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Literature Review

Magnetic resonance imaging in radiotherapy treatment target volumes definition for brain tumours: a systematic review and meta-analysis

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Abstract

Purpose: The aim of this study is to establish clinical evidence regarding the use of magnetic resonance imaging (MRI) in target volume definition for radiotherapy treatment planning of brain tumours.

Methods: Primary studies were systematically retrieved from six electronic databases and other sources. Studies included were only those that quantitatively compared computed tomography (CT) and MRI in target volume definition for radiotherapy of brain tumours. Study characteristics and quality were assessed and the data were extracted from eligible studies. Effect estimates for each study was computed as mean percentage difference based on individual patient data where available. The included studies were then combined in meta-analysis using Review Manager (RevMan) software version 5.0.

Result: Five studies with a total number of 72 patients were included in this review. The quality of the studies was rated strong. The percentages mean differences of the studies were 7·47, 11·36, 30·70, 41·69 and −24·6% using CT as the baseline. The result of statistical analysis showed small-to-moderate heterogeneity; $\tau^2 = 36{\cdot}8$; $\chi^2 = 6{\cdot}23$; df = 4 ($p = 0{\cdot}18$); $I^2 = 36\%$. The overall effect estimate was −1·85 [95% confidence interval (CI); −7·24, 10·94], $Z = 0{\cdot}40$ ($p = 0{\cdot}069 > 0{\cdot}5$).

Conclusion: Brain tumour volumes measured using MRI-based method for radiotherapy treatment planning were larger compared with CT defined volumes but the difference lacks statistical significance.

Keywords: brain tumours; computed tomography; magnetic resonance imaging; meta-analysis; radiotherapy treatment planning

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INTRODUCTION

Brain tumours are one of the leading causes of death among cancer patients.[1] Approximately, 238,000 new cases of brain tumours and other

central nervous system tumours were diagnosed in 2008 with about 175,000 mortality worldwide.[2] Radiotherapy remains the best option for the treatment of un-resectable brain tumours and is responsible for about 78% of non-surgical cancer treatments.[3] The aim of radiotherapy treatment method is to deliver high radiation dose to tumour volume (TV) while sparing adjacent normal tissues.[4,5] This is usually achieved using advanced radiotherapy treatment techniques such as three-dimensional (3D) conformal radiation treatments and intensity-modulated radiotherapy.[6] These treatment methods confine radiation beam strictly to three-dimensional shape of the target/TV.[4] The success of these techniques relies upon the accuracy of TV definition. Inaccuracies in delineating the TV could significantly increase the likelihood of the treatment failure.[1,5,7]

To date, computed tomography (CT) remains the most widely used imaging modality in TV definition and dose calculation for Radiotherapy Treatment Planning (RTP).[8,9] This is due to its high geometrical accuracy and electron density information required for treatment dose calculation.[8] However, several authors reported that CT alone does not always adequately delineate TV, most especially when the tumour resides within complex bony structure such as base of the skull.[10–12] Owing to this challenge several other imaging modalities were introduced into RTP to complement CT through the process of image registration. The use of image registration techniques such as positron emission tomography-computed tomography (PET-CT), positron emission tomography-magnetic resonance imaging (PET-MRI), single-positron emission computed tomography-computed tomography (SPECT-CT), single-positron emission computed tomography-magnetic resonance imaging (SPECT-MRI), PET-CT plus magnetic resonance imaging (MRI), SPECT-CT/MRI in RTP were reported in different studies.[13–23] These imaging methods were shown to define TV with greater certainties as the information obtained from different imaging modalities were complementary in many instances.[24–27] However, these methods have many downsides which include; errors associated with image registration process, patient inter-procedure positioning error as well as cost and time implication associated with the use of multiple imaging modalities.[8,28,29]

In the past, MRI alone was introduced into RTP due to its excellent soft tissues characterisation and multi-planar capability.[11] It was shown to give greater tumour information than CT at many different anatomical sites.[30,31] However, as at then, this technique had not seriously challenged CT in TV definition for RTP due to its inherent image distortion and lack of electron density information required for treatment dose calculation.[29–31] This precluded its use alone but only to complement CT in TV definition for RTP.[30–33] Recently, several MRI distortion correction techniques such as gradient distortion correction technique were demonstrated with some successes.[34–37] In view of this, several authors probed the feasibility of using MRI alone in TV definition for RTP of brain tumours using CT as a yard stick.[10–12,29,38] However, conflicting findings were noted among these studies. Although MRI-based method was shown to measure larger TV than CT-base method in a number studies,[10–12,29] with CT defined TV larger in one other study.[38] Nevertheless, no systematic review was conducted to establish the most appropriate treatment planning method between the two imaging methods.

