Quality of life measurements estimation from MRI data in metastatic brain tumour patients

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ABSTRACT

Brain metastases occur when tumour cells developed anywhere in the body spread to the brain. Radiotherapy (RT) is a treatment option for brain metastases that aims to eliminate the tumor cells within the brain, but it also causes healthy tissue damage that can lead to cognitive decline.

In order to measure the effects of different RT treatments on the patients, the quality of life (QoL) is measured to determine which one leads to the best cognitive outcome. For this purpose, tests with varying degrees of specificity, such as, neurocognitive assessment (NCA), patient reported outcome (PRO) and Karnofsky Performance Scale (KPS) aim to quantify the cognitive change of the patients before and after RT. However, the high cost of NCAs, patient dependency of PROs and unreliability of KPS highlight the need for a new approach to measure the cognitive state of patients. Such novel approach could estimate the QoL of the patients solely based on anatomical markers from MRI scans, reducing costs and patient interactions alike. In order to develop such tool, the anatomical markers related to cognitive must be identified first.

In response, we performed a systematic review to analyse existing literature on the anatomical changes captured in MRI that have been linked to cognitive decline. We searched the Pubmed database where studies that evaluated cognitive change as a result of a specific anatomical change after RT were selected. Out of 298 publications, 16 were chosen, wherein tumor morphology, lesion number and location, peritumoral edema and necrosis were identified as the most relevant anatomical markers for the estimation of the QoL of brain metastatic patients based on MRI data.

We identified multiple limitations within our review regarding inhomogeneous patient cohorts, low-quality image processing and the lack of correlation between the anatomical changes and the effect that might have in the QoL of patients. Consequently, although the studies reviewed all reached similar conclusions, further research based on larger samples with more uniform patient cohorts and advanced imaging must be conducted, to be able to definitively quantify the effect these anatomical changes have in the QoL of patients after RT.

I. INTRODUCTION

One of the most common complications [1] when it comes to cancer is the migration of the tumour cells to the brain, which is known as brain metastase. Brain metastases occur in about one-third of oncology patients [1] and its development is strongly correlated with poor survival [2].

Radiotherapy (RT) is one of the treatment options for brain metastases based on delivering harmful radiation to the affected site with the aim of eliminating malicious cells. However, RT is not a selective treatment, meaning it damages tumour and healthy cells alike, triggering various forms of tissue decay, such as, cortical thinning and white matter abnormalities [3]. These changes can lead to the development of cognitive decay and affect the quality of life (QoL) of the patient after RT.

Previous studies indicate that 50% to 90% of the patients that undergo RT will eventually develop some degree of cognitive decline [4][5]. In order to monitor the QoL of the patients, multiple methods have been developed with varios level scrutiny. The gold standard method is a neuropsychological interview or neurocognitive assessment (NCA) conducted by a professional, which due to its resource requirements are used the least, but also provide the most detail for multiple cognitive domains, such as, language and memory, among others.

The next level of insight is derived from patient-reported outcome (PRO) questionnaires, which are more prevalent than NCAs due to the low resource requirements. In this questionnaire, the patients themselves complete the quetioneer, meaning that PROs rely on how cooperative the patients are. Moreover, QoL can also play a role in the patients' capability of completing a PRO test, leading to a potencial bias that the worse performing patients will more likely to miss such tests. Consequently, PRO questionnaires are liable to missing datapoints.

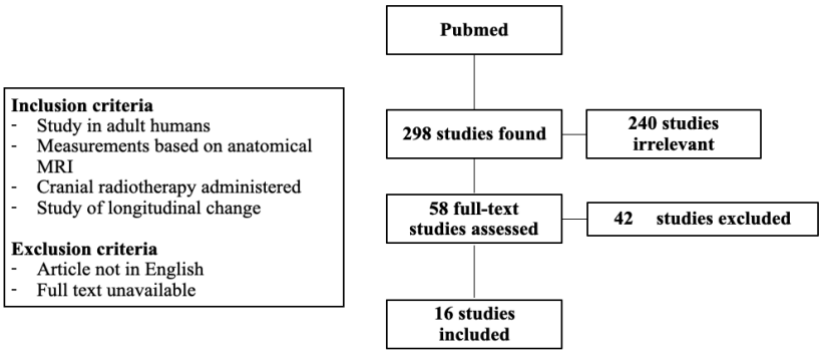

Figure 1: Flow-chart of article selection, and overview of inclusion and exclusion criteria.

