Diffusion MRI outlined viable tumour volume beats GTV in intra-treatment stratification of outcome

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Title:

Diffusion MRI outlined *viable tumour volume* beats GTV in intra-treatment stratification of outcome.

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Abstract

Background and purpose
In radiotherapy, treatment response is generally evaluated many weeks after end of the treatment course. If the treatment outcome could be predicted during radiotherapy better tumour control could be achieved through timely adaptation of the treatment strategy. In this study intra-treatment change based on the diffusion MRI outlined viable tumour volume (VTV) was assessed and compared to the standard GTV to study their outcome prediction capacity.

Materials and methods
Thirty-eight brain metastases from twenty-one cancer patients were analysed in this prospective trial. Diffusion and structural MRI was acquired on a 1 T machine before, during, and at follow-up 2-3 months after radiotherapy. The VTV was defined as a region with high cellularity using high b-value diffusion MRI scans. Further, the diffusivity of the VTV was derived as the apparent diffusion coefficient (ADC). Treatment outcome was determined using RECIST defined bounds in the T1W MRI follow-up scan. Longitudinal statistical analysis was performed using a linear mixed effect model.

Results
The GTV declined in both responding and non-responding (significantly) tumours with inseparable rates during radiotherapy. The VTV volume fraction reduced significantly in the responding tumours only. The ADC of the VTV increased significantly in responding metastases whereas it decreased in non-responding metastases. Furthermore, no association between baseline tumour size or primary disease and outcome was observed.

Conclusion
GTV size change during radiotherapy is not a reliable predictor of outcome in brain metastases. On the other hand, change in the volume fraction of VTV and diffusivity of VTV shows ability to stratify treatment outcome.
Keywords: treatment response; diffusion weighted MRI; brain metastases; viable tumour volume; gross tumour volume; radiotherapy

**Introduction**

Assessment of treatment response in radiotherapy is important for validation of treatment efficacy. In general, treatment response is evaluated with standard radiology, i.e. a geometrical change of the tumour mass evaluated by structural MRI or CT. Unfortunately geometrical changes usually do not reach end-state before several weeks after end of radiotherapy. This implies that there is a window of uncertainty in which it is unknown whether the tumour cells are dying effectively or regrowth is occurring due to insufficient treatment.

Early treatment response in radiotherapy refers to tumour changes induced during the course of radiotherapy (intra-treatment response). If an early tumour change is detectable it can potentially be used for prediction of the radiological end-state of the tumour, i.e. becomes a biomarker of treatment response. It is known that the micro environment of the tumour is affected instantly after the onset of irradiation [1], progressing from a physiochemical stage at micro-second time scale into micro structural changes starting in the order of tens of seconds. However such changes are below the detection threshold of standard imaging. Biological imaging on the other hand represents a class of imaging techniques that registers changes in cell physiology and micro structure, and thus has the potential to non-invasively detect early changes following radiation. One very promising technique is diffusion weighted MRI (DW MRI) which, without the use of exogenous agents or ionising radiation, measures the state of the cellular environment of the tissue. In brief, the contrast in DW-MRI arises from the difference in water molecules motion in the extracellular space of different types of tissue. In its simplest interpretation a low diffusivity may reflect a high cell
density and vice versa. The diffusivity can be quantified if at least two diffusion images are acquired with different diffusion sensitizations (b-values) and expressed as the apparent diffusion coefficient (ADC).

A previous report on intra-treatment response in brain metastases showed that ADC may enable treatment stratification after about seven treatment fractions [2]. This study assumed that the DW-MRIs acquired longitudinally were independent measurements. Essentially this may have underestimated the statistical significance of the potential difference between ADC changes for responding versus non-responding tumours, since inter-patient variations were not modelled.

The aim of the present study is to investigate the intra-treatment change in brain metastases using two different tumour volume definitions, the conventional gross tumour volume (GTV) [3] and a viable tumour volume (VTV) which is a DW-MRI defined tumour sub volume with low diffusivity (high cellularity). Using a unique longitudinal setup with repeated MRI the intra-treatment changes of the GTV, the ADC of the VTV and the tumour composition, were compared. The changes were tested for their capability to predict outcome, using a linear mixed effect (LME) model, which allowed accounting for inter-patient variations.