This review is therefore, aimed at critically evaluating the available literature data that evaluated the use of MRI in TV definition for brain tumours using CT as the baseline. This will establish strong and reliable clinical evidence with regards to the use of MRI alone in TV definition for RTP of brain tumours.

REVIEW METHODS

Study identification

A systematic search was conducted on six electronic databases from January 2000 to December 2013 and later updated to 2015. The electronic databases searched were Medline, ScienceDirect, Web of Knowledge, CINAHL, Amed and Cochrane Central Register of Controlled Trials. Medline search method was primarily adopted and this was adjusted subsequently to suit the

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other databases. Medical Subject Headings and free text key terms were used during the search. Search terms were classified to cover the target participants, interventions and the outcome. The electronic search was limited to only English language published articles but no sex, age or geographical restriction was applied. This was supplemented by Grey literature search and hand search of key journals. In addition, reference lists of potential studies for inclusion were scrutinised for more relevant studies.

Study selection

This review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA).[39] The study selection was conducted by the primary reviewer based on the pre-determined inclusion criteria set in the review protocol. Only studies that compared CT and MRI in TV definition for RTP of brain tumours were considered for inclusion. The selection was done in two stages.[40] The first stage selection was based on titles and abstracts of all the studies retrieved during the search. The second stage was done based on the full report of the article.

Data extraction

Standardised electronic data extraction form established by Cochrane collaboration was used for the data extraction. The data extraction form was initially pilot tested on a couple of included studies to identify any mislaid or surplus data.[40,41] Participants' characteristics, details of the interventions (CT and MRI together with their respective imaging parameters used) as well as study characteristics and outcomes were the primary information extracted from each of the studies. The outcomes retrieved were the summary statistics (means and standard deviations) for both MRI and CT defined volumes as well as the number of participants. The available individual patient data (IPD) from three out of the five included studies were accessed and retrieved.

Quality assessment

Effective public Health Practice Project (EPHPP) quality assessment tool for quantitative studies was used for the quality assessment in this review.[42] This tool contains seven components (A–H) with a total number of 18 questions each with answer options; yes, no or unclear. A clear guide on how to answer each of the questions, rating of every component as well as overall rating is contained on a separate document known as dictionary for EPHPP.

Statistical analysis

TV obtained from both CT and MRI were the primary outcomes in this review. The effect estimate was calculated as percentage of non-overlap (percentage mean difference) taking CT volumes as a baseline using Cohen's d methods.[43] This was calculated using Microsoft excel 2007 based on IPD retrieved from the three of the five studies. For the remaining two studies, this was calculated based on the published summary statistics. The available IPD were then transferred on to SPSS version 14.0 and re-analysed using Paired t-test for independent variables for purpose of consistency.[40] The summary statistics obtained from the re-analysis of the three studies and the ones published in the remaining two studies were combined in meta-analysis using RevMan software version 5.0. The statistical method used was inverse variance method using random effect analysis model with 95% confidence interval (CI). Visual examination of the overlap of whisker lines on the forest plot and χ^2 test was done to assess the presence and also quantify the extent of heterogeneity.[44,45]

RESULTS

A total number of 609 studies were identified during the search but only nine studies[10–12,29,38,46–49] were left after duplicates and irrelevant studies were discarded based on titles and abstract. Out of the nine studies left, only five studies[10–12,29,38] met the criteria for inclusion based on full article report. The study selection stages and results were presented in the PRISMA flow chart (Figure 1).

Five studies with a total number of 72 patients were included in this review. The sample size, mean TV and standard deviation of each of the studies are given in Table 1. Summary of each of the included studies is included in Table 2.