The last layer of tests estimating the QoL of patients includes the Karnofsky Performance Scale (KPS) [6]. The KPS is a tool used by physicians to classify the patients based on their functional impairment. This metric is recorded every time the patient has a visit with their doctor, providing an insight into the evolution of the QoL via the KPS throughout the treatment. However, the KPS score lacks the detail and reliability that the PRO or NCAs provide.

Although each of these three techniques have their own strong suits, the high costs of NCAs, patient dependency of the PROs and the nonespecificity of the KPS highlights the need for the development of a new QoL estimation technique that will resolve all those issues. An option for such technique, would be to estimate the QoL status of the patient solely based on anatomical markers from MRI scans, which are acquired routinely before any kind of treatment and followups. This setup would not imply any additional cost nor patient interaction.

In order to develop such tool, the anatomical changes that occur due to RT that affect patient outcome must be identified. Consequently, in this literature review, we gathered all current research regarding the anatomical changes that occur after RT on patients with brain metastases captured in MRI related to the QoL outcome of the patients. It should be noted that we focused our search on articles that employed the KPS to quantify the cognitive outcome of the patients.

II. Methods

A. Search strategy

We performed our literature search via Pubmed on the 7th of July 2022 in accordance to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [7]. The keywords for our search assumed the presence of the phrases MRI, RT, Brain Metastases and KPS within the title or abstract of the article. As a result of this search, 298 articles were selected for further screening. The exact search strings can be found at the end of the review, under “Supplementary Resources”.

B. Study selection

We defined the inclusion criteria for this review as depicted in Figure 1. The most important factor for the inclusion of the studies was the identification of an anatomical factor affecting the cognitive outcome of the patients that had undergone any type of RT. Based on this guideline, the final number of studies included was 58. Afterwards, we assessed the full-text contents from these 58 studies and selected the ones that presented significant findings regarding the effect of radiation delivery to the KPS of the patients, amounting to a final selection of 16 articles.

C. Data extraction

We designed specific formulas for the purpose of data extraction. These forms focused on information regarding the location of the primary tumour, where the brain metastasis originated from, sample size, the type of RT treatment and the dosage received in addition to the follow-up imaging time. We also recorded any use of chemotherapy within the patient population. Furthermore, the anatomical markers affecting KPS changes were also identified as long as they presented statistically significant results.

Table 1: Criteria for assessing risk bias and study relevancy

		Yes	No
Case Selection	Case and control selection	Setting, time frame and eligibility criteria for recruitment provided	Data on setting, method of selection and eligibility criteria for recruitment incomplete
	Multicentre study	The data is acquired from different institutions	The data belongs to a single institution
	Case description	Information on participants complete (demographics, primary disease, received treatments)	Data on participants incomplete
Study design	Relation to treatment	Changes are related to RT dose	Dose of RT is not related to changes
	Relation to KPS	The effect of the anatomical change in the KPS score is described	The effect of the anatomical change in the KPS score is not reported
Analysis strategy	Analysis described	Methods of image analysis and computation adequately described, including imaging parameters and software used	Methods unclearly or incompletely described

D. Data quality and relevancy

Aiming to ensure the quality of the selected 16 studies, we designed a checklist to assess their characteristics. The checklist is divided in three categories, case selection, study design and analysis strategy. The completed checklist is presented in Table 1.

The first category, case selection, aims to evaluate any bias present within the studies. "Case and control selection" indicates wheather the study referenced the context under which it was carried out, such as, the time frame and criteria established for patient selection. The "multicenter study" subcategory is representative of the number of institues involved in the study. "Case description" indicates if the demographic data of the participants was provided which can be an indicator of how representative the study is.

Regarding the study design, the first subcategory of "relation to treatment" aims to identify those studies that associated the role of radiation on patient outcome. On the same note "relation to KPS" indicates which studies presented significant results relating a specific anatomical marker to a change in post-RT KPS score.

Finally, the analysis strategy category, showcases if an study has described the methodolody and tools used to measure the anatomical changes that occurred within the brain after radiation delivery.

III. Results

The selected papers for this literature review identified five different anatomical markers: (1) tumour morphology, (2) number of metastatic lesions, (3) location of the lesions, (4) the extent of peritumoural edema and (5) necrosis. Of the selected studies, 11 identified tumour volume and other morphological metrics, such as, diameter, cumulative volume and dynamic index of being related to cognitive decline. Moreover, five studies focused on the relevancy of number of lesions while four focused on their location. Finally, three articles highligthed the role of the peritumoural edema on patient outcome and a total of two studies pointed at necrosis as the main factor for cognitive decline.