Materials and methods

Patients

In this prospective study thirty patients diagnosed with brain metastases and planned for whole-brain external beam radiation therapy with a standard dose regimen of 30 Gy in 10 fractions (5 fractions/w), were enrolled. Nine patients could not be included in any parts of the analyses due to missing follow-up scan. Between one and three metastases were included from each patient. Selection was performed by an experienced radiologist
(HHJ) (>12 years of experience in onco-radiology). Metastases with small volumes (<1 cm³), suspicious of haemorrhage or melanin content, or located in areas with clear geometrical distortion were avoided. Radiotherapy was delivered with 6 MV or 15 MV photons as whole-brain irradiation. All patients were concomitantly treated with 150 mg of anti-inflammatory steroid (Prednisolon). Standard contraindication to MRI and to gadolinium contrast was applied, and patients with life expectancy less than 6 months were not included. The study was approved by the Danish Scientific Ethical Committee and the Danish data protection authorities (protocol no. H-4-2012-180).

**MRI protocol**

The MRI protocol consisted of twelve scan sessions. The first scan session (pre-RT) was performed 0-3 days before start of radiotherapy. The next ten scan sessions were performed on each of the treatment days timed to start within 1 hour before or after radiotherapy. The follow-up scan session was performed 2-3 months after end of the radiotherapy course. DW, T2W and T2*W images where acquired on every scan session (3 patients did not have the T2*W). For treatment outcome assessment pre-RT and follow-up scan sessions consisted of additional high resolution T1W scans with gadolinium contrast enhancement (DOTAREM, 279.3 mg/ml, Guerbet, France). A 1 T MRI system (Philips Panorama, Philips Healthcare, The Netherlands) was used in all acquisitions with an eight channel head coil. Patient motion during DW acquisition was partly mitigated by co-registration of the DW images acquired at different b-values using the scanner software (MR systems Panorama HFO, Release 3.5, Philips Medical Systems, The Netherlands). Full MRI sequence details are previously published [4], and repeated here in brief for the DW-MRI only: Single shot echo planar imaging (EPI) spin echo (SE) sequence with fat saturation and eight b-values (0, 50, 100, 150, 400, 500, 600, 800 s mm⁻²). Resolution 1.8 mm × 1.8 mm, slice thickness 4 mm. Three gradient
directions were used to obtain trace images.

**GTV, VTV and tumour composition**

Two types of delineation were performed by the radiologist (HHJ) for each imaging session. In one type, T2W images were used to determine the intra-treatment gross tumour volumes (GTV). This delineation was assumed to comprise the entire metastases avoiding peri tumoural oedema. In the other type, DW images with b=800 mm2/s were used to outline the intra-treatment high intensity regions within the metastases following international recommendations [5]. To avoid including necrotic areas all MR images acquired for any given session were used for guidance. The resultant outline was considered the viable tumour volume (VTV). Tumour composition was calculated as VTV over GTV. A freehand manual contouring tool (Eclipse v.10.0, Varian Medical Systems, Inc., USA) was used.

**ADC calculation**

The diffusion parameter ADC was estimated using a preferred mono-exponential model [4][6] and the highest b-values (400, 500, 600, 800 s mm−2). Low b-values were avoided to eliminate contribution from perfusion [7][8]. ADC estimation was based on mean signal intensities of the VTV. Calculations were performed with in-house developed Matlab R2010a scripts (The Mathworks Inc., USA). The system related coefficient of variation was estimated to be ~ 3 % using calculated ADCs of the cerebrospinal fluid in one patient throughout the RT course.

**Outcome definitions**

Treatment outcome assessment was based on the change in GTV between pre-RT MRI and follow-up MRI using the Gadolinium enhanced high resolution T1W scans. A
modified version of the RECIST 1.1 [9] was applied, in which the entire tumour volume
was used as endpoint. The volumetric response was based on numerical thresholds for
complete response (CR—target lesion gone), partial response (PR—at least 30%
decrease in sum from baseline), progressive disease (PD—at least 20% growth in sum
compared to smallest sum post treatment) and stable disease (SD—all other),
respectively. In this study lesions fitting CR or PR criteria were categorized as
responders and lesions fitting SD or PD criteria were categorized as non-responders.

