Determination of an optimal treatment margin for intracranial tumours treated with radiotherapy at Groote Schuur Hospital

A study by Dr Andre Vos

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In fulfilment of the requirements for the degree

MMED RADIATION ONCOLOGY

Faculty of Health Sciences

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Table of contents

Declaration

I, Andre Vos, hereby declare that the work on which this dissertation is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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Dr Andre Vos

05 June 2020

Abstract

Background

Accurate delivery of radiotherapy is a paramount component of providing safe oncological care. Margins are applied when planning radiotherapy to account for subclinical tumour spread, physiological movement and set-up error. Set-up error is unique to each radiotherapy institution and should be calculated for each organ site to ensure safe delivery of treatment.

Aim and setting

The aim of this study is to calculate the random and systematic set-up error for a cohort of patients with intracranial tumours treated with 3D Conformal Radiotherapy at the Department of Radiation Oncology, Groote Schuur Hospital, South Africa. After obtaining above mentioned data the ideal CTV-PTV expansion margin was calculated using published CTV-PTV expansion margin recipes.

Patients and methods

The Electronic Portal Images (EPID) of 20 patients who met the inclusion criteria were compared to their Digitally Reconstructed Radiograph (DRR). The set-up error for each patient was measured after which the random (σ) and systematic (Σ) set-up error for the study group could be calculated. With both these values known the CTV-PTV expansion margin could be determined.

Results

The largest error was in the Superior/Inferior (SI) direction, followed by the Medial/Lateral (ML) direction and least in the Anterior/Posterior (AP) direction with 87.7%, 76.2% and 91.6% of the errors in the ML, SI and AP directions respectively being less than 3mm.

There was no error larger than 5mm in the ML or AP direction with 6.1% of the SI error larger than 5mm.

The random and systematic error in all three directions for this patient cohort were less than 2mm conforming to acceptable standards of delivering safe radiotherapy. Using Stroom's margin recipe ($2\Sigma + 0.7\sigma$) a CTV-PTV expansion margin of 5mm can safely be applied for this patient cohort.

Conclusion

When treating patients with intracranial tumours at Groote Schuur Hospital the CTV-PTV expansion margin can safely be reduced from 1cm to 5mm.

Acknowledgements and contributions

I, Andre Vos was the main author of this manuscript. I collected all the data for the study, and I was responsible for the compilation of the literature review. My co-authors provided guidance in interpreting the data and writing it up in a publishable format.

My co-authors also helped with the editing and preparation of this manuscript when it was submitted in article format to the South African Journal of Oncology (SAJO) for publication.

I would like to thank Michelle Henry who helped with the statistics and Louise Vos and Retha Badenhorst who assisted me with the initial literature review.

I also would like to thank my wife Imke for all her personal support during this whole process.

List of Tables

List of Figures

Abbreviations

ICRU – International Commission on Radiation Units and Measurements

GTV – Gross Tumour Volume

CTV - Clinical Target Volume

PTV - Planning Target Volume

3DCRT – 3-Dimensional Conformal Radiotherapy

CT – Computed Tomography

MRI – Magnetic Resonance Imaging

MV – Megavoltage

AP – Anterior-posterior

ML – Medial-lateral

SI – Superior-inferior

EPID – Electronic Portal Imaging Device

DRR – Digital Reconstructed Radiograph

SD – Standard Deviation

Σ - Systematic error

σ - Random error

1. Introduction

Accuracy of radiation delivery in radiotherapy is critical to ensure adequate coverage of a tumour and minimisation of normal tissue dose. It is important to establish uncertainties in dose distribution so that suitable treatment margins can be used for optimal therapy.

The International Commission on Radiation Units and Measurements (ICRU) report 50 introduced the concept of a gross tumour volume (GTV), a clinical target volume (CTV) and a planning target volume (PTV)[1] in radiotherapy. The GTV is classified as the gross demonstrable extent and location of the malignant growth.[1] The CTV is a tissue volume that contains a demonstrable GTV or subclinical malignant disease that must be eliminated. The CTV is a clinical-anatomical concept and can be described as including structures with clinically suspected but unproved involvement.[1,2] The GTV almost always corresponds to those parts of the malignant growth where the tumour cell density is the highest, hence the importance of delivering adequate dose to the whole GTV.[2] The PTV is a geometrical concept used for treatment planning and it is defined to select appropriate beam sizes and beam arrangements to ensure that the prescribed dose is actually delivered to the CTV.[1,2]

Errors in radiotherapy can either be random or systematic. Systematic errors are a deviation that occur in the same direction and are of a similar magnitude for each fraction throughout the treatment course affecting the accuracy of the treatment. Random errors are a deviation that can vary in direction and magnitude during the treatment, affecting the precision of the treatment.[3]

Positional uncertainties affect the dose distribution to target structures thus possibly compromising the clinical outcome of the treatment.[4,5] Hurkmans et al. made a number of suggestions in their review article to reduce setup error, thus improving overall accuracy of treatment.[6] Some of the suggestions were to perform portal images during a few treatment sessions over the course of treatment to ensure accuracy of treatment,[7,8] to distinguish between systematic and random errors when analysing setup data,[9,10] to use automated matching with portal images if a small measurement error is required[11,12] and to use high-quality fixation devices, for example a

thermoplastic mask.[13]

The amount of setup error is however unique to each institution. When determining the CTV-PTV margin, it is therefore recommended to use institution-specific data on setup error.[14,15,16]

2. Research methods and design

2.1. Patient group

The study group consisted of 20 patients with intracranial tumours who were treated with 3D Conformal Radiotherapy (3DCRT) at the Department of Radiation Oncology, Groote Schuur Hospital, South Africa.
The inclusion criteria were as follows:

- Patients with intracranial tumours immobilised in a five-point thermoplastic mask on a S frame from 2013 onwards using 3DCRT.
- Any intracranial tumour were included, regardless of histology, age of patient, gender of patient or stage of disease.
- Patients with either radical or palliative intent could be included.
- Patients who had their electronic portal imaging done on day 1–3 and weekly thereafter as per departmental protocol. A minimum of five sets of electronic portal images were required for inclusion.

