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# **Intravoxel Incoherent Motion Magnetic Resonance Imaging to Predict Tumor Response to Radiation Therapy: Review and Future Directions**

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## **Abstract**

**Keywords:** IVIM, MRI, radiotherapy, tumor response

## **Introduction**

Radiotherapy is a hallmark of cancer treatment. Almost 70% of cancer patients will have a radiotherapy during their oncological care, as part of a curative or palliative strategy. Radiation can be used exclusively or in combination with other treatments to cure cancers in approximately 40% of the cases. In these situations, the evaluation of treatment response after radiation can be challenging. Due to the post-radiation inflammatory reactions, morphological and anatomical criteria on imaging are often insufficient to predict the response in the weeks or months following radiotherapy. Concerning magnetic resonance imaging (MRI), sequences have been developed to better estimate the radiation response by using the water diffusion or perfusion properties of the tissues (1, 2). In the late 80's, Le Bihan et al. introduced a new concept called Intra-Voxel Incoherent Motion MR imaging (IVIM) in the brain. IVIM describes the random microscopic motion that occur within a voxel with both intracellular or extracellular water molecules and the incoherent motion due to microcirculation of blood assuming a capillary system organized in a pseudo random fashion. Thus, this method gives information about diffusion and indirectly to tissular perfusion without contrast injection through the quantification of three parameters: the pure diffusion coefficient, the perfusion-related diffusion coefficient and the perfusion fraction. Over the past decade, IVIM has experienced a revival of interest and an important development, especially in the field of cancer imaging. To date, IVIM has

been used primarily at the time of diagnosis to study a wide range of tumors (3, 4). However, its use during radiotherapy and to predict its effectiveness is more limited. Here, we reviewed all IVIM studies investigating the radiation response and discussed their results in the context of the current understanding of the radiation response. We aimed to highlight methodological considerations for future studies using IVIM to evaluate radiation response and to discuss specific issues for this technique.

### **Basic principles of IVIM**

The IVIM theory has already been widely described previously (5, 6). Here, we briefly summarize the basic principles of IVIM. Diffusion MRI measures the signal attenuation due to the Brownian movement of water molecules in a tissue after the application of diffusion sensitive gradients. In IVIM, a voxel is considered to have extravascular and intravascular signal sources. It leads to two distinct diffusion coefficients:  $D$ , the molecular diffusion coefficient due to Brownian motion in the extravascular compartment, and  $D^*$ , the pseudo-diffusion coefficient representing the complex motion of water in the intravascular network. That is why the signal decay can be represented as a bi-exponential model function of  $b$ -values:

$$S_b = S_0(f e^{-bD^*} + (1 - f)e^{-bD}) \quad [1]$$

A wide range of  $b$ -values to measure different diffusion-weighted data are needed to correctly fit the bi-exponential model to calculate IVIM parameters. Several algorithms can be used to computing IVIM-related parameters, without consensus on the best fitting approach, yet (7). As  $D^*$  is about 10 times greater than  $D$ , the intravascular contribution in the bi-exponential model can be neglected at high  $b$ -values. Derived from this hypothesis, a two-step fitting approach, employing segmented nonlinear least squares can be used: first,  $D$  is calculated with high  $b$ -values (classically  $b$ -values  $> 200 \text{ s/mm}^2$ ), and then with  $D$  solved, all data are used to calculate  $f$  and  $D^*$ .

### **Systematic Review**

#### Method

A total of 50 studies was identified through PubMed, Google Scholar and Embase searches conducted through April 2022. We excluded articles that were not written in English, did not report IVIM parameters in humans, were published before 2014 and case reports of only a single subject. These criteria excluded 10 studies, leaving a total of 40 reports of IVIM parameters performed before or during radiotherapy in order to predict radiation response.

### Cervical cancer

Studies are summarized in *Table 1*. The 12 studies were conducted at 3T with an average TR/TE of 3500/69 ms. IVIM parameters were acquired with  $11 \pm 3$  b-values, with generally more than half of the b-values  $\leq 200$  s/mm<sup>2</sup>. Most studies used a maximal b-value of 1000 s/mm<sup>2</sup> [800-2000]. 8/12 (66%) studies performed an MRI with acquisition of IVIM parameters during the radiation treatment. 4/12 (33%) studies used a segmentation method based on the whole tumor volume (VOI) to assess IVIM parameters. Across all studies, we observed a trend of increase of the values of D, D\* and f during radiotherapy compared to baseline and this increase was significantly higher in responder patients in five studies (8–12). At baseline, higher value of D and lower value of f were associated to poor response to radiotherapy (8, 13–15).