Statistics

The longitudinal data set (comprising pre-RT and during-RT sessions) was analysed
using linear mixed effect models (LME) with Matlab R2016b (The Mathworks Inc.,
USA) with the statistics toolbox. Details on model and Matlab implementation can be
found as supplementary material (Supplementary material 1).

The LME was used to model separately the changes in the ADC of the VTV, the GTV
and tumour composition, with fraction number. The LME was implemented both with
fixed effect and random effect terms allowing modelling of inter-patient variability of
both the slope and intercept. The analysis was performed in two steps. In the first step
the LME was used to test the null hypothesis, i.e. whether the regression coefficients
(e.g. change in ADC with fraction number) are equal to zero. This was done separately
for responders and non-responders and yielded p-values. In the second step, in order to
evaluate whether there was a significantly different response (rate of change) between
responders and non-responder the 95% confidence intervals of the regression
coefficients were calculated (came from the LME analyses), and if no overlap was
found statistical significance was assumed.
Results

Primary diagnoses of patients were non-small cell lung cancer (NSCLC) (n=7), small cell lung cancer (SCLC) (n=3), breast cancer (n=5), malignant melanoma (n=4), b-cell lymphoma (n=2). In total thirty-eight (N=38) brain metastases from these patients were analysed (figure 1). Nine metastases could be categorized as non-responders (23.7 %) and were found in eight different patients (38 %). The remaining twenty-nine metastases thus were categorized as responders (76.3 %) and were found in fifteen of the patients (71 %). The baseline size of the metastases was for 94.7 % of the metastases less than 9 cm$^3$ and two metastases from malignant melanoma were very large (> 20 cm$^3$). Overall no correlation between baseline size and outcome was observed. NSCLC metastases was the largest group (n=15) and had a relatively large fractions (40 %) in the non-responder category compared to the other primary diseases. Almost all melanoma (91 %) and all breast cancer metastases (100 %) were categorized as responders. All primary diagnoses except breast cancer were present in the non-responder category also.

For the longitudinal part of the analyses nine metastases were excluded due to image artefacts, leaving behind twenty-nine (N=29). The remaining were nine (n=9) non-responding metastases and twenty (n=20) responding metastases. All metastases were successfully delineated on T2W MRI for GTV estimation and on DW MRI (b=800 s/mm$^2$) for defining the VTV (figure 2).

Non-responding metastases showed no mean GTV change during the first six radiotherapy fractions and a mean reduction of about 25 % during the remaining 4 radiotherapy fractions, stabilizing at fraction 9 (figure 3). Responding metastases showed a similar trend however with a larger variation in GTV. The LME analysis indicates that there is a mean overall reduction in volume of 2.8 percentage points from
baseline per fraction in both the responding metastases (p=0.054) and non-responding metastases (p=0.010). There were no difference in the rate of volume reduction between non-responders and responders during the course of radiotherapy since there is considerable overlap in the corresponding confidence intervals of the regression coefficients (Table 1).

Responding metastases showed low baseline ADC and increased with constant rate (p=0.005) during the course of radiotherapy (Figure 4). Non-responding metastases showed higher baseline ADC and decreased with a near constant rate (p=0.045) to a level comparable to what the responders reached by the end of the treatment course. The non-overlapping confidence intervals of the average drop and rise of the non-responding and responding metastases, respectively, indicate that there is a significant difference in the way ADC evolves between responders and non-responders (Table 1).

Overall at first glance the tumour composition remained constant at about 75 % regardless of treatment outcome, i.e. in both the responding and non-responding group (Figure 5). The LME analyses however showed that responding metastases in fact had a small but significant decline (p=0.01) in the volume fraction of VTV (Table 1). Raw data of individual responding metastases supported this finding showing that the fairly large standard deviations are mainly caused by inter-patient baseline variations (data not shown). As regards the non-responding metastases LME analysis showed that there is no significant change in the intra-treatment volume fractions of VTV (p=0.95).