Exclusion criteria included any tumour that was extracranial or patients who were treated with any other modality than 3DCRT.

2.2. Radiotherapy technique

All patients were scanned in the supine position using a CT scanner (Toshiba) while being immobilised with a five-point thermoplastic mask attached to a couch overlay device. During immobilisation care was taken to ensure good imprint of the mask over the face and shoulders.

The mask covered the entire head of the patient down to mid-shoulder. The isocentre was marked on the mask during simulation using wall-mounted lasers. During treatment the same reference system was used to ensure correct patient positioning.

The CT images were reconstructed in 3 mm slices and then transferred to the treatment planning system (Varian Eclipse) for contouring by the physician. If available, MRI images were fused with the CT image to aid in contouring. The GTV and the organs at risk were delineated with a CTV margin added depending on the underlying tumour histology for that particular patient. A PTV was created by adding a 1 cm isotropic margin around the CTV. Planning risk volumes were created around critical structures such as the optic chiasm, brainstem and spinal cord.

Treatment was delivered using one of two 6 MV Linear Accelerators (Varian Unique) using a 3DCRT technique. Treatment lasted between 5 and 8 weeks depending on the diagnosis and intent of treatment.

2.3. Image analysis

Verification of position was done by obtaining orthogonal MV portal images on day 1–3 and weekly thereafter as per departmental protocol. Those images were compared to the digitally reconstructed radiograph (DRR) as constructed from their initial planning CT by using the auto-matching function on the imaging software (Varian/ARIA Offline review). A total of 260 portal images (130 anterior-posterior [AP] and 130 lateral) were analysed and compared to 40 DRRs (20 AP and 20 lateral) for the 20 patients.

The inter-fractional setup error, which is the deviation between expected and actual patient position were measured in each direction. The measurements were registered in the three translational directions for each patient: medial-lateral (ML) (X), superior-inferior (SI) (Y) and AP (Z).

Deviations in the ML direction were measured using the AP images. Deviations in the SI direction were measured by evaluating both the AP and lateral images and in the AP direction only the lateral images were used.

The intra-fractional setup error, which is the deviation in treatment that occurs during a single fraction of radiotherapy was ignored as they contribute very little to overall setup error in the head and neck area.[6]

Rotational setup errors were measured by three-dimensional image analysis as part of the auto-matching function on the imaging software. Out of plane rotational errors smaller than 3° in general do not cause an important deformation of the projected anatomy in portal images.[6]

Gross errors as determined by departmental protocol (shifts larger than 5 mm in any direction) were corrected prior to treatment.

All measurements were manually verified by the author by overlying the portal image over the DRR. Measured deviations were entered into a spreadsheet.

2.5. Data analysis

After evaluating studies who also calculated an institution-specific CTV-PTV margin a similar approach to data analysis was followed.[17,18]

The setup errors in all three directions were used to calculate the random and systematic setup error for each individual patient and the patient group. The individual patient systematic setup error (μ) was calculated by taking the mean of the measured setup error for each imaged fraction in each direction. The individual patient random error was calculated by taking the standard deviation (SD) of the setup errors around the corresponding mean individual value. The group mean setup error (M) was calculated by taking the mean of the entire group setup error. The group systematic setup error (Σ) was derived by taking the SD of the individual mean setup error about

the group mean setup error. The group random error (σ) was derived by taking the mean of all the individual patient random errors.