An overview of the studies is found in Table 2 and the assessment of bias and their characteristics can be found in Table 3.

A. Tumour morphology

Out of the evaluated 16 studies, 11 highlighted the role of tumour morphology in the cognitive outcome of the patients. Tumour morphology references metrics such as the cumulative volume of the metastatic lesion, maximum diameter, and dynamic index.

For the cumulative volume of the metastatic lesions, five studies quantified the thresholds over which this becomes a major factor for the functional impartment of the patient. According to the study by Caballero et al. a volume under 2.35 cm3 improves the neurological outcome of the patients together with extending their survival by a median of 18 months.

Along the same line, Bowden et al. stated that an aggregate lesion volume, that is corresponding to multiple lesions, below 5 cm^3 leads to longer survival rates, with an average increase of four months and improved prognosis for the cognitive abilities.

Table 2: Characteristics of selected studies

Article	Primary tumor	Total Patients	Chemotherapy in RT group	RT Type (total dose in Gy)	Mean Follow-up	Anatomical marker
Pan (2008)	Mixed	63	63	GKS (24–45)	2.5 months	PE
Xu (2012)	Breast	147	147	SRS (24)	1 year	Necrosis
Lee (2014)	Mixed	109	N/A	GKS (16-26)	6.5 months	TM and PE
Caballero (2012)	Mixed	310	310	SRS (15-20)	3 months	TM and NL
Elliott (2018)	N/A	98	3	GKS (20)	2.8 months	TM and LL
Bowden (2015)	Mixed	720	720	GKS (20-50)	3 months	TM and NL
Matsunaga (2011)	Colorectal	152	N/A	GKS (8-30)	3 months	TM and LL
Jawahar (2002)	Mixed	61	4	GKS (11-21)	11 months	TM
Mohammadi (2017)	Mixed	896	475	SRS (24 Gy)	6.2 months	TM, LL and Necrosis
Serizawa (2005)	Mixed	521	148	GKS (13.3-33.3)	2 months	NL and LL
Joshi (2019)	Gastrointestinal	328	N/A	SRS (20)	N/A	TM
Serizawa (2014)	Mixed	2838	1670	SRS (20)	N/A	TM and NL
Zubatkina (2018)	Melanoma	78	27	GKS (20-24)	2.5 months	TM
Banfill (2012)	Mixed	58	N/A	SRS (18-24)	3 months	TM
Pessina (2017)	Melanoma	53	4	SRS (14-30)	20.9 months	NL
Spanberger (2013)	Mixed	129	46	WBRT	N/A	PE

PE = Peritumoral edema, TM = Tumour morphology, NL = Number of lesions, LL = Location of lesions
GKS = Gamma Knife Surgery, SRS = Stereotactic Radiosurgery, WBRT = Whole Brain Radiotherapy.

The 2014 study by Sherizawa et al. discovered that the cumulative lesion volume did not possess a significant effect in the cognitive decline of the patient as long as it was below 15 cm^3. According to another study by Lee et al. the threshold for the cumulative tumour volume to be harmful to the patient is 26 cm^3. They also stated that surpassing this value will lead to not only a worsened cognitive state, but a shorter survival time.

A study by Joshi et al. indicated that cumulative lesion volume was harmful to the cognitive abilities of the patients if it surpassed the 12 cm^3 volume. Moreover, they also discovered that this guideline is only applicable for metastatic brain lesions differentiated from primary tumours of the lung, melanoma, renal and gastrointestinal, but not from the breast.

Table 3: Assessment on bias and relevancy

Article	Case selection			Study design		Analysis strategy
	Case and Control Selection	Multicenter study	Case Description	Relation to treatment	Relation to KPS	Analysis described
Pan (2008)	✓	-	✓	✓	-	✓
Xu (2012)	✓	-	✓	-	-	✓
Lee (2014)	✓	-	✓	✓	-	-
Caballero (2012)	✓	-	✓	-	-	-
Elliott (2018)	✓	-	✓	✓	-	-
Bowden (2015)	✓	-	✓	-	-	-
Matsunaga (2011)	✓	-	✓	✓	-	✓
Jawahar (2002)	✓	-	✓	✓	-	✓
Mohammadi (2017)	✓	-	✓	✓	-	✓
Serizawa (2005)	✓	-	✓	-	-	-
Joshi (2019)	✓	✓	✓	-	-	✓
Serizawa (2014)	✓	✓	✓	-	-	-
Zubatkina (2018)	✓	-	✓	✓	-	✓
Banfill (2012)	✓	-	✓	-	-	✓
Pessina (2017)	✓	-	✓	-	-	-
Spanberger (2013)	✓	-	✓	-	-	✓

Banfill et al. defined their own margin for cumulative volume threshold, this being 10 cm^3, which they correlated with an improved cognitive outcome for the patient. In contrast to the other four studies listed, Banfill et al. also disclosed the underlying mechanism that might influence this, stating that lesions above 10 cm^3 in volume presented a more aggressive biology and an infiltrative nature with a tendency of accelerated growth.