**Discussion**

The aim of this study was to explore the intra-treatment change in brain metastases and assess potential association to the outcome. The intra-treatment change was based on the standard ICRU defined GTV [3], and a DW-MRI defined biological delineation we
termed the viable tumour volume, VTV. It was found that the GTV reduces in both responding and non-responding metastases starting from about fraction number six during radiotherapy and therefore was unable to stratify response. Interestingly, the volume fraction reduction of VTV was statistically significant only in responding metastases. Most notably, the ADC increased significantly in responding metastases and decreased in non-responding metastases. Further, there were no indication of a correlation between the baseline GTV and treatment outcome, or between the primary diagnose and treatment outcome. We also observed that metastases within the same patient could be of both the responder type and non-responder type underlining that stratification of responder versus non-responder should be at metastases level rather than patient level.

In this study the treatment response was defined as volume change with numerical bounds from the RECIST criteria rather than a one-dimensional change. There are several reasons for this strategy for this patient cohort as discussed in an earlier publication [2], for example that in irregularly shaped lesions a one-dimensional score is a poor surrogate for response [10]. However this remains a controversial topic and this study does not advocate the use of volumetric assessment in general since volumes may be too sensitive to delineation uncertainties [11].

The concept of a viable tumour volume is not new in radiotherapy. It was first suggested by Ling et al in a broader sense as a biological target volume (BTV) [12]. They proposed in year 2000 that the physical conformality of radiotherapy is soon to reach a maximum with the introduction of 3D conformal radiotherapy whereas biological imaging in radiotherapy will be the beginning of a new era. Many studies have since provided bits of evidence of the clinical potential of biological imaging for dose escalation, dose painting and adaptation with PET [13][14] and biological MRI
Our study confirms that geometrical information is not sufficient to effectively treat a cancer lesion which is a complex heterogeneous structure. Data show that the DW MRI defined VTV is a potential imaging biomarker for treatment response and a potential volume structure to be used in radiotherapy treatment planning. Early-phase clinical trials are however needed to interrogate further its clinical potential. We and our collaboration institution have already planned further studies.

The present study is however unique in its design with daily MRI throughout a 10-fraction radiotherapy protocol, a setup that has not been reported by others. That provided a possibility to perform a robust statistical analysis even with noise-prone scans since each patient is present with up to 12 MRI exams. We used a mixed linear effect model to analyse the way GTV, VTV/GTV and ADC of VTV evolved over the radiotherapy course and compared responders with non-responders. LME was well fitted for this study because it allowed unbalanced data and modelling of inter patient intercept and slope differences.

We observed a relatively clear GTV decline in both responders and non-responders starting at about fraction number 6. Interestingly, this is in good agreement with the earliest time point at which a reasonably safe stratification between responding and non-responding brain metastases can be made based on ADC change relative to pre-RT [2]. It confirms that about 8-9 days into the treatment (5 fractions/w) and/or after deposition of 19-21 Gy the tissue reaction is detectable by both conventional MRI and DW MRI, whereas outcome prediction is enabled by DW-MRI only. The reduction in GTV in the non-responder group seems rather counterintuitive and could lead to false mid-treatment conclusion about treatment efficacy. In fact similar findings are reported by Brink et al [16] and Elsayad et al [17] who found that patients with more tumour volume reduction during the radiotherapy course had poorer tumour control. Another
counterintuitive observation was that the volume fraction of the viable tumour remained
slightly smaller in the non-responding group throughout the treatment. It may indicate a
phenotypical characteristic of treatment resistant brain metastases but this is highly
speculative.