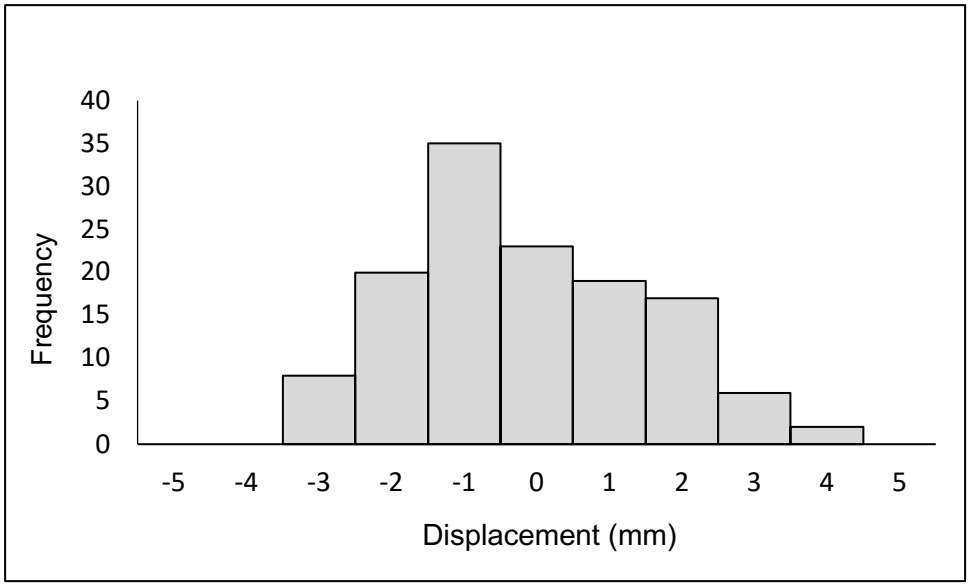
3. Results

Table 1 illustrates that 87.7%, 76.2% and 91.6% of the errors in the ML, SI and AP directions were less than 3 mm. The errors were largest in the SI direction, followed by the ML direction and smallest in the AP direction. There were no errors larger than 5 mm in the ML and AP direction and 6.1% of errors were larger than 5 mm in the SI direction.

TABLE 1: Frequencies of setup error distribution.

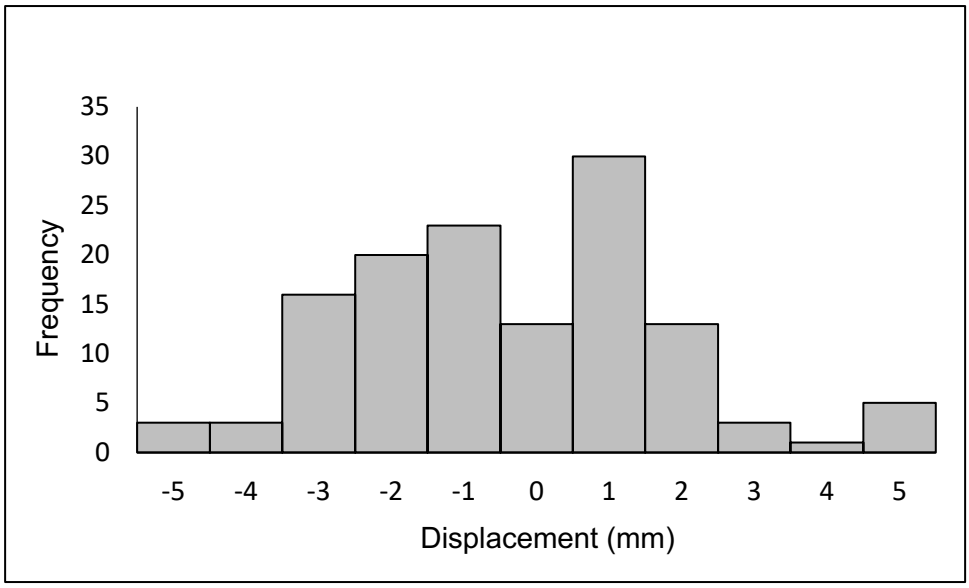
Setup error (mm)	Medial-lateral (X)	Superior-inferior (Y)	Anterior-posterior (Z)
> −5	0	3 (2.3%)	0
> −4	0	3 (2.3%)	0
> −3	8 (6.2%)	16 (12.3%)	0
> −2	20 (15.4%)	20 (15.4%)	4 (3.1%)
> −1	35 (26.9%)	23 (17.7%)	20 (15.4%)
0	23 (17.7%)	13 (10%)	42 (32.3%)
> 1	19 (14.6%)	30 (23.1%)	35 (26.9%)
> 2	17 (13.1%)	13 (10.0%)	18 (13.8%)
> 3	6 (4.6%)	3 (2.3%)	9 (6.9%)
> 4	2 (1.5%)	1 (0.8%)	2 (1.5%)
> 5	0	5 (3.8%)	0

The distribution of the setup errors in each of the directions is shown in graph format in Figure 1 (ML), Figure 2 (SI) and Figure 3 (AP).



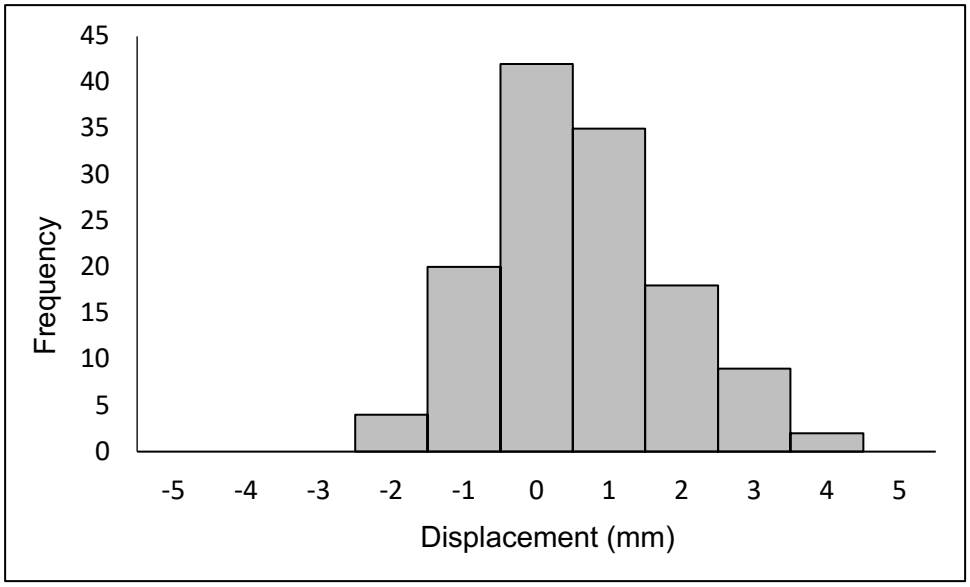
Source: Authors' own work

FIGURE 1: The distribution of setup errors in the medial-lateral direction.



