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ORIGINAL ARTICLE - BRAIN TUMORS

Long-term apparent diffusion coefficient value changes in patients undergoing radiosurgical treatment of meningiomas

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Abstract

Purpose A noninvasive method to predict the progress or treatment response of meningiomas is desirable to improve the tumor management. Studies showed that apparent diffusion coefficient (ADC) pretreatment values can predict treatment response in brain tumors. The aim of this study was to analyze changes of intratumoral ADC values in patients with meningiomas undergoing conservative or radiosurgery.

Method MR images of 51 patients with diagnose of meningiomas were retrospectively reviewed. Twenty-five patients undergoing conservative or radiosurgery treatment, respectively, were included in the study. The follow-up data ranged between 1 and 10 years. Based on ROI analysis, the mean ADC values, $ADC_{10\%min}$, and $ADC_{90\%max}$ were evaluated at different time points during follow-up.

Results Baseline ADC values in between both groups were similar. The ADC_{mean} values, $ADC_{10\%min}$, and $ADC_{90\%max}$ within the different groups did not show any significant changes during the follow-up times in the untreated (ADC_{mean} over 10 years period: $0.87 \pm 0.05 \times 10^{-3}$ mm^2/s) and radiosurgically treated (ADC_{mean} over 4 years period: $1.02 \pm 0.12 \times 10^{-3}$ mm^2/s) group. However, statistically significant difference was observed when comparing the ADC_{mean} and $ADC_{90\%max}$ values of untreated with radiosurgically treated ($p < 0.0001$) meningiomas. Also, $ADC_{10\%min}$ revealed statistically significant difference between the untreated and the radiosurgery group ($p < 0.05$).

Conclusions ADC values in conservatively managed meningiomas remain stable during the follow-up. However, meningiomas undergoing radiosurgery reveal significant change of the mean ADC values over time, suggesting that ADC may reflect a change in the biological behavior of the tumor. These observations might suggest the value of ADC changes as an indicator of treatment response.

Keywords Meningioma · ADC · Diffusion · Radiosurgery

Introduction

Meningiomas are the most common intracranial tumors and account for up to 30% of all primary intracranial tumors in adults [21, 35]. They are typically slow-growing tumors that arise from the meningothelial cells of the arachnoid. Histological grading of meningiomas is based on the current WHO classification. The majority of lesions are benign WHO grade I lesions, representing approximately 90% of cases. The histological subtypes of grade I meningiomas differ from the more aggressive meningiomas, WHO grade II (atypical) and WHO grade III (anaplastic), 5–7% and 1–3% of cases, in their number of mitoses, cellularity, nuclear-to-cytoplasmic ratio, histological patterns, and their relatively low risk of recurrence or aggressive growth pattern [17, 34, 35].

Stereotactic radiosurgery (SRS) is an important and well-established modality in the treatment armamentarium of meningiomas either as stand-alone therapy or in combination with microsurgery [4, 5, 19]. Radiosurgery in meningiomas has shown to be effective and associated with low toxicity rates. Long-term results have shown good clinical outcomes as well as tumor control rates for meningiomas [3, 20, 22, 25].

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Magnetic resonance imaging (MRI) is the modality of choice for the investigation of meningiomas. Although typical meningiomas have characteristic imaging features, there are multiple atypical variants that may be diagnostically challenging, and the value of MRI in predicting WHO grades in meningiomas is limited [34]. Standard MRI sequences (T1, T2) have limited value with regard to assess the biological behavior particularly of slowly growing tumor, e.g., during or following radiation or chemotherapy [23].

Diffusion-weighted magnet resonance imaging (DWI) provides information on water diffusivity, which is expressed by the apparent diffusion coefficient (ADC) [15]. It has been shown that DWI can be used to distinguish benign from malignant tumors and to differentiate meningiomas from other tumors such as hemangiopericytomas, which appear similar to meningiomas on T1- and T2-weighted sequences [14, 23, 26, 33]. DWI provides information regarding the microstructure of a tumor, and it has been shown that an increase of cell density leads to restricted water diffusion and to decreased ADC [9, 28–30]. In gliomas it has been shown that ADC can be used as a predictor of treatment response or as an early response assessment [11, 18]. As meningiomas may show delayed volume changes following treatment, a measure of tumor cell density and ADC could be important for treatment evaluation [12, 27]. Few studies in meningiomas have investigated ADC values and reported lower ADC values in WHO grade II/III compared with grade I meningiomas [26]; other studies did not find such a correlation [24].