The ADC footprint of responders versus non-responders shown in this study is
consistent with the prevailing cellular model of tumour response. According to this cell
swelling can be expected within 24 h after treatment initiation due to cell membrane
damage (loss of homeostasis). This can result in decrease in ADC or reduced ADC
increase in a heterogeneous tumour mass [18] [19]. In responding tumours an increase
in ADC can be expected as early as one week after initiation of treatment [20]. This is
an indication of tumour necrosis and lysis [21] or even apoptosis [22] which are all
mechanisms that leads to a reduction in cell density and consequently increase
extracellular space and ADC [23]. Our data showed that the baseline ADC in the
responder group was lower than in the non-responder group supporting previous
findings by other research groups [24][25][26]. On a cellular level one can explain high
baseline ADC to be associated with a portion of the tumour being necrotic, a condition
often associated with hypoxia which is known to diminish the sensitivity to
radiotherapy due to a reduction in the radiation induced local production of reactive
oxygen species that accounts for the crucial indirect pathway of DNA damage [27]. The
ADC in this study was calculated as a mean ADC of the VTV, which by our own
definition should be the viable tumour and therefore ought to be free of necrotic tissue.
Cellular heterogeneity of the metastases and limited image resolution does not however
allow sharp edges between necrotic and non-necrotic tissue, hence the VTV delineation
in non-responding tumours may very likely also contain necrotic sub volumes which
may increase mean ADC.
This study has several other limitations as well: small sample size (lacks statistical power), heterogeneous patient cohort, low-field MR system (reduces SNR). Also the ADC analyses is not voxel based which truncates information about the potential tumour heterogeneity of the VTV. This study should therefore be regarded as exploratory and needs validation, preferably in a more homogenous patient cohort, however, in standard radiotherapy the intensive longitudinal setup used in this study is highly unfeasible and patient unfriendly since two different locations, machines and staff groups need to be involved. Fortunately, a recent technological development in radiotherapy the so-called MR-Linac combines a linear accelerator and an MR scanner [28], allowing in-room MRI throughout the radiotherapy course including biological MRI [29]. The longitudinal setup used in the present study is easily attained with an MR-Linac, increasing its clinical potential greatly.

In conclusion, this investigation shows that intra-treatment biological information acquired by DW-MRI is a better biomarker of treatment response than intra-treatment GTV reduction, which showed no association to treatment outcome. In particular, the ADC change of the DWI-MRI outlined viable tumour volume (VTV) was able to predict response. This can potentially be used for intra-treatment adaptation for better tumour control, and becomes particularly feasible in MR-Linac treatments which are being developed and tested currently.

Acknowledgements

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References


### Tables

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Table 1. Results of linear mixed effect (LME) analysis. Bonferroni correction \((\alpha/\text{number of tests})\) may be applied to compensate for multiple testing. This corresponds to using a significance level of 0.0083 instead of 0.05.
Figures

Figure 1.
Baseline tumour volume plotted against follow-up volume of the thirty-eight included metastases. Primary diseases are indicated with different symbols. The dashed line at 70 % follow-up volume indicates the numerical bound between complete remission (CR) / partial response (PR) and stable disease (SD). Metastases below this line are in this study defined as non-responders, and above the line as responders. The dashed line at 120 % follow-up further subdivides non-responders between SD and progressive disease (PD).
Figure 2.
Example of GTV and VTV delineation of a brain metastasis on baseline axial MRI of one of the enrolled breast cancer patients.
Figure 3.
Relative change in GTV size from baseline to end of radiotherapy. Error bars indicate 1 SD.
Figure 4.
Change in absolute mean ADC values of VTVs from baseline to end of radiotherapy. Error bars indicate 1 SD.
Figure 5.
Change in tumour composition during radiotherapy. At baseline about 78% of the GTV consists of viable tumour i.e. VTV. Error bars indicate 1 SD.
**Supplementary material 1:**

The linear mixed effect model (LME) was used to model separately the changes in the ADC of the VTV, the GTV and tumour composition, with fraction number. The used model corresponds to

\[ y_{im} = \beta_0 + \beta_1 fraction_{im} + b_{0m} + b_{1m} fraction_{im} + \varepsilon_{im} \]

In this model ‘\( y \)’ is a continuous response variable (ADC of the VTV, the GTV or the tumour composition) and ‘\( fraction \)’ is the predictor variable (fraction number or equivalently dose). Specifically, \( y_{im} \) is the observation \( i \) for level \( m \) of grouping variable subject (patient), \( \beta_0 \) and \( \beta_1 \) are the fixed effects for intercept and slope, respectively, \( b_{0m} \) is the random effect of intercept for level \( m \) of grouping variable subject, \( b_{1m} \) is the random effect of slope for level \( m \) of grouping variable subject. In Matlab the model, e.g. the ADC change of the VTV, was implemented with the following formula:

\[ \text{ADC~fraction+}(\text{fraction-1|subject})+(1|subject). \]

This formula has two separate random effect terms (in parentheses), implying that the slope and intercept is not correlated.