Source: Authors' own work

FIGURE 2: The distribution of setup errors in the superior-inferior direction.



Source: Authors' own work.

FIGURE 3: The distribution of set-up errors in the anterior-posterior direction.

3.1. Clinical target volume-planning target volume margin

The SD of the random and systematic population errors was calculated and is indicated as σ and ∑. In some literature these errors are annotated as σ^{random} and $\sigma^{systematic}$ but σ and ∑ are preferred to clearly distinguish between the two types of errors.

As illustrated in Table 2 the systematic error ranges between 1.08 mm and 1.88 mm with the random error ranging between 0.73 mm and 1.18 mm. Errors in the SI direction are the largest followed by errors in the ML direction and least in the AP direction.

TABLE 2: The systematic and random error as calculated in the medial-lateral, superior-inferior and anterior-posterior direction.

Function	Medial-lateral	Superior-inferior	Anterior-posterior
Σ	1.42 mm	1.88 mm	1.08 mm
σ	0.82 mm	1.18 mm	0.73 mm

There are various margin recipes available to calculate the CTV-PTV margin. Most recipes ignore systematic errors and only use random errors. Examples would include Bel et al.'s recipe of 0.7σ[19] and Antolak et al.'s recipe of 1.65σ.[20]

As illustrated in Table 3, both of these result in much smaller margins as they underestimate the effect of systematic errors. The two main recipes incorporating systematic and random errors, are Stroom's $(2\sum + 0.7\sigma)$[21] and Van Herk's $(2.5\sum + 0.7\sigma)$[22], which result in much larger margins. Stroom's recipe ensures on average that 99% of the target volume receives 95% of the prescribed dose or more. Van Herk's recipe guarantees that 90% of patients in the population receive a minimum cumulative CTV dose of at least 95% of the prescribed dose.

The importance of this concept is illustrated by the work done by Van Herk demonstrating to what extent random and systematic errors affect tumour control. A nomogram published by Van Herk shows tumour probability control loss as a function of margin, with random errors being half as important as systematic errors.[23]

TABLE 3: The clinical target volume-planning target volume margin calculated using different recipes.

Source	Recipe	Medial-lateral	Superior-inferior	Anterior-posterior
Bel et al.	0.7σ	0.58	0.83	0.51
Antolak & Rosen	1.65σ	1.36	1.95	1.21
Stroom et al.	$2\Sigma + 0.7\sigma$	3.42	4.58	2.67

4. Discussion

Hurkmans et al. compiled a summary of recent publications looking at the random and systematic setup errors in the three directions in the head and neck regions.[6] Using this data, Hurkmans et al.

determined that a SD of less than 2 mm for both the random and systematic error can be considered as 'state of the art'.[6]

As demonstrated in Table 2 both random and systematic errors in all three directions are well within the 2 mm mark, thus conforming to accepted standards for good clinical practice.

Hurkmans et al.'s study did not find any directional dependence in the systematic or random errors of the studies they reviewed. In our study the predominant error was in the SI direction. A possible explanation for this can be that the AP and lateral images were reviewed to determine the SI error which could have led to greater variability in the measurements.

It would be unwise to utilise a margin recipe only using random errors to calculate a CTV-PTV expansion margin for safe radiotherapy.

It was decided to use Stroom's margin recipe for this study since it correlates with our institution's clinical practice of ensuring that the entire target volume is encompassed by the 95% isodose line. Stroom's recipe ($2\Sigma + 0.7\sigma$) suggests a margin of 5 mm for this patient cohort if CTV-PTV expansion is done in an isotropic fashion.

Should the clinician decide to use anisotropic CTV-PTV expansion a margin of 5 mm in the SI direction, 3.5 mm in the ML direction and 3 mm in the AP direction can be considered.

An additional area of research includes how Image Guided Radiotherapy (IGRT) techniques like Cone Beam CT can reduce CTV-PTV margin expansion. These technologies are increasingly becoming standard of care in an effort to deliver the safest possible radiotherapy.

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Instructions to the author

Attached are the author guidelines as found on the website for the South African Journal of Oncology (SAJO).

The manuscript was submitted as an original research article to the journal on 22 February 2020 and was subsequently accepted for publication.

Overview

The author guidelines include information about the types of articles received for publication and preparing a manuscript for submission. Other relevant information about the journal's policies and the reviewing process can be found under the about section. The **compulsory cover letter** forms part of a submission and must be submitted together with all the required **forms.** All forms need to be completed in English.

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An original article provides an overview of innovative research in a particular field within or related to the focus and scope of the journal, presented according to a clear and well-structured format. Systematic reviews should follow the same basic structure as other original research articles. The aim and objectives should focus on a clinical question that will be addressed in the review. The methods section should describe in detail the search strategy, criteria used to select or reject articles, attempts made to obtain all important and relevant studies and deal with publication bias (including grey and unpublished literature), how the quality of included studies was appraised, the methodology used to extract and/or analyse data. Results should describe the homogeneity of the different findings, clearly present the overall results and any meta-analysis.