### Rectal cancer

Studies are summarized in *Table 2*. 3/11 studies (27%) were conducted at 3T and 8/11 (73%) at 1.5 T. The average TR/TE was 3756/80 ms. IVIM parameters were acquired with  $11 \pm 8$  b-values, with an average maximal b-value of 1000 s/mm<sup>2</sup> [800-2000]. None studies performed an MRI during the radiation treatment: 9/11 (82%) performed an MRI with IVIM acquisition before and after the radiotherapy and 2/11 (18%) only before the radiotherapy. 8/11 (73%) studies used a segmentation method based on the whole tumor volume (VOI). Only diffusion-related IVIM parameter D showed a significant change during radiotherapy, with higher variation in good responders. The values of f and D\* (measured before radiotherapy) were predictive of pathological complete response in three studies (16–18). 3 studies had negative results (19–21).

### HNSCC and nasopharyngeal cancer

Studies are summarized in *Table 3*. 5/9 studies (55%) were conducted at 3T and 4/9 (45%) at 1.5 T. The average TR/TE was 4120/80 ms. IVIM parameters were acquired with  $11 \pm 2$  b-values, with an average maximal b-value of 1100 s/mm<sup>2</sup> [800-2000]. 7/9 (77%) studies performed an MRI with acquisition of IVIM parameters during the radiation treatment. 3/9 (33%) studies used a segmentation method based on the whole tumor volume (VOI). The value of D and f before radiotherapy were predictive to the response of radiotherapy (22, 23). IVIM parameters showed significant changes (generally increase) during radiotherapy in four study (24–27) and a low value of the diffusion coefficient D was associated to complete response after radiation treatment without finding a cut-off value.

### Other malignancies

Studies are summarized in *Table 4*. 2 studies reported changes of IVIM parameters during radiotherapy in esophageal squamous cell carcinoma (OSCC). One used a 1.5T field and the other a 3T. The average TR/TE was 4314/65.9 ms. The 2 studies used a maximal b-value of 800 s/mm<sup>2</sup> with an average of  $10.5 \pm 2.1$  b-values and IVIM acquisition during radiotherapy. Baseline diffusion parameters were higher in non-responder patients. D and f increased during radiation treatment with greater changes in responder patients

4 studies reported changes of IVIM parameters during radiotherapy in brain tumors (2 : brain metastases, 1 : meningioma and 1 : glioma). 3 were conducted at 3T and one at 1.5T. The average TR/TE of 6000/90 ms. IVIM parameters were acquired with  $7 \pm 3$  b-values and IVIM acquisition during radiotherapy. The average maximal b-value was 1200 s/mm<sup>2</sup> [800-2000]. All studies used a segmentation method based on the whole tumor volume (VOI). IVIM parameters increased during treatment. A higher D at baseline and a lower f during the first weeks of radiation was associated with early progression (28).

## Discussion

### Standardization of IVIM acquisition

IVIM parameters seem to be promising biomarker of tumor response, however they are sensitive but non-specific (confounding factors are necrosis, altered vasculature...). They are also very sensitive to variations in acquisition parameters. Therefore, there is a need for standardization of practices and acquisition protocols to minimize distortion and have reproducible measure. In order to obtain robust IVIM parameters-derived prediction models, acquisition parameters should be as reproducible as possible for each tumor site; especially with full reporting of number of b-values, maximal b-value, repetition/echo times used.

The choice of the segmentation method has an impact in IVIM parameters measurement. IVIM parameters derived from a whole tumor volume region of interest (ROI) are more robust than other ROI methods (single-slice or small sample ROI) to predict tumor response after radiotherapy. A reason for this could be the sampling of the whole tumor volume reducing the bias caused by sampling errors and allowing to have a better picture of the tumor heterogeneity (18, 29). The whole tumor volume ROI is also more repeatable and reproducible with better interobserver agreement (30). The repeatability of quantitative imaging markers depends on the size of the ROIs, with generally low repeatability for small ROIs (31, 32).

