and GK groups were statistically higher with p values of 0.045 and 0.039 respectively. Individual pellet measurements in the target showed differences of up to 14.1% , 4.2% and 5.9% (for GK, CK and linac respectively) when

204 compared to the TPS-predicted mean dose in their individual contoured pellet
205 structure.

206 Similar trends were observed in the comparison of OAR alanine pellet measurements
207 to those observed in target alanine pellet measurements, ranging from -1.1% to +4.3%
208 (Figure 4B). Gantry-based linac measurements showed a spread at 4.6% ranging
209 from -1% to +3.6% with a median of +1.2%. CK measurements ranged between 0.0%
210 to +1.9% with a median of +1.1%. GKs had a spread of 2.0% ranging from -1.1% to
211 +0.9% and a median of +0.4%. Here the only significance was in the gantry-based
212 linac group being higher than the GK group with a p value of 0.047.

213 TPS-predicted doses for the alanine pellets in the OAR ranged from 0.3 Gy up to 7.5
214 Gy. Figure 4 shows the percentage difference between the mean dose measured by
215 OAR alanine pellets with the TPS-predicted mean dose, normalised to 12.0 Gy.

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217
218 The results for axial and sagittal films (example shown in Supplementary Figure 1)
219 showed consistency in the gamma passing rates achieved. The gamma passing
220 rates for 3% / 2mm local gamma and 5% / 1mm global gamma are shown in Figure
221 5.

222 Higher passing rates for all films were observed for global than for local gamma
223 criteria. For the 3% / 2 mm local gamma criterion, all but two films showed passing
224 rates above 75%. The CK, GK and gantry-based linac groups had median passing
225 rates of 88.7, 92.8 and 85.5 respectively, showing no statistical differences between
226 them. For the 5% / 1 mm global gamma criterion, all but 3 films showed passing rates
227 above 90% (see Figure 5). Here the CK, GK and gantry-based linac groups had
228 median passing rates of 99.3, 98.4, 98.3 respectively, again showing no statistical
229 differences between them. For the 2% / 2 mm global gamma criterion, all but 3 films
230 showed passing rates above 90% (see Supplementary Figure 2). Here the CK, GK
231 and gantry-based linac groups had median passing rates of 99.3, 99.0, 96.6
232 respectively, with a p value of 0.028 between the GK and the gantry-based linac
233 groups, all other comparisons being non-significant.

When the regions of interest used for the gamma analysis were reduced to smaller areas to include the target region only, passing rates improved substantially for all centres, showing very good agreement (>95%) between TPS-predicted and delivered dose distributions. The majority of failed pixels for all films analysed were found to be outside the target, between the 2 Gy (threshold level) and the 12 Gy isodose line.

4. Discussion

The reference output measurements performed in the standard conditions for each platform at all centres were within $\pm 2.4\%$ of the expected dose, well within the $\pm 3\%$ recommendation of IPEM report 81 [21]. Moreover, the results seen in this study are consistent with the results reported by the NPL over 20 years of reference audits [22]. The differences from expected dose seen in the GK and CK groups were comparable, and much smaller than those seen in gantry-based linacs. This could be related to these platforms having more predictable output in reference conditions, due to having a more straight forward design. The ^{60}Co sources in the GK have a predictable decay, which is reflected in the good agreement seen in these measurements and the tighter tolerances of 1.0 - 1.5% deviation used by GK centres. The compact single energy linear accelerator of the CK may be the reason for the reduced fluctuations observed in output measurements, compared to multi-energy and multi-modality conventional gantry-based linacs which comprise the majority of units within this category. The systematic difference between the auditor and the centres (+0.5%) may be partly explained by the instruments used. While the auditors used a 0.125cc ionisation chamber for all measurements, the centres used a range of different detectors, which in most cases had a larger sensitive volume. Therefore, a small degree of volume averaging can be attributed to the difference observed, especially since 15 out of 33 participating platforms used Flattening Filter Free (FFF) type beams. However, further measurements need to be performed to fully explain this difference.

Overall, good agreement was observed between alanine and TPS, with three centres falling outside (greater than) two standard deviations of the mean (two centres in the target dose measurements and one in the OAR measurements). Although there were some statistical differences between the groups these had p values which were only

just less than 0.05 and were not consistent across the measurement methods and PTV/OAR, hence no strong statistical conclusions can be drawn about each platform. The gantry-based linac group was seen to have the largest spread in percentage differences compared to CK and GK, but with a relatively good overall agreement with the TPS. The reasons behind this spread are most likely attributed to the diversity of techniques, platforms, beam energies, TPSs, calculation algorithms, clinician preferences and influences from the local radiotherapy practices. In comparison, the CK and GK groups had almost identical settings and practices within their subgroups. It is also possible that the variations in the commissioning methodologies used for gantry-based linacs, especially with regards to the dosimeters used for the measurement of small radiation fields, has an impact on the accuracy of dose calculation. Although numerous studies have been conducted on appropriate detectors for small field applications [23–28], there has been a lack of international guidelines until the recently published IAEA TRS 483 [29]. It is expected that these new guidelines will improve the standardisation of commissioning methodologies.