Regarding the measure of the diameter of the largest lesion within the metastasis, Elliott et al. described that a larger diameter than 2 cm correlates with the developments of neurological deficits. Jawahar et al. recorded a similar result, this time stating that the cutoff length to ensure a good prognosis is a maximum diameter of 3 cm. In line with these two studies, Sherizawa et al. determined that cognitive decline was to be expected in patients whose maximum lesion diameter exceeded 2.5 cm.

Mohammadi et al. provided a more detailed look into the role of the maximum diameter of the lesions. Their study uncovered that diameters below 1 cm resulted in better local control and cognitive effect while not surpassing 2 cm resulted in a decreased chance of necrosis development.

Finally, the last metric related to functional impairment was the tumour dynamic index (TDI). TDI indicates the rate at which the tumour increases or decreases its size. According to Zubatkina et al. a rapid shrinkage of the lesions is directly related to a poor prognosis. However, they did not specify a reference rate to measure this phenomenon. In contrast, Matsunaga et al. described that an increase in volume above 25% will lead to functional impairment on the patient's side.

B. Number of lesions

Five studies investigated the effect that the number of metastatic lesions have in the cognitive outcome of the patient.

Caballero et al., Bowden et al. and Pessina et al. all reached the conclusion that a single lesion is the best case for a positive functional outcome. To be more specific, Caballero et al. indicated that from two lesions upwards the survival is greatly reduced, an average of five months in comparison to single lesions. In contrast, Bowden et al. disclosed that the survival is reduced on average by 3 months, while Pessina et al. did not specify on the exact effect that multiple lesions might have on the outcome.

Moreover, Serizawa et al. (2005) discovered that a total of ten lesions was the number of lesions that impaired the cognitive abilities of the patients. This results were corroborated in a later study by the same research group, Serizawa et al. (2014) nine years later with a cohort five times larger than the first one.

C. Location of lesions

Four papers studied the role of the location of the lesions in the development of cognitive impairment. Two of these papers, Mohammadi et al. and Elliott et al. agreed in the conclusion that lesions near eloquent areas directly influence the cognitive outcome of the patient. The term "eloquent" is representative of those brain areas that are paramount to perform the most basic neurological functions. For instance, regions such as the sensorimotor cortex, basal ganglia, hippocampus or cerebellum [8] among others.

In contrast, the other two papers by Matsunaga et al. and Serizawa et al., indicate that the presence of metastatic lesions in the meninges, also known as leptomeningeal carcinomatosis, is the most significant factor that determiners cognitive decline.

D. Peritumoural edema

Among the selected 16 papers, three mentioned the importance of evaluating the peritumoural edema. Pan et al. identified this feature as a powerful prognosis marker in those cases where the edema disappears after the radiation delivery. Along the same line, Lee et al. estated in their study that even a reduction of the peritumoural edema will result in an impoved cognitive outcome, yet they did not specify the exact percentage of reduction necessary for a positive outcome.

Spanberger et al. opted for a different strategy and analysed the pre-operative MRI images to determine the presence of edema. Based on this approach, they concluded that the existance of a small pre-operative edema was related to a worse cognitive outcome after RT. They supported their claims based on the fact that smaller edemas seemed to present brain-invasive growth patterns and lower microvascular density.

E. Necrosis

Necrosis was considered a risk factor by two papers. Mohammadi et al. discussed that the presence of metastatic lesions near or within the corpus callosum

deemed the patient more prone to develop necrosis, which they recorded leads to the worsening of cognition. Xu et al. also reached to the conclusion that necrosis can reduce the survival by an average of 8 months and gravely impair the functional abilities of the patients.

IV. Discussion

The purpose of this literature review was to gather all pre-existing research regarding anatomical changes captured in MRI related to the cognitive outcome of the patients as measured via KPS. Starting from an initital search result comprising 298 articles, we conducted this review based on 16. 11 of these studies focused on tumour morphology, five on the number of lesions, four evaluated the role of the location of the lesions, three did so for the peritumoural edema, and a final two analyzed the effect of necrosis on cognitive outcome of the patients after RT.