#### Implementation during radiotherapy: MR LINAC

*Kooreman et al* tested the feasibility of performing daily IVIM sequences on 44 patients treated on LINAC 1.5T MRI (Unity®, Elekta, Crawley) for prostate cancer. They collected the different IVIM parameters (D, D\*, f) at each fraction within the prostate tumor and healthy prostate tissue (31). *Table 5* shows the main acquisition parameters used to perform the MRI sequence. Analysis of IVIM parameters showed that pre-treatment values of the coefficient D were significantly higher in the non-tumor tissue than in the tumor ( $1.46 \pm 0.02 \times 10^{-3}$  vs.  $1.19 \pm 0.04 \times 10^{-3}$  mm<sup>2</sup>/s). No significant difference was found for f and D\*. All IVIM parameters increased progressively during radiation therapy (except coefficient D in non-tumoral tissue). Maximum b-values on MR LINAC are limited due to lower maximum gradient strength (15 mT/m) and lower slew rate (65 T/m/s) compared to values used in diagnostic systems (30 to 80mT/m with 200 T/m/s). That is why *Kooreman et al* used a maximum b-value of 500 s/mm<sup>2</sup> only to minimize the echo time and have a sufficient signal to

noise ratio (SNR). The choice of the b-value is also influenced by the  $2 \times 4$  channel (four anterior, four posterior) receive coil array, which results in a lower SNR compared to ??? . Another limitation for IVIM measurement on the Unity system is its split gradients design that can lead to biases in spatial measurements of IVIM parameters and distortions. The Elekta Unity MR-LINAC consortium have recommended to use a maximum b-value of 500 s/mm<sup>2</sup> and have showed that accurate diffusion measurement is reliable within a radius of 7 cm from the iso-center (33). Implementation of IVIM sequences on MR-LINAC would allow the development of new strategies such as dose painting. However, several challenges remain to be addressed for quantitative sequences on MR-LINAC before safely performing a daily IVIM-based ‘radiation boost’. For example, geometric distortions or spatial resolution need to be improved before performing techniques such as dose painting (34). Daily IVIM-parameters obtained at each fraction of radiotherapy may be useful to predict patient outcomes after integration in radiomic models (35, 36).

## **Conclusion**

In conclusion, IVIM can provide diffusion and perfusion related information during radiotherapy to evaluate tumor response. Radiation therapy seems to lead to an increase in all parameters, higher in better responders. However, no clear patterns of changes or cut-offs can be identified from the analysis of limited literature data. Further investigations are required to better understand changes in IVIM parameters during radiotherapy. Full reporting of acquisition parameters and better standardization are expected to facilitate comparison among studies. MR guided radiotherapy is a promising tool for the future development of IVIM during the radiotherapy.

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Study	Number of patients	Timing of the MRI exam in weeks	TR/TE (ms)	$b$ -value max (s/mm <sup>2</sup> )	Number of $b$ -values	$b$ -values $\leq 200$ s/mm <sup>2</sup>	Type of segmentation	Predictive IVIM parameters
Zhu et al, 2016 (37)	21	Before RT/during RT (W2 and W4) / post-RT	2834/105	1000	14	9	sROI	none ?
Zhu et al, 2017 (14)	37	Before RT/ during RT (W2 and W4) / post-RT	shortest	800	9	7	mROI	$f_b$
Zhu et al, 2017 (12)	30	Before RT and during RT (W2 and W4)	2834/105	1000	14	9	mROI	$f_{W2}, f_{W4}, D_{W4}$
Kato et al, 2019 (10)	17	Before RT and during RT (W2 and W4)	4800/65	800*	6	4	sROI	$\Delta\%D_{W2}, \Delta\%f_{W2}, \Delta\%D^*_{W2}$
Xu et al, 2019 (9)	41	Before RT/during RT (W3) / post-RT	3900/minimum	1000	14	9	mROI	$\Delta\%f, D_{W3}, f_{W3}$
Bian et al, 2019 (8)	28	Before RT/during RT (D7 and D21) / post-RT	3500/minimum	850	5	3	sROI	$\Delta\%D, D_b, f_{D7}, D_{D7}, \Delta\%f$
Gao et al, 2020 (38)	51	Before RT and during RT	5000/100	1000	14	9	VOI	$\Delta\%D, \Delta\%f$
Zheng et al, 2020 (13)	85	Before RT	4000/76,9	2000	10	6	VOI	$D, f$
Liu et al, 2020	53	Before RT and during RT (D3)	3883 /59	1200	11	7	mROI	$D_b, D_{D3}$
Zhang et al, 2020 (39)	84	Before RT	2000/87	1000	11	8	VOI	$D$
Perucho et al, 2021 (11)	45	Before and post-RT	2000/54	1000	13	9	VOI	$f_b$
Zheng et al, 2021 (15)	93	Before RT	4000/77	1200	8	6	sROI	$D, f$