A noninvasive radiobiological method to predict treatment response in meningiomas would be desirable to improve tumor management. Therefore, the purpose of this study was to analyze whether intratumoral ADC values change over time in untreated compared with radiosurgically treated meningiomas.

Materials and methods

Patients

We retrospectively analyzed MRI of 51 patients with meningiomas or suspected meningiomas that fulfilled the imaging criteria for these tumors (26 untreated and were conservatively managed whereas 25 were treated with radiosurgery). The follow-up data ranged between 1 and 10 years. This study was approved by the regional ethics committee.

Radiosurgery parameters

We analyzed the radiosurgery treatments of 25 patients. Thirteen radiosurgery procedures were performed with a Gamma Knife Perfexion (Elekta, Stockholm, Sweden) system, and 12 tumors were treated with a TrueBeam Novalis STx (Varian, CA, USA) system. One patient was treated with a hypofractionated scheme (5 × 5 Gy); all other patients underwent a single-dose radiosurgery treatment. The selection criteria for radiosurgical treatment was decided by an interdisciplinary tumor board decision and depended mainly on the location, size of the tumor, as well as patient's condition and age.

MR imaging acquisition

MRI data were acquired with 1.5T Avanto or Espree scanner (Siemens, Erlangen, Germany) with twelve-channel head array coil. Our study MRI examination included sagittal T1 MPRAGE with contrast agent (repetition time (TR)/echo time (TE)/inversion time (TI) = 2200/4.9/900 ms, 1-mm slice thickness, 20% gap between slices, flip angle 8°, acquisition time (TA) 3:20). Diffusion-weighted images were acquired by

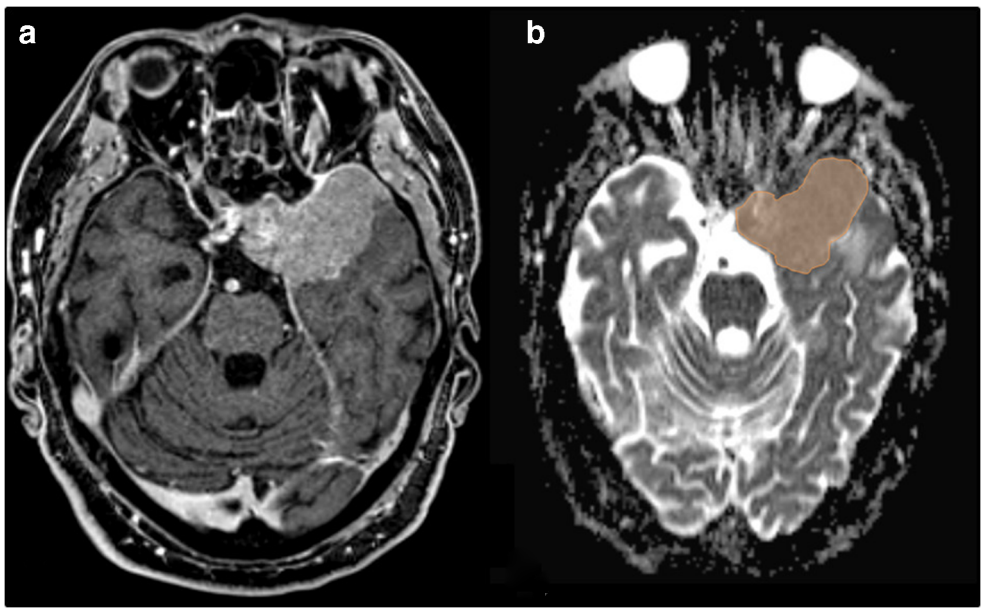

Fig. 1 Illustrative case of a conservatively followed patient with a left sphenoid wing meningioma. Left, contrast enhanced T1 MPRAGE; right, ADC map with ROI

using the diffusion-weighted single-shot echo-planar imaging (EPI) sequence (TR/TE: 3400/89 ms; 5-mm slice thickness; 1.5-mm gap between slices; 2 averages; TA 1:38 min; obtained with *b* values of 0 and 1000 s/mm^2 in the read, phase, and slice directions).

Data analysis

Quantification of ADC values

Comparing ADC with T1-weighted sequences care was taken to place the ROI within visually tumor margins avoiding the surrounding normal brain (Fig. 1). A global ROI was then set on the adjacent slice above and below, if the tumor was large enough. The ADC values of these three ROIs were then averaged (ADC_{mean}) and extracted using PMOD software (PMOD Technologies LLC, Zürich, Switzerland). Global ROIs were used to derive $ADC_{90\%max}$ values using a cut-off at 90%, representing the highest 10% values of the ADC range. $ADC_{10\%min}$ values was calculated with a cut-off at 10%, representing the lowest 10% of the ADC values.