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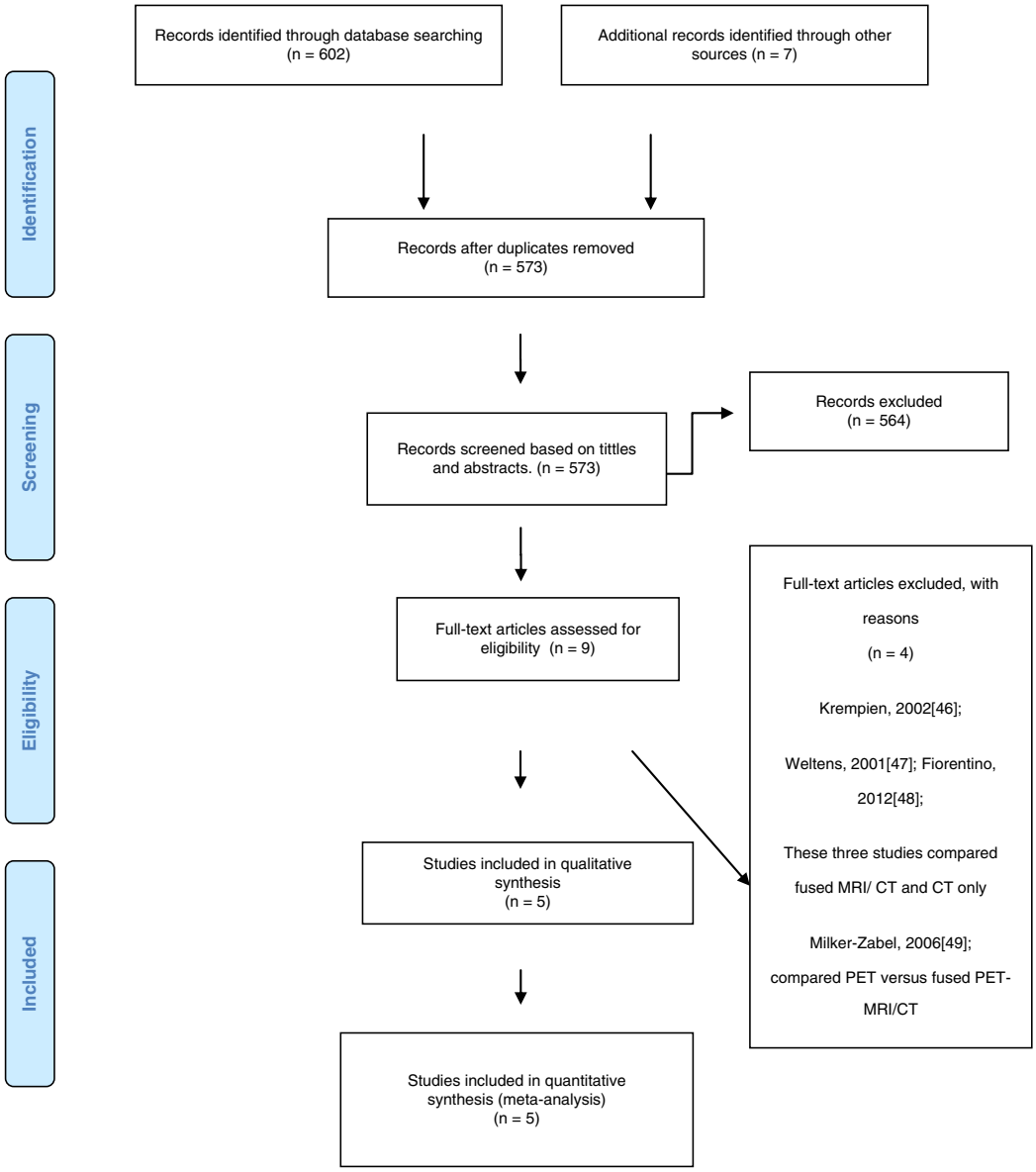

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) 2009 flow diagram.

The results of the four studies[10–12,29] revealed that MRI consistently defined larger TV than CT. The percentage mean differences of the included studies are contained in Figure 2. On the basis of the IPD, the only one study[38] that favoured CT indicated that MRI underestimated the TVs in 90% of cases. The other two studies indicated that MRI identified larger volumes in 54·5[11] and 96%[29] of cases, respectively. The overall effect estimate was −1·85 (95% CI; −7·24, 10·94), $Z = 0{\cdot}40$ ($p = 0{\cdot}069 > 0{\cdot}5$) as shown in Figure 3.