Judging by the studies evaluated in this review, the tumour morphology is the strongest prognostic factor when it comes to the estimation of the cognitive outcome in the case of brain metastases. Not only did the majority of the papers mention this marker as determinant for patient outcome, but the results obtained throughout all these studies reached consistent conclusions.

Within the subject of tumour morphology, the cumulative tumour volume of all the lesions was the most highlighted attribute. Critical volumes for patient outcome identified within the studies included 5 cm^3, 10 cm^3, 12 cm^3 , 15 cm^3 and 26 cm^3. All five of these studies were conducted under similar conditions, but the one by Serizawa et al. stands out for the large sample, 2838 patients, which may be indicative that the volume threshold of 15 cm^3 is the most representative result among all of them.

Regarding the maximum lesion diameter, all four studies that measured its influence recorded values of 2 cm, 2.5 cm and 3 cm. Once again, it should be noted that the study by Serizawa et al., provides the most representative results at 2.5 cm, due to its large patient cohort. In any case, and although four studies might not be a large enough research to draw definite conclusions, it is relevant to note that all of them obtained very similar results around the 2-3 cm range.

The papers of Zubatkina et al. and. Matsunaga et al., identified the change rate of the lesions to be determinant markers for patient prognosis. Although both these papers found a significant relation between the change rate of lesions and the cognitive decline of the patients, the results they presented remain vague and lacking the support of a large cohort. These characteristics indicate that further research is needed to confidently relate the change rate of the lesions with a cognitive effect, capable of quantifying the relation.

The results related to the role of the number of brain lesions all reached very similar conclusions, these being that cognitive outcome decreases proportionally to the number of lesions within the brain. The papers by Caballero et al., Bowden et al. and Pessina et al. varied in the specific neurological and survival outcomes for multiple lesions, but they all agreed on the fact that a single brain lesion will result in the best cognitive outcome. Serizawa et al. conducted two studies, nine years apart in 2005 and 2014 that provided further results around this topic. Their claim that cognitive decline worsened significantly in the presence of more than ten brain lesions was supported both in their 2005 and 2014 studies. The reproducibility of these results and the fact that the second research was conducted in a large cohort may be representative of the validity of these results.

As for the location of the lesions, two main conclusions were reached, the importance of the vicinity of the lesions with eloquent sites and the presence of leptomeningeal carcinomatosis. Out of the four studied papers, Mohammadi et al. and Elliott et al., found significant evidence that supported the hypothesis that lesions near eloquent sites lead to a worse patient prognosis. Previous research has already evaluated the effect of radiation delivery around paramount areas of the brain [9], which further supports the claims made within these studies. On another note, according to Matsunaga et al. and Serizawa et al., leptomeningeal carcinomatosis is directly related to a worse patient outcome, which has been widely proven by previous research given the aggressive nature of this type of metastasis [10].

When it comes to the relevance of the peritumoural edema in patient outcome, Pan et al. and Lee et al. both agreed that the resolution, or at least, the considerable reduction of the edema will result in a better cognitive outcome. Spanberger et al. were the only study that focused on pre-operative edema, not accounting for its evolution after surgery nor RT. In their study, they disclosed that a small edema is highly related to a worse prognosis. Overall, and although the peritumoural edema seems to play a role in the cognitive outcome of the patients, all three of these studies fail to quantify the parameters above which this marker possesses a significant effect on cognitive state and rely on adjectives such as “small” and “reduction”.

Finally, two studies also mentioned the role of necrosis on the cognitive outcome of the patients, those by Mohammadi et al. and Xu et al. Both papers discovered that the development of necrosis after RT related to worse prognosis. These findings fall in line with previous research regarding the role of necrosis on the neurocognitive abilities of patients [11] but further research would be advised to tailor these conclusions exclusively to brain metastases.

We identified five main limitations to these 16 studies. On the one hand, they all based their research on basic MRI imaging, such as, T1, T2 or FLAIR sequences. Although these scans are proficient in imaging brain lesions, opting for more advanced protocols like diffusion or functional MRI might provide an added level of depth to the imaging analysis and aid in the detection of new anatomical markers that determine patient outcome [12].

A further limitation identified among the selected studies, is the scarce number of multicenter studies. Although multicenter studies can lead to bias if the acquisition and processing of the data is not performed uniformly among all institutions, they are crucial when it comes to evaluating the reproducibility, generalizability and clinical applicability of the results [13].