**Table 1:** Reports of IVIM parameters in order to predict radiation response in locally advanced cervical cancer.

*RT* : radiotherapy ; *TR* : repetition time ; *TE* : echo time ; *MRI* : magnetic resonance imaging ; *sROI* : single Region Of Interest : defined in only one slice ; *mROI* : multiple Regions Of Interest : defined in multiple adjacent slices ; *VOI* : volume of interest : IVIM parameters calculated in the whole volume of the tumor ;  $\Delta\%$  : relative percentage change; *W* : week ; *D* : day; *b* : before

\* gradients oriented in the 3 orthogonal directions (not specified in the other publications of the table)

Study	Number of patients	Field	Timing of the MRI	TR/TE (ms)	$b$ -value max (s/mm <sup>2</sup> )	Number of $b$ used	$b$ -values $\leq 200$	Type of segmentation	Predictive IVIM parameters
Nougaret et al, 2016 (40)	31	1.5T	Before RT and post-RT	3925/min	1500	34	32	VOI	D
Lu et al, 2017 (16)	42	1.5T	Before RT and post-RT	4500/97	800	12	9	mROI	$\Delta\%D$ , $D_{\text{post}}$ , $D_{\text{b}}^*$ , $f_b$
Petrillo et al, 2017 (19)	35	1.5T	Before RT and post-RT	2700/83	800	7	4	VOI	$\emptyset$
Bakke et al, 2017 (41)	27	1.5T	Before RT and post-RT	6500/117	900*	3	1	VOI	$f_b$
Petrillo et al, 2018 (42)	88	1.5T	Before RT and post-RT	2700/83	800	7	4	VOI	$\Delta\%D$ , $\Delta\%f$ , $\Delta\%D^*$
Liang et al, 2019 (43)	60	3T	Before RT	2000/60	1000	9	6	VOI	D
Fusco et al, 2019 (20)	34	1.5T	Before RT and post-RT	2700/83	800	7	4	VOI	$D^*$ , $f$
Yang et al, 2021 (44)	42	3T	Before RT and post-RT	3800/57	800	9	8	mROI	$\Delta\%D$ , $\Delta\%f$ , $\Delta\%D^*$
Liu et al, 2019 (21)	41	1.5T	Before RT	4500/97	800*	12	9	VOI	$\emptyset$
Hu et al, 2021 (17)	50	3T	Before RT and post-RT	2000/80	2000	11	8	sROI	$\Delta\%D$ , $D_{\text{post}}$ , $D_{\text{post}}^*$ , $D_{\text{b}}^*$ , $f_b$
Li et al, 2022 (18)	79	1.5T	Before RT and post-RT	6000/70	1200	11	4	VOI	D, $D^*$ , $f$

**Table 2:** Reports of IVIM parameters in order to predict radiation response in non-metastatic rectal cancer.

*RT* : radiotherapy ; *TR* : repetition time ; *TE* : echo time ; *MRI* : magnetic resonance imaging ; *sROI* : single Region Of Interest : defined in only one slice ; *mROI* : multiple Regions Of Interest : defined in multiple adjacent slices ; *VOI* : volume of interest : IVIM parameters calculated in the whole volume of the tumor ;  $\Delta\%$  : relative percentage change;  $b$  : before

\* gradients oriented in the 3 orthogonal directions (not specified in the other publications of the table)