Word limit	3500-4000 words (excluding the structured abstract and references)
Structured abstract	250 words to include a Background, Aim, Setting, Methods, Results and Conclusion
References	60 or less
Tables/Figures	no more than 7 Tables/Figure
Ethical statement	should be included in the manuscript
Compulsory supplementary file	ethical clearance letter/certificate

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Abstract: The Abstract should provide the context or background for the study and should state the study's purpose, basic procedures (selection of study participants, settings, measurements, analytical methods), main findings (giving specific effect sizes and their statistical and clinical significance, if possible), and principal conclusions. The Abstract should not exceed 250 words. Please minimize the use of abbreviations and do not cite references in the abstract. Refer to the relevant article type's guideline you are submitting for the abstract sections.

Introduction: The Introduction should put the focus of the manuscript into a broader context and explain its social and scientific value. Address this to readers who are not experts in this field and include a brief review of the key literature. If there are relevant controversies or disagreements in the field, they should be mentioned. Conclude with a brief statement of the overall aim of the experiments and a comment about whether that aim was achieved. Cite only directly pertinent references, and do not include data or conclusions from the work being reported.

Methods: The Methods section should provide clarity about how and why a study was done in a particular way. It should provide enough detail for reproduction of the findings. Protocols for new methods should be included, but well-established methodological procedures may simply be referenced. A full description of the methods should be included in the manuscript itself rather than in a supplemental file. Only information that was available at the time the plan or protocol for the study was being written must be included; all information obtained during the study belongs in the Results section. If an organization was paid or otherwise contracted to help conduct the research (examples include data collection and management), then this should be detailed in the methods.
The methods section should include:

- The selection and description of participants or description of materials.
- The aim, design and setting of the study.
- The description of the processes, interventions and comparisons. Generic drug names should generally be used. When proprietary brands are used in research, include the brand names in parentheses.
- The type of statistical analysis used, including a power calculation if appropriate.
The Methods section should include a statement indicating that the research was approved or exempted from the need for review by the responsible review committee (institutional or national). If no formal ethics committee is available, a statement indicating that the research was conducted according to the principles of the Declaration of Helsinki should be included.

Results: Present your results in logical sequence in the text, tables, and figures, giving the main or most important findings first. Do not repeat all the data in the tables or figures in the text; emphasize or summarize only the most important observations. Provide data on all primary and secondary outcomes identified in the Methods Section. Give numeric results not only as derivatives (for example, percentages) but also as the absolute numbers from which the derivatives were calculated, and specify the statistical significance attached to them, if any. Restrict tables and figures to those needed to explain the argument of the paper and to assess supporting data. Use graphs as an alternative to tables with many entries; do not duplicate data in graphs and tables. Avoid nontechnical uses of technical terms in statistics, such as "random" (which implies a randomizing device), "normal," "significant," "correlations," and

"sample." Separate reporting of data by demographic variables, such as age and sex, facilitate pooling of data for subgroups across studies and should be routine, unless there are compelling reasons not to stratify reporting, which should be explained.

Conclusion: It is useful to begin the discussion by briefly summarizing the main findings, and explore possible mechanisms or explanations for these findings. Emphasize the new and important aspects of your study and put your findings in the context of the totality of the relevant evidence. State the limitations of your study, and explore the implications of your findings for future research and for clinical practice or policy. Discuss the influence or association of variables, such as sex and/or gender, on your findings, where appropriate, and the limitations of the data. Do not repeat in detail data or other information given in other parts of the manuscript, such as in the Introduction or the Results section.Link the conclusions with the goals of the study but avoid unqualified statements and conclusions not adequately supported by the data. In particular, distinguish between clinical and statistical significance, and avoid making statements on economic benefits and costs unless the manuscript includes the appropriate economic data and analyses. Avoid claiming priority or alluding to work that has not been completed. State new hypotheses, when warranted and label them clearly.

Acknowledgements: Those who contributed to the work but do not meet our authorship criteria should be listed in the Acknowledgments with a description of the contribution. Authors are responsible for ensuring that anyone named in the Acknowledgments agrees to be named. Refer to the acknowledgement structure guide on our *Formatting Requirements* page.

Also provide the following, each under their own heading:

- Competing interests: This section should list specific competing interests associated with any of the authors. If authors declare that no competing interests exist, the article will include a statement to this effect: *The authors declare that they have no financial or personal relationship(s) that may have inappropriately influenced them in writing this article.* Read our **policy on competing interests**.

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The above manuscript section guidelines are adapted from the recommendations from the International Committee of Medical Journal Editors: preparing for submission, available from http://www.icmje.org/recommendations/browse/manuscript-preparation/preparing-for-submission.html on April, 24, 2017.

Comments from reviewers

Find attached comments made by two independent reviewers during the editing process. All of the changes as suggested by the reviewers were made and are reflected in the current manuscript.

Reviewer B:

GENERAL
Please rate the manuscript on the following areas:
1. Is the topic of current interest and appropriate for the Journal?:
Yes

2. Importance?:
Moderate

4. Purpose of Study?:
Defined

5. Methods
Description, level of detail?:
Adequate

6. Statistical Analysis
Description, level of detail?:
Adequate

7. Data
Presentation, level of detail?:
Adequate

8. Conclusion?:
Justified

9. Timeliness?:
Current

10. Overall Evaluation?:
Good

11. Recommendation?:
Acceptable with minor revision

COMMENTS TO AUTHORS
All comments you enter in this section will be provided verbatim to authors.
13. Summary of major findings and shortcomings?:
I would have preferred to see some explanation as to why there was such discrepancy between the different dimensions.