DISCUSSION

A total of five studies ($n = 72$) identified through systematic searches were included in this review. Each of the included studies recruited patients with brain tumours who had both CT and MRI for RTP. The overall estimate of the review showed that MRI when compared with CT, gives larger TV but the difference was not statistically significant. We could not compare this finding with any other study as no systematic review or meta-analytic study was identified on

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Table 1. Sample size and summary statistics of the included studies

s/no.	Study ID	Sample size	Intervention type	Mean volumes	SD
1.	Khoo[10]	7	MRI	19·6	14·2
			CT	17·6	10·8
2.	Weber[38]	10	MRI	64·72	17·15
			CT	85·87	31·41
3.	Kristensen[29]	11	MRI	55·34	35·99
			CT	51·43	33·49
4.	Datta[12]	21	MRI	71·64	58·42
			CT	50·56	37·21
5.	Prabhakar[11]	25	MRI	19·67	13·73
			CT	15·05	10·13

Abbreviations: MRI = magnetic resonance imaging; CT = computed tomography.

the subject area. However, comparison was done among the included studies.

Four of the studies were in good agreement in favour of MRI-based method, whereas one other study revealed contrasting finding. The four studies revealed that MRI-based method defined larger TV than CT-based method with effects estimates ranging from small to moderate based on Cohen's interpretation.[43] In contrast, the other study revealed that CT-based method identified larger volume than MRI in patients with glioblastoma multiforme.[38]

Similarly, detailed evaluation of each of the included studies based on the IPD revealed that in some cases, MRI defined larger volume than CT, whereas in some instances CT defined TVs were larger. This was noted even among the studies where the mean TV appeared larger on MRI. A study by Kristensen et al.[29] revealed that MRI defined larger TV in 55·5% ($n = 6$) of cases, whereas CT defined TV were larger in the remaining 54·5% ($n = 5$).[29] Prabhakar et al.[11] reported larger TV in 96% ($n = 24$) of cases on MRI and 4% ($n = 1$) on CT. Similarly, MRI and CT TV were larger in 71·43% ($n = 5$) and 28·57% ($n = 2$) of cases, respectively, in the study of conducted by Khoo et al.[10] In contrast, Weber et al.,[38] reported larger TV on CT in 90% ($n = 9$) of cases, whereas the remaining 10% ($n = 1$) TVs were larger on MRI.[38] The variability in effect size across and within the studies could be attributed to slight variation in patients characteristics, intervention design (equipment type and imaging parameters used) as well as the use of small sample size in the included studies.

With regards to the patients' characteristics, different diagnosis of brain tumours such as glioma, meningioma, glioblastoma pituitary adenoma were reported in different studies. Moreover, there was variation in location and size of the tumours among the patients. It is worthy of note that tumour located adjacent to bony structures would be better demonstrated on MRI as the quality of its image is not compromised due to artefact from the adjacent bony structure. On the other hand, CT gives better information and thus identifies a larger volume than MRI where the tumour has bony component. This is because CT is better than MRI in bone detail demonstration. This could be the possible reason in the variation of the effect sizes within the studies. In addition, Huck[50] revealed that effect estimates vary with different set of participants no matter how similar they are with the original population. As different studies used different sets of population, this might also be additional reason for variation in the effect sizes across the studies.

On the part of the intervention design, different studies used CT and MRI scanner from different manufacturers and specification. Some studies used 0·23T, whereas some used 1·5 MRI scanners. Moreover, the use of different imaging protocols/parameters was reported in different studies. These include; slice thickness, kilovoltage and tube current for CT as well as matrix size, Repetition time, slice thickness for the MRI procedure. The use of different imaging parameters and protocols could affect the image quality and thus the outcome in different ways across the studies. This is in accordance with the evidence provided by Stall et al.[51] who noted that the TV identified using different MRI protocols would appear differently.