CK measurements in the target, showed that the TPS with Raytracing calculation algorithm under-estimated the dose in all four centres visited. This finding is in agreement with another study utilising the same alanine service for target dose measurements in CK plans [30].

All GK centres used a TMR10 algorithm that does not account for density inhomogeneities and assumes water density within a CT-generated or depth-helmet measured skull contour. A recent study investigating the GK convolution algorithm (employs density corrections) in comparison to the TMR10, showed a 6% difference between the two where 1.5% of this was attributed to depth helmet measurements [31]. Our alanine measurements showed good agreement with the TPS and suggest that these sources of error do not contribute significantly to dosimetric inaccuracies. Further work investigating this convolution algorithm may be required to evaluate its accuracy before it is used clinically.

Alanine measurements in the OAR were performed along a steep dose gradient where any positional uncertainties may be expressed as large dose differences. Doses to the OAR pellets ranged by up to an order of magnitude, caused by individual planning priorities and protocols used by participating centres. As some centres delivered very

low doses to this region the reported doses were normalised to 12 Gy (a nominal brainstem tolerance dose value used by many centres) in order to provide a useful measure of relative accuracy to the centres with different approaches. There was also a higher uncertainty in the lower dose measurements due to lower signal to noise ratios in the alanine readout.

The gamma passing rates showed clinically acceptable agreement between the film-measured dose and the treatment planning system calculated dose distributions for both sagittal and axial films [32]. All treatment modalities showed comparable variations in passing rates between the centres assessed and the passing rates alone do not suggest significant differences between the different platforms. Other studies have suggested that gamma index analysis is non-ideal for direct comparison in multi-institution assessments due to inherent differences in the dose distributions, particularly in dose gradient and maximum doses [32–34]. Local Gamma criteria may favour linac centres in which the dose gradient could be less steep than GK and CK, and Global Gamma criteria may favour GK centres in which the maximum (normalisation) dose is higher and the dose gradients are steeper. Whilst the methodology for film analysis employed in this study was designed to diminish sensitivities to different dose distributions it is impossible to achieve this with gamma index analysis. Gamma passing rates are also sensitive to the position of the film relative to the dose plan, the position of the region of interest used for the analysis and the 2 Gy threshold levels applied. An analysis method that is less sensitive to these dose distribution differences could be preferable, enabling a more reliable direct comparison between competing plans. Future studies of this nature must develop novel methodologies to enable more meaningful and clinically relevant comparisons, such as 3D dosimetry and improvements in the analysis of dose distributions moving towards a DVH-based assessment. The use of dose-plane-histograms (analogous to dose-volume histograms (DVH) in a single plane) may provide a more clinically relevant analysis [35,36]. Despite its pitfalls, the gamma analysis method used, enabled quantification of the dose shaping abilities of all SRS platforms active in the UK. The results showed clinically acceptable dosimetric performance by all platforms, although noticeable dosimetric differences were apparent outside the target volume, which are unlikely to be clinically relevant. These dosimetric inaccuracies, seen in most centres, are related to the TPS's limitations in simulating

out of field doses and typically resulted in underestimation of doses to the OAR, as found by other studies [37]. Another study conducting film-based end-to-end tests in CK plans recorded higher gamma passing rates (>90%) for the criterion of 2%-2mm local gamma [38], compared to the median passing rates seen in this study of 76.8, 81.0 and 75.1% for CK, GK and gantry-based linacs respectively. The differences seen are explained by the higher 50% dose threshold used in that study that excludes the low doses included in our film analysis.

While other multi-platform assessments have been conducted on stereotactic applications [30,39,40] only a few have been performed specifically for SRS [41]. This study is novel in the diversity of treatment platforms included and the advanced dosimetry methods employed. In this study, thirty-three treatment plans with differing planning approaches were generated, all for the same realistic patient scenario of a single metastatic lesion located anterior to the brainstem. Aside from these planning differences, some subtle differences were observed in the accuracy of the measured dose distributions. However, the most influential and clinically relevant variation observed in the protocols assessed, was found in prescription practices (Table 1), highlighting the potential need for standardisation.

Although a statistical analysis was performed, the small numbers in each group means a larger population would be needed for a more robust analysis. However, this was a national study and a larger study could only be realised at a multi-national level. Such a larger study may also reveal more subtle differences in the individual approaches followed in each centre. Another limitation of this work is the lack of incorporation of MRI in the end-to-end assessment, which is an integral step in intracranial SRS.