14. Major points that must be addressed?
Please provide a numbered list to facilitate responses with page and/or

line numbers and detailed information on specific recommendations.:
None

15. Minor points or recommended revisions
Please provide numbered list to facilitate responses with page and/or line numbers and detailed information on specific recommendations.:
Line 63 - should read set-up data and not date?
Line 114 - should read compared to and not compared against?
line 126 - I would suggest changing the structure of the sentence slightly

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Reviewer C:

GENERAL
Please rate the manuscript on the following areas:
1. Is the topic of current interest and appropriate for the Journal?:
Yes

2. Importance?:
Moderate

4. Purpose of Study?:
Defined

5. Methods
Description, level of detail?:
Adequate

6. Statistical Analysis
Description, level of detail?:
Adequate

7. Data
Presentation, level of detail?:
Adequate

8. Conclusion?:
Justified

9. Timeliness?:
Current

10. Overall Evaluation?:
Good

11. Recommendation?:
Acceptable with minor revision

COMMENTS TO AUTHORS
All comments you enter in this section will be provided verbatim to authors.
13. Summary of major findings and shortcomings?:
The authors present a well-executed determination of appropriate planning target volume margins for intracranial tumours at their institution. The manuscript is generally well-written and the methods are appropriate. Some elaboration in the Discussion would help to provide context for their results.

14. Major points that must be addressed?
Please provide a numbered list to facilitate responses with page and/or line numbers and detailed information on specific recommendations.:
None

15. Minor points or recommended revisions
Please provide numbered list to facilitate responses with page and/or line numbers and detailed information on specific recommendations.:
1. Abstract: Recommend describing resultant margin estimate in the Results instead of the Conclusions
2. Page 1, paragraph 1: ICRU report 58 describes interstitial brachytherapy reporting. Recommend referencing ICRU 50 or 62, which are external beam guidelines, instead.
3. Page 2, paragraph 8: The reference to “films” is confusing. The text up to this point suggests the images are all electronic.
4. Page 3, paragraph 5: Recommend a reference for these methods.
5. Page 3, paragraph 5: “mi” is not a conventionally used symbol for these quantities. The authors may be referring to the Greek letter “mu”
7. Page 12, Table 3: Should be “Bel” instead of “Ber”
8. Page 12, Table 3: Recommend adding van Herk margin recipe to Table 3 since it is discussed in the immediately preceding paragraph
9. Page 13: The authors should discuss how did they selected the Stroom recipe over van Herk recipe.
10. Page 13: The authors should discuss if they have a hypothesis for why the uncertainty is greatest in the superior-inferior direction.

Datasheet

Attached hereto is a copy of the Excel spreadsheet used for this study. Information captured on the datasheet includes:

1) The patients' RT number
2) Diagnosis
3) Stage
4) Location of their tumour
5) Sex of the patient
6) Age of the patient
7) Fractionation used for their treatment
8) Intent of their treatment
9) Start and end date of their treatment