On another note, we also consider the small cohorts studied across all articles to be one of the largest liabilities for the described results. Research based on small samples possesses a reduced statistical value and low reproducibility [14].

Moreover, most of the studies we evaluated were comprised of patient cohorts with a mixed origin of primary tumour. Research has already indicated that the importance of anatomical changes that lead to cognitive decline vary depending on the primary tumour. For instance, the total tumour volume is a strong prognostic factor for brain metastases from melanoma, kidney, lung and gastroinstestinal origin, but is not a defining factor when the primary tumour if located on the breast [15] Thus, the results we described in this review might not be applicable to all types of brain metastases.

Finally, the last main limitation identified for this review, relies on the fact that none of the studies were able to correlate the anatomical changes to a specific reduction in the KPS score. All studies relied on ambiguous terms to describe the cognitive decline of the patients as a result of a anatomical change, but there was no record of a quantified reduction on the KPS score.

In light of the existing limitations, there are clear steps that future research on the topic could adopt to ensure more representative conclusions. The preferred study design for such a project would be based on a large sample of uniform primary tumour locations acquired across multiple institutions with advanced imaging protocols. Moreover, future research should also strive to quantify the reduction on the KPS that each anatomical marker triggers.

Regarding our own limitations, this review might have been affected by a search strategy based on a single source, PubMed as no further search engines were consulted, which may have lead to the exclusion of some relevant literature.

V. Conclusion

In conclusion, this review identified five anatomical markers related to the cognitive outcome of patients with brain metastases after radiation delivery. Tumour morphology, number and location of lesions, extent of peritumoural edema and necrosis were identified as determinant anatomical changes that affect the functional abilities of RT patients. However, further research is necessary to be able to apply these finding to all cases of brain metastases, independently of the primary tumour, and quantify the exact effect that these anatomical changes will have in the KPS score.

VI. Supplementary Resources

A. Search string

((((KPS[tiab] OR karnofsky performance scale[tiab] OR karnofsky performance score[tiab] OR karnofsky OR performance score[tiab] OR karnofsky performance status[tiab] OR "Karnofsky Performance Status"[Mesh]))))
AND
((((MRI[tiab] OR magnetic resonance imaging[tiab] OR magnetic resonance image[tiab] OR magnetic resonance[tiab] OR "Magnetic Resonance Imaging"[Mesh]))))
AND
((((brain[tiab] OR metastases[tiab] OR brain metastases[tiab] OR metastatic[tiab] OR metastase[tiab] OR brain metastase[tiab] OR "Brain Metastases"[Mesh]))))
AND
((((radiotherap*[tiab] OR radio-therap*[tiab] OR radiationtherap*[tiab] OR radiation-therap*[tiab] OR

irradiation[tiab] OR "cancer treatment"[tiab] OR "oncological treatment"[tiab] OR "oncology treatment"[tiab] OR "Radiotherapy"[Mesh])))

VII. References

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VIII. LAYMAN'S SUMMARY

Radiotherapy (RT) is a treatment option for brain metastases that aims to eliminate the tumor cells within the brain, but it also causes healthy tissue damage that can lead to cognitive decline. In order to measure the effects of different RT treatments on the patients, the quality of life (QoL) is measured to determine which one leads to the best cognitive outcome. For this purpose, tests with varying degrees of specificity aim to quantify the cognitive change of the patients before and after RT. However, their high costs, patient dependency and unreliability highlight the need for a new approach to measure the cognitive state of patients. Such novel approach could estimate the QoL of the patients solely based on anatomical markers from MRI data. We performed a systematic review to analyse existing literature on the anatomical changes captured in MRI that have been linked to cognitive decline. We searched the Pubmed database where studies that evaluated cognitive change as a result of a specific anatomical change after RT were selected. Out of 298 publications, 16 were chosen, wherein tumor morphology, lesion number and location, peritumoral edema and necrosis were identified as the most relevant anatomical markers for the estimation of the QoL of brain metastatic patients based on MRI data. We identified multiple limitations within our review regarding inhomogeneous patient cohorts, low-quality image processing and the lack of correlation between the anatomical changes and the effect that might have in the QoL of patients. Consequently, although the studies reviewed all reached similar conclusions, further research based on larger samples with more uniform patient cohorts and advanced imaging must be conducted, to be able to definitively quantify the effect these anatomical changes have in the QoL of patients after RT.