Currently, the assessment of dosimetric deliveries in a multi-platform, multi-centre SRS setting with individual planning priorities remains a challenge. However, independent dosimetric assessments as presented in this study are important interventions which have a crucial role in ensuring accurate dose delivery to patients. Moreover, when data from multiple centres is pooled together, it enables participants to benchmark their services against the rest of their community, assess their safety,

evaluate their practices and consider improvements to their service. As stated the basis of this audit was to support an initiative in the UK to regulate the provision of cranial SRS services. Consistent dosimetry has been recognised as essential in the evaluation of outcomes from those centres commissioned to provide such clinical services. Overall, there was a smaller spread of data seen in the CK and GK groups, however each had some statistically significant differences with the other platforms. Future multicentre SRS studies may benefit from some standardisation and consensus of practice.

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Figure 1: Schematic representation of a sagittal view through the centre of the phantom, showing the positions of the detectors in relation to the target and brainstem structures.

Short title: Multi-institutional audit of dosimetric delivery in radiosurgery

Platform No.	Platform	Energy	Technique	Coplanar / Non-coplanar	TPS	Dose Calculation Algorithm	Density Heterog. Correction	Peripheral Prescr. Dose (Gy)	Max Dose (Gy)	Pr Iso. Relative to Dmax (%)
1	VRN TrueBeam STx	10MV FFF	4DCA	NC	BL iPlan	Pencil Beam	Yes	21.0	26.4	80%
2	BL Novalis Tx	6MV	9FF	NC	BL iPlan	Pencil Beam	Yes	17.5	22.7	77%
3	VRN 2100x	6MV	4CCA	NC	BL iPlan	Circular Cone	Yes	18.0	23.6	76%
4	ELK Synergy	6MV	5VMAT	NC	Pinnacle	Convolution	Yes	18.0	22.9	79%
5	ACC Tomotherapy	6MV FFF	Tomo Therapy	C	Tomo Therapy	Non-Voxel Broad Beam	Yes	18.0	20.7	87%
6	BL Novalis Tx	6MV SRS	8FF	NC	Pinnacle	Convolution	Yes	18.0	22.4	80%
7	ELK Agility	6MV	3DCA	NC	Monaco	MC Photon	Yes	18.0	19.9	90%
8	BL Novalis Tx	6MV SRS	4DCA	NC	BL iPlan	Pencil Beam	Yes	18.0	23.1	78%
9	VRN TrueBeam	6MV	4DCA	NC	BL iPlan	Pencil Beam	Yes	18.0	22.8	79%
10	ELK VersaHD	6MV	5VMAT	NC	Monaco	MC Photon	Yes	21.0	26.3	80%
11	VRN TrueBeam	10MV FFF	2VMAT	C	Eclipse	AAA	Yes	20.0	23.3	86%
12	BL Novalis Tx	6MV SRS	4DCA	NC	BL iPlan	Pencil Beam	Yes	18.0	23.2	78%
13	VRN TrueBeam	6MV FFF	1VMAT	C	Eclipse	AAA	Yes	16.0	19.9	80%
14	VRN TrueBeam	10MV FFF	1VMAT	C	Eclipse	AAA	Yes	16.0	20.3	79%
15	ELK BeamMod	6MV	8 FF	NC	Pinnacle	Convolution	Yes	21.0	23.5	89%
16	VRN TrueBeam STx	6MV	5DCA	NC	BL iPlan	Pencil Beam	Yes	18.0	22.7	79%
17	ELK VersaHD	6MV FFF	3VMAT	NC	Monaco	MC Photon	Yes	18.0	34.8	52%
18	VRN TrueBeam	10MV FFF	4VMAT	NC	Eclipse	Acuros	Yes	20.0	30.0	67%
19	ELK BeamMod	6MV	7DCA	NC	Pinnacle	Convolution	Yes	18.0	24.1	75%
20	VRN TrueBeam STx	6MV	5DCA	NC	BL iPlan	Pencil Beam	Yes	21.0	27.1	77%
21	VRN ix2100	6MV	7VMAT	NC	Eclipse	AAA	Yes	21.0	30.5	69%
22	VRN TrueBeam STx	6MV FFF	5DCA	NC	BL iPlan	Pencil Beam	Yes	18.0	22.2	81%
23	ELK GK Perfexion	⁶⁰ Co	17 shots	NC	Gamma Plan	TMR10	No	18.0	40.9	44%
24	ELK GK Perfexion	⁶⁰ Co	19 shots	NC	Gamma Plan	TMR10	No	20.0	40.0	50%
25	ELK GK Icon	⁶⁰ Co	20 shots	NC	Gamma Plan	TMR10	No	18.0	36.7	49%
26	ELK GK Icon	⁶⁰ Co	22 shots	NC	Gamma Plan	TMR10	No	18.0	36.0	50%
27	ELK GK Perfexion	⁶⁰ Co	11 shots	NC	Gamma Plan	TMR10	No	18.0	39.1	46%
28	ELK GK Perfexion	⁶⁰ Co	22 shots	NC	Gamma Plan	TMR10	No	18.0	40.9	44%
29	ELK GK Perfexion	⁶⁰ Co	22 shots	NC	Gamma Plan	TMR10	No	18.0	41.4	43%
30	ACC CK VSI	6MV FFF	138 beams	NC	Multi Plan	Ray Tracing	Yes	21.0	32.3	65%
31	ACC CK VSI	6MV FFF	123 beams	NC	Multi Plan	Ray Tracing	Yes	18.0	25.7	70%
32	ACC CK VSI	6MV FFF	139 beams	NC	Multi Plan	Ray Tracing	Yes	18.0	34.0	53%
33	ACC CK VSI	6MV FFF	109 beams	NC	Multi Plan	Ray Tracing	Yes	20.0	30.8	65%