													APPLIED SHIFT				MEASURED SHIFT			
Study nr	RT nr	Diagnosis	Stage	Location	Sex	Age	Fractionation	Intent	Start date	End date	Fraction	Date	Lat	Long	Vert	Rtn	Lat	Long	Vert	Rtn
1	17/2472	DIPG	N/A	Pons	M	39	1.8Gy 30#	P	25.10.17	06.12.17	1	25-Oct	0	0	0	0	-0.2	0.1	0.2	-0.2
											2	26-Oct	0	0	0	0	-0.1	0.2	0.3	-0.1
											3	27-Oct	0	0	0	0	0.1	0.1	0.2	-0.1
											8	03-Nov	0	0	0	0	-0.1	0.2	0.2	0.1
											14	13-Nov	0	0	0	0	-0.2	0.1	0.2	0.1
											19	20-Nov	0	0	0	0	-0.1	0.2	0.2	-0.1
											24	27-Nov	0	0	0	0	-0.2	0.1	0.2	-0.1
											28	04-Dec	0	0	0	0	-0.2	0.2	0.1	0.1
2	17/2148	Astrocytoma	Grade 3	Cerebrum	F	32	2Gy 29#	P	09.11.17	16.11.17	1	09-Oct	0	0	0	0	0	-0.1	0.1	0
											2	10-Oct	0	0	0	0	-0.3	0.1	0.1	0
											3	11-Oct	0	0	0	0	-0.1	-0.1	0.1	0
											8	18-Oct	0	0	0	0	-0.2	-0.1	0.3	-2.9
											13	25-Oct	0	0	0	0	-0.1	-0.1	0.2	0
											18	01-Nov	0	0	0	0	-0.2	-0.1	0.3	-0.1
											24	09-Nov	0	0	0	0	-0.1	-0.1	0.1	-0.1
											27	14-Nov	0	0	0	0	-0.3	-0.2	0.1	-0.1
3	17/1630	Glioblastoma	Grade 4	Frontal	M	67	2Gy 30#	P	25.07.17	07.09.17	1	25-Jul	0	0	0	0	-0.1	0.1	-0.1	0.1
											2	26-Jul	0	0	0	0	-0.1	0.1	-0.1	0.1
											3	27-Jul	0	0	0	0	-0.2	0.2	-0.1	0
											8	03-Aug	0	0	0	0	-0.2	0.1	-0.1	0.1
											13	11-Aug	0	0	0	0	0	0.1	-0.1	0
											18	18-Aug	0	0	0	0	-0.1	0.2	-0.2	0
											23	25-Aug	0	0	0	0	-0.1	0.1	-0.2	0.1
											28	05-Sep	0	0	0	0	-0.3	0.2	-0.2	0.1
4	15/1215	Chordoma	N/A	Clivus	M	27	2Gy 15#	P	11.05.17	01.06.17	1	11-May	0	0	0	0	0	0.3	0.3	0
											2	12-May	0	0	0	0	-0.1	0	0.4	0
											3	15-May	0	0	0	0	-0.1	0.1	0.3	0
											8	23-May	0	0	0	0	-0.2	-0.1	0.2	0
											13	30-May	0	0	0	0	-0.1	-0.2	0.4	0
5	15/2535	Pit Adenoma	N/A	Pituitary	F	63	1.8Gy 28#	R	15.03.17	26.04.17	1	15-Mar	0	0	0	0	0.1	-0.1	-0.1	0.1
											2	16-Mar	0	0	0	0	0.1	-0.2	0	0.1
											3	17-Mar	0	0	0	0	0.1	-0.1	0	0.1
											8	27-Mar	0	0	0	0	0.2	-0.1	0	0
											13	03-Apr	0	0	0	0	0.2	-0.2	0.1	0.1
											18	10-Apr	0	0	0	0	0.2	-0.2	0.1	0.1
											23	19-Apr	0	0	0	0	0.2	-0.2	0	0.1
6	16/2916	Glioblastoma	Grade 4	Frontal	F	58	2.25Gy 20#	P	19.12.16	19.01.17	1	19-Dec	0	0	0	0	0.2	0.5	0.2	-1
											2	20-Dec	0	0	0	0	0.2	0.5	0.1	-1.7
											3	21-Dec	0	0	0	0	0.1	0.5	0.2	0
											8	30-Dec	0	0	0	0	0	0.4	0.2	-0.2
											13	09-Jan	0	0	0	0	0	0.1	0.1	0
											18	16-Jan	0	0	0	0	-0.1	0.5	0.3	-0.1
7	16/2437	Meningioma	Grade 1	Suprasellar	F	45	1.8Gy 30#	R	28.12.16	09.02.17	1	28-Dec	0	0	0	0	0.4	0.2	0	0
											2	29-Dec	0	0	0	0	0.4	-0.2	0.1	0
											3	30-Dec	0	0	0	0	0.3	-0.2	0.1	0
											8	09-Jan	0	0	0	0	0.3	-0.1	0.1	0
											13	16-Jan	0	0	0	0	0.3	-0.2	0.1	0
											18	23-Jan	0	0	0	0	0.3	0	0	-0.1
											22	30-Jan	0	0	0	0	0.3	-0.2	0.1	-0.1
											28	07-Feb	0	0	0	0	0.3	0	0	-0.1
8	16/2549	Meningioma	Grade 2	Frontal	M	42	1.8Gy 33#	R	09.01.17	24.02.17	1	09-Jan	0	0	0	0	0.2	0.1	0	0
											2	10-Jan	0	0	0	0	0.2	0.1	0	-0.1
											3	11-Jan	0	0	0	0	0.2	0.1	0	-0.1
											8	18-Jan	0	0	0	0	0.1	0.1	0.1	-0.1
											13	26-Jan	0	0	0	0	0.2	0.1	0	0
											18	02-Feb	0	0	0	0	0.1	0	0	0
											23	09-Feb	0	0	0	0	0.2	0	0	0
											28	17-Feb	0	0	0	0	0.2	-0.1	0.1	0
9	14/437	Pit Adenoma	N/A	Pituitary	M	54	1.8Gy 28#	R	02.11.16	13.12.16	1	02-Nov	0	0	0	0	0	-0.1	0	0.1
											2	03-Nov	0	0	0	0	-0.1	0	0.1	0
											3	04-Nov	0	0	0	0	0	-0.3	0.2	0
											8	14-Nov	0	0	0	0	0	-0.2	0.2	0
											13	21-Nov	0	0	0	0	-0.1	-0.1	0.2	-0.1
											18	28-Nov	0	0	0	0	-0.1	-0.1	0.1	0
											23	05-Dec	0	0	0	0	-0.2	-0.2	0.2	0
10	10/2263	Meningioma	Grade 1	Sphenoid	F	45	1.8Gy 30#	R	26.09.16	04.11.16	1	26-Sep	0	0	0	0	0	-0.4	0	0.1
											2	27-Sep	0	0	0	0	0.1	-0.3	0	0
											3	28-Sep	0	0	0	0	0	-0.3	0	0
											8	05-Oct	0	0	0	0	0.1	-0.3	0	0
											13	13-Oct	0	0	0	0	0.2	-0.3	0.1	0
											18	20-Oct	0	0	0	0	0.1	-0.5	0.1	0
											23	27-Oct	0	0	0	0	0.2	-0.6	0.1	0