The variability with regards to the effect size within the studies could be due to random error in the outcome measurement. Scientific measurements are not without error either of human nature or from the equipment involved. Moreover, as two imaging modalities are involved and it is nearly impossible to replicate exactly the same patient position on each of the modalities. However, any slight change in patient position might affect the size of the TV. Thus, patient inter-procedure

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Table 2. *Characteristics of the included studies*

Study	Kristensen[29]	Weber[38]	Datta[12]	Prabhakar[11]	Khoo[10]
Participants	11 patients with intracranial brain tumours	10 consecutive glioblastoma patient	21 glioma patients	25 patients with different diagnosis of brain tumours	7 patients with base of the skull meningiomas
Intervention	Low field (0·23T) open MR system. Images acquired were T1 FFE3D axial with and without gadolinium contrast agent and sagittal. The parameters used were TR, TE, flip angle, matrix and FOV of 23 ms, 8 ms, 35°, 512 × 512 and 300 mm^2, respectively. Slice thickness was 0·5 cm. Image distortion was corrected using GDC software	Low field (0·23T) open MR equipment was used to simulate the patients within 24–48 hours after CT. Gadolinium-enhanced contrast images were acquired for the planning. MR distortion was corrected using GDC	1·5T MRI system. Spin-echo sequence non-contrast T2-weighted (TR/TE, 2/n: 3000/12, 80/1) and contrast-enhanced T1-weighted (1012/14/2) axial sections were acquired using a 256 × 256 matrix size, a bandwidth of 65 Hz/pixel, and an FOV of 250 mm	Contrast-enhanced MRI performed with slice thickness of 2·5 mm	1·5T Siemens Vision MR scanner was used to acquire T1W volumetric sequences. The TR, TE, flip angle and inversion time used were 9·7, 4 ms, 12° and 300 ms, respectively. Matrix used was 256 × 256 along with FOV of 230 × 230 mm. 3 mm contagious slice were reconstructed from the volumetric information. Distortion assessment done using Radionics skull phantom revealed negligible distortion of about 1 m over the skull volume. No further distortion was conducted
Comparator	CT simulation conducted in the same patient's position set up as MRI using 0·5 cm slice thickness	Contrast-enhanced CT images using 3 mm slice thickness. Positioning error	Contrast-enhanced axial CT images acquired using 240 mm FOV and 512 × 512 matrix size	CT conducted using sequential mode, 60–80 slices were acquired for all the patients using 2·5 mm slice thickness with contrast agents	High speed (GE medical system) or Somaton DR2 (Siemen Medical engineering, Germany) CT scanner were used for the planning. Contrast-enhanced axial images were obtained 3 mm slice thickness in the region of the tumour and 5-mm thick slice outside the tumour area
Outcomes	Tumour volume as delineated on CT and MRI. The volumes were delineated independently by two specialised radiologist by means of visual display tools. The unit of measurement used was cubic centimeter (cm^3)	GTVs identified on the imaging studies. These were identified independently by two experienced radiation oncologist	GTV and CTV delineated best on contrast-enhanced CT and MRI studies. These volumes were delineated by and experienced neuro-radiologist together radiation oncologist	Tumour volume as delineated on CT and MRI. The unit of measurement used was cubic centimeter (cm^3)	GTV identified on the contrast-enhanced CT and MRI studies. These volumes were delineated by two independent radiation oncologists
Results	The mean MRI and CT volumes were 55 + 34 cm^3 and 51 + 32 cm^3, respectively	The GTVs delineated on CT were significantly larger than that of MRI. The mean MRI and CT volumes were 64·72 ± 17·5 cm^3 and 85·87 ± 31·41 cm^3	The mean value for MRI and CT volumes were 71·64 + 58·42 cm^3 and 50·56 + 37·21 cm^3, respectively	The mean value for MRI was 19·67 ± 16·13 cm^3 and median of 16·13 cm^3 with a range of 3·25–50·37 cm^3. Mean volume for CT was 15·05 ± 10·13 cm^3 with a median of 11·63 cm^3 and range of 3–6·29 cm^3	The mean MRI and CT tumour volumes were 19·6 + 14·2 cm^3 and 17·6 + 10·8 cm^3, respectively

Abbreviations: MRI, magnetic resonance imaging; CT, computed tomography; CTV, clinical tumour volume; FOV, field of view; GDC, gradient distortion correction; GTV, gross tumour volume; TE, echo time; TR, repetitive time.

positioning error could also be among the reasons for variation in the effect size within the studies.

Thus, when choosing the best or appropriate method for RTP of brain tumour, the tumour location and characteristics should be considered. In addition, the implication of using the likely best treatment planning option should also be taken into consideration. CT is readily available, cost effective, shorter imaging time relative to MRI and identifies more information where there is bony involvement. However, it involves the use of ionising radiation and thus carries a potential risk. On the other hand, MRI gives more information in cases where the tumour is adjacent to bone, it does not involve ionising radiation and has wide range of imaging protocols. Nevertheless, it is costly and requires the use of longer image acquisition time.