Table 1: Summary of equipment, techniques and prescription practices of the audit participants. The centres are grouped by platform and in random order, different to the order shown in the results, to avoid identification of individual centres. On-board imaging for positioning the phantom was used by all participants except centres 3, 23, 24, 27, 28 and 29. (VRN=Varian, BL=Brainlab, ELK=Elekta, ACC=Accuray, GK=Gamma Knife, CK=Cyberknife (with cones), DCA=Dynamic Conformal Arcs, FF=Fixed Fields, CCA=Circular Collimator Arcs, VMAT=Volumetric Modulated Arc Therapy)

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Pre- assessment

1. A high resolution DICOM image set of the phantom was send to the host centre with instructions for contouring the target and the brainstem.
2. The host centre outlined the structures and reported back to auditors.
3. After approval from the auditors, the host centre practised on the planning scenario available and prepared a plan prior to the day of the audit.

On day of assessment

1. The phantom was presented to the host centre with dummy film and alanine pellets in place.
2. The immobilisation device (frame/mask) was applied to the phantom followed by a CT-scan in stereotactic conditions following the local SRS protocol.
3. The acquired scan was fused/co-registered with the previously sent image set and the alanine pellets were delineated.
4. The plan was recalculated on the CT scan acquired on the day and exported to the treatment platform for delivery.
5. Output measurements in reference conditions were performed by both the auditor and auditee.
6. The dummy film and alanine pellets were replaced with real film and alanine pellets.
7. The audit phantom was accurately positioned on the treatment platform, with/without the use of on-board imaging, and the plan was delivered.

Post- assessment

1. The participating centre provided the auditors with RTDOSE DICOM files and dose-volume histograms from the delivered treatment plan for comparison to the measured alanine and films.
2. Alanine pellets and films were returned to the responsible laboratories for analysis
3. Alanine and film measured doses were compared to the TPS predicted doses.
4. The results were checked by a second person and a provisional report with the results was prepared and sent to the participating centre.

Figure 2: Flowchart diagram showing the main steps of the procedure followed in performing the end-to-end assessments.

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Figure 3: Output measurements in local reference conditions for the 33 platforms that participated in the audit. An uncertainty of $\pm 0.7\%$ ($k=1$) is indicated by the error bars as a standard protocol based on the calibration certificate of the detector. The “acceptable” tolerances of $\pm 2\%$ are indicated.

Figure 4: Alanine pellet measurements performed in the target (4A) and organ at risk (4B). Platform groups are indicated in the legends. The mean for all centres is represented by the solid blue line, the dotted lines represent one standard deviation of the mean and the dashed lines represent two standard deviations of the mean.

Figure 5: Axial (5A&5B) and Sagittal (5C&5D) film passing rates of the local gamma criterion of 3% - 2mm and the global gamma criterion of 5% - 1mm for the 33 platforms that were assessed.

Supplementary Figure 1: Example of dose distribution comparisons between the film-measured doses (thin lines) and the treatment planning system- calculated doses (thick lines) for the axial and the sagittal films used.

Supplementary Figure 2: Axial (A&B) and Sagittal (C&D) film passing rates of the local gamma and the global gamma criteria of 2% - 2mm the 33 platforms that were assessed.

Table 1

Platform number	Platform	Energy	Technique	Coplanar / Non-coplanar	TPS	Dose Calculation Algorithm	Density Heterog. Correction	Peripheral Prescr. Dose (Gy)	Max Dose (Gy)	Pr Iso. Relative to Dmax (%)
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Figure 3

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Supplementary Files

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Dear Editor,

I hereby confirm that none of the authors of the submitted manuscript have a conflict of interest to declare.

Regards,

Alexis Dimitriadis

BSc, MSc, PhD

“Multi-institutional dosimetric delivery assessment of intracranial stereotactic radiosurgery on different treatment platforms”

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