Study	Number of patients	Field	Timing of the MRI	TR/TE (ms)	$b$ -value max (s/mm <sup>2</sup> )	Number of $b$ used	$b$ -values $\leq 200$	Type of segmentation	Predictive IVIM parameters
Ding et al, 2015 (24)	31	3T	Before RT/during RT (W3)	3600/80	800*	12	9	mROI	D
Hou et al, 2016 (22)	43	1.5T	Before RT/during RT	4225/106	1000*	10	6	mROI	D, $\Delta\%D$
Xiao-ping et al, 2016 (25)	50	1.5T	Before RT/during RT	4225/106	1000*	10	6	sROI	D, $\Delta\%D$
Lu et al, 2016 (23)	102	3T	Before RT and post-RT	3300/47	800	9	7	VOI	$f_b$
Paudyal et al, 2017 (45)	34	3T	Before RT and during RT (W1, W2 and W3)	4000/shortest	2000	10	5	VOI	D
Marzi et al, 2017 (26)	34	1.5T	Before RT/during RT / post-RT	4500/77	800*	9	6	mROI	D, D*, $f$
Fujima et al, 2017 (27)	28	1.5T	Before RT and during RT	4500/64	2000*	12	8	mROI	$f_b$ , $\Delta\%D$
Qin et al, 2018 (46)	81	3T	Before RT and post-RT	4225/106	1000	10	6	VOI	D
Xiao et al, 2019 (47)	47	3T	Before RT/ at D5, D10, D15, D20, D25 of RT	4495/69	1000*	14	9	mROI	D, D*, $f$

**Table 3:** Reports of IVIM parameters in order to predict radiation response in non-metastatic nasopharyngeal or head and neck squamous cell carcinoma.

*RT* : radiotherapy ; *TR* : repetition time ; *TE* : echo time ; *MRI* : magnetic resonance imaging ; *sROI* : single Region Of Interest : defined in only one slice ; *mROI* : multiple Regions Of Interest : defined in multiple adjacent slices ; *VOI* : volume of interest : IVIM parameters calculated in the whole volume of the tumor ;  $\Delta\%$  : relative percentage change ; *W* : week ; *D* : day ; *b* : before ; *CIC* : chemotherapy induction cycle

\* gradients oriented in the 3 orthogonal directions (not specified in the other publications of the table)

Study	Number of patients	Type of tumor	Field	Timing of the MRI	TR/TE (ms)	<i>b</i> -value max (s/mm <sup>2</sup> )	Number of <i>b</i> used	<i>b</i> -values ≤ 200	Type of segmentation	Predictive IVIM parameters
Li et al, 2018 (48)	33	OSCC	1.5T	Before RT/during RT (20Gy) / post-RT	6000/76.8	800	12	9	mROI	D, Δ%D
Zheng et al, 2018 (49)	23	OSCC	3T	Before RT/during RT / post-RT	2628/55	800	9	7	mROI	D, <i>f</i>
Gaeta et al, 2014 (50)	15	Bone metastases (breast cancer)	1.5T	Before RT and post-RT	1880/73	1000	8	5	sROI	∅
Shah et al, 2021 (51)	16	Brain metastases	3T	Before RT and post-RT	4000/100	2000	10	5	VOI	D*, <i>f</i>
Mahmood et al, 2017 (52)	21	Brain metastases	3T	Before RT/at each fraction/ post-RT	7411/110	800*	8	4	VOI	D
Franconeri et al, 2021 (53)	17	Meningioma	3T	Before RT/at D10, D20, D30 of RT/post-RT	5800/75	1000	7	5	VOI	D, D*
Jabehdar et al, 2021 (28)	38	Glioma	1.5T	Before RT/during RT (D10, D20)	6800/73.7	1000*	3	1	VOI	<i>f</i> <sub>D10</sub>

**Table 4:** Reports of IVIM parameters in order to predict radiation response in various tumor locations.

*RT* : radiotherapy ; *TR* : repetition time ; *TE* : echo time ; *MRI* : magnetic resonance imaging ; *sROI* : single Region Of Interest : defined in only one slice ; *mROI* : multiple Regions Of Interest : defined in multiple adjacent slices ; *VOI* : volume of interest : IVIM parameters calculated in the whole volume of the tumor ; Δ% : relative percentage change ; *W* : week ; *D* : day ; *OSCC* : oesophageal squamous cell carcinoma

\* gradients oriented in the 3 orthogonal directions (not specified in the other publications of the table)

Sequence	Single-shot echo planar image (ss-EPI)
Field of view (mm <sup>3</sup> )	430 × 430 × 60
Voxel size (mm <sup>3</sup> )	4 × 4 × 4
TR/TE (ms)	2960/82
b-values (# averages) (s/mm <sup>2</sup> )	0 (8), 30 (8), 150 (8), 500 (16)
Fat suppression technique	SPAIR

*Table 5* : Acquisition parameters used to perform the IVIM sequence in *Kooreman et al, Front Oncol 2021 (31)*