11	16/166	Pit Adenoma	N/A	Pituitary	M	70	1.8Gy 28#	R	04.04.16	16.05.16	1	04-Apr	0	0	0	0	-0.2	0.3	0	0
											2	05-Apr	0	0	0	0	-0.3	-0.1	0	0
											3	06-Apr	0	0	0	0	-0.2	-0.1	-0.1	0
											8	14-Apr	0	0	0	0	0	0.2	0	-0.1
											13	21-Apr	0	0	0	0	-0.3	-0.1	0	-0.1
											18	29-Apr	0	0	0	0	-0.2	0.1	0	0
											23	09-May	0	0	0	0	-0.3	0.3	0	-2
12	15/2897	Meningioma	Grade 1	Parietal	F	44	2.25Gy 18#	R	08.03.16	07.04.16	1	08-Mar	0	0	0	0	0.2	-0.3	0	-0.1
											2	10-Mar	0	0	0	0	0.1	-0.3	0	0
											3	11-Mar	0	0	0	0	0.1	-0.3	0	-2
											8	18-Mar	0	0	0	0	0	-0.3	0.1	-0.1
											13	30-Mar	0	0	0	0	0	-0.5	0	0
13	16/355	GBM	Grade 4	Frontal lobe	M	38	2Gy 30#	P	01.03.16	16.04.16	1	01-Mar	0	0	0	0	-0.2	-0.6	-0.2	0
											2	03-Mar	0	0	0	0	-0.2	-0.6	0.1	0
											3	04-Mar	0	0	0	0	-0.2	-0.2	0.1	0
											8	11-Mar	0	0	0	0	-0.1	-0.6	0	0
											13	18-Mar	0	0	0	0	-0.3	-0.6	-0.1	0
											19	31-Mar	0	0	0	0	-0.2	-0.5	-0.1	0
											24	07-Apr	0	0	0	0	-0.3	-0.4	0.1	0
14	15/2218	Meningioma	Grade 1	Sphenoid	F	60	1.8Gy 30#	R	15.12.15	02.02.16	1	18-Dec	0	0	0	0	-0.1	-0.2	-0.1	-0.1
											6	23-Dec	0	0	0	0	0.1	-0.4	0.1	0
											11	31-Dec	0	0	0	0	-0.1	-0.3	0	-0.1
											16	11-Jan	0	0	0	0	-0.1	-0.3	0	-0.1
											21	19-Jan	0	0	0	0	0	-0.2	0.2	-0.1
											26	27-Jan	0	0	0	0	0	-0.3	0.1	0
15	15/765	Pit Adenoma	N/A	Pituitary	M	70	1.8Gy 28#	R	23.10.15	07.12.15	2	26-Oct	0	0	0	0	0	-0.1	0.3	-0.2
											8	03-Nov	0	0	0	0	0.1	0.2	0	0
											13	11-Nov	0	0	0	0	-0.1	0.2	-0.1	-0.2
											20	20-Nov	0	0	0	0	0.1	0.1	0.3	-0.2
											26	01-Dec	0	0	0	0	0.2	0.1	0.2	-0.1
16	18/1366	LG Glioma	Grade 2	Parietal	M	34	1.8Gy 28#	R	02-Jan	11-Feb	1	02-Jan	0	0	0	0	-0.1	0.5	-0.1	-0.1
											2	03-Jan	0	0	0	0	-0.1	0.1	0	-0.1
											3	04-Jan	0	0	0	0	-0.1	0.2	0.1	0
											8	11-Jan	0	0	0	0	0	0.2	0.1	0
											13	18-Jan	0	0	0	0	-0.1	0.1	0.1	0
											18	25-Jan	0	0	0	0	-0.1	0.1	0	0
											23	04-Feb	0	0	0	0	-0.2	-0.1	0	0
17	19/0578	DIPG	Grade 4	Pons	F	10	1.8Gy 30#	P	03-Mar	28-Mar	1	05-Mar	0	00-Jan	0	00-Jan	0	0.1	0	-0.1
											2	06-Mar	0	0	0	0	0.1	0.1	0	-0.1
											3	07-Mar	0	0	0	0	0.2	0.1	0	-0.1
											8	15-Mar	0	0	0	0	0.1	0.1	0	0
											13	25-Mar	0	0	0	0	0.1	0.1	0	0
18	19/0344	GBM	Grade 4	Parietal	M		2Gy 30#	P	06-Mar	28-Mar	1	06-Mar	0	0	0	0	0.1	-0.3	0.1	0
											2	07-Mar	0	0	0	0	-0.1	-0.2	0.1	0
											3	08-Mar	0	0	0	0	0	-0.3	0.1	0
											8	20-Mar	0	0	0	0	-0.1	0.1	0.2	0
											15	28-Mar	0	0	0	0	-0.1	0	0.3	0
19	19/0500	GBM	Grade 4	Parietal	M		2Gy 30#	P	07-Mar	28-Mar	1	07-Mar	0	0	0	0	0	-0.2	-0.1	0
											2	08-Mar	0	0	0	0	-0.1	-0.2	-0.1	0
											3	11-Mar	0	0	0	0	-0.2	0.1	-0.1	0
											8	19-Mar	0	0	0	0	0	-0.1	-0.1	0
											14	28-Mar	0	0	0	0	-0.1	-0.1	0.1	0
20	18/3004	GBM	Grade 4	Temporal	F	68	2Gy 30#	P	18.12.18	01.02.19	1	18-Dec	0	0	0	0	-0.1	-0.3	-0.1	0
											2	19-Dec	0	0	0	0	0	-0.3	0	0.1
											3	20-Dec	0	0	0	0	-0.2	-0.2	-0.1	0
											8	31-Dec	0	0	0	0	-0.1	-0.2	-0.1	0
											14	09-Jan	0		0	0	-0.1	-0.1	-0.1	0.1
											19	16-Jan	0	0	0	0	0	0	0	0