STRENGTH AND LIMITATION OF THE EVIDENCE

All the studies included were quasi-experimental research and of good quality based on the effective public Health quality assessment tool for quantitative studies. There was excellent control of confounders due to adoption of repeated measure design, where the same group of participants received both CT and MR interventions. However, the quality of the studies varies slightly based on the rigour of approach which with the research design was executed. It was not clear in some studies if some methods have not been used or were omitted from the report. These methods include; blinding of the observers, use of at least two independent observers, time interval between CT and MRI intervention procedures and interval between outcome assessments of different groups. In addition, participants' demographics, details of the imaging design such as type of the particular imaging modality used, and the imaging parameters as well as distortion correction method were also not reported in detail in some studies. For instance, Khoo et al.[10] was the only study that reported on the participants' demographics and blinding of the observers with regards to the participants identity and clinical details. In addition, except Khoo et al.[10] who reported an interval of 2 weeks, no study disclosed the interval between TV assessment on CT and MRI modality. This was believed to reduce familiarity of cases and thus bias in the outcome assessment. However, the strength of this study was limited due its small sample size. In the study conducted by Khoo et al.,[10] a total of seven participants were involved. This was the least among all the studies in this review. Moreover, Weber et al.[38] and Datta et al.[12] were the only studies who reported interval of 1–2 days between CT and MRI procedure to avoid change in the tumour status due to time.

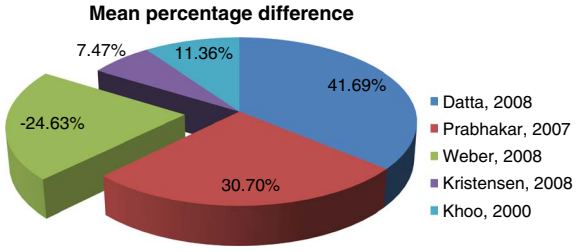

Figure 2. Percentage mean differences of the included studies.

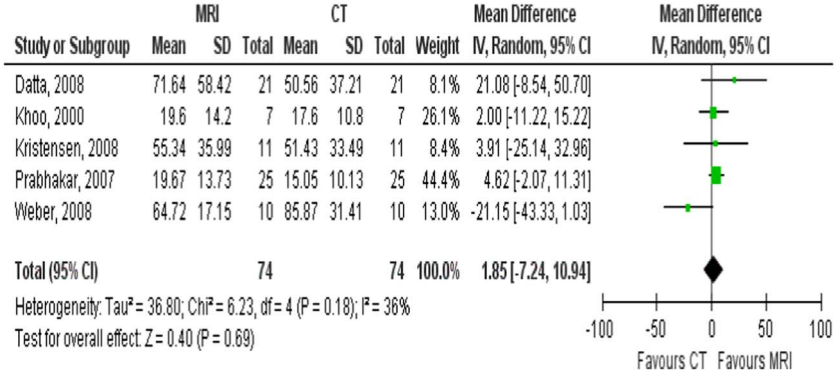

Figure 3. Forest plot: overall estimate.
Abbreviations: CT, computed tomography; CI, confidence interval; MRI, magnetic resonance imaging.

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However, it is worthy of note that, omitting a method in a report does not categorically mean it has not been employed during the research. Therefore, these issues should be treated with cautions when interpreting the strength of the evidence of this review.

Furthermore, the review method is associated with some methodological flaws which might introduce bias that could affect the strength of its findings and conclusion. This includes the use of single reviewer in conducting the study selection, quality assessment and data extraction. However, the extent to which biases were introduced was somehow limited as we followed strictly, the predetermined selection criteria set in the protocol to limit the selection bias. Identification bias was also limited by including large number of sources during the study identification. Standardised data extraction form and quality assessment tool used were also were good method of minimising bias.[41] However, an update of this review is recommended with more rigorous methodological design when more data becomes available.

CONCLUSION

This study concluded that the TVs measured on MRI-based method for RTP of brain tumours were larger in many instances compared with TVs defined using CT-based method. However, this difference was not statistically significant.

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Conflicts of Interest

The authors declare no conflicts of interest.

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