Statistics

Descriptive statistics were used to characterize the patient population. Data are presented as mean ± SD. To test differences between untreated and treated meningiomas, we used the unpaired *t* test (SPSS version 24, IBM, New York, USA).

Results

Clinical features

The mean age of the 51 patients was 58 ± 12 years (37 female). Twenty-six patients remained untreated (mean age 58 ±

Table 1 Summary of the data parameters of conservative-treated meningiomas (n = 26)

	Volume [cm^3]		ADC mean [× 10^{-3} mm^2/s]		$ADC_{min10\%}$ [× 10^{-3} mm^2/s]		$ADC_{max90\%}$ [× 10^{-3} mm^2/s]		Time [M]
	Baseline	Last f.u.	Baseline	Last f.u.	Baseline	Last f.u.	Baseline	Last f.u.	
1	3.07	3.10	0.784	0.740	0.679	0.545	0.941	0.935	49
2	1.02	2.56	0.806	0.898	0.668	0.742	0.989	1.116	86
3	29.20	37.30	0.737	0.713	0.636	0.631	0.849	0.808	54
4	13.50	18.90	0.886	1.033	0.768	0.620	1.085	1.239	42
5	0.27	0.27	0.678	1.004	-	-	-	-	59
6	3.55	3.55	0.852	0.823	0.685	0.689	1.047	0.994	43
7	6.81	7.64	0.795	0.794	0.696	0.724	0.906	0.829	42
8	2.52	2.52	0.737	0.759	0.633	0.666	0.830	0.855	85
9	0.60	0.73	0.809	0.809	0.641	0.634	1.009	0.950	57
10	0.73	1.78	0.809	0.777	0.647	0.650	1.009	0.917	83
11	1.97	1.97	0.765	0.775	0.478	0.514	1.120	1.036	37
12	1.52	3.38	0.851	0.697	0.687	0.579	1.139	0.830	59
13	1.38	2.01	1.165	1.178	1.065	1.053	1.317	1.352	86
14	0.96	0.96	0.901	0.828	0.725	0.571	1.148	1.259	48
15	2.01	2.44	0.887	1.034	0.691	0.802	1.046	1.222	39
16	0.12	0.40	0.653	0.697	0.420	0.388	0.858	0.936	72
17	2.05	2.52	0.890	0.865	0.707	0.628	1.168	1.114	73
18	1.83	2.18	0.842	0.883	0.737	0.771	0.968	1.021	41
19	2.68	4.09	1.093	0.984	0.868	0.751	1.335	1.202	54
20	0.42	1.16	0.934	0.880	0.648	0.605	1.340	1.196	50
21	0.55	1.06	0.993	0.873	0.844	0.767	1.146	1.021	56
22	7.43	11.80	0.875	0.883	0.713	0.697	1.040	0.929	48
23	0.20	2.28	0.693	1.087	0.484	0.939	0.869	1.274	69
24	2.76	2.76	0.872	0.833	0.768	0.707	1.004	0.929	48
25	3.84	5.66	0.818	0.808	0.652	0.809	0.963	0.978	43
26	0.88	0.88	1.269	1.320	1.069	0.914	1.473	1.593	36
mean ± SD	3.53 ± 5.98	4.77 ± 7.74	0.861 ± 0.142	0.884 ± 0.152	0.704 ± 0.148	0.696 ± 0.142	1.064 ± 0.167	1.061 ± 0.192	56 ± 16

ADC apparent diffusion coefficient, $ADC_{min10\%}$ minimum 10th percentile, $ADC_{max90\%}$ maximum 90th percentile, *f.u.* follow-up, *M* months

Table 2 Summary of the data of radiosurgically treated meningiomas (n = 25)

	Volume [cm^3]		ADC mean [$\times 10^{-3}$ mm^2/s]		$ADC_{min10\%}$ [$\times 10^{-3}$ mm^2/s]		$ADC_{max90\%}$ [$\times 10^{-3}$ mm^2/s]		Time [M]
	Baseline	Last f.u.	Baseline	Last f.u.	Baseline	Last f.u.	Baseline	Last f.u.	
1	0.97	0.90	0.971	0.981	-	-	-	-	27
2	1.18	1.31	1.188	1.305	1.038	1.151	1.436	1.466	62
3	5.97	4.47	0.768	0.738	0.625	0.576	0.903	0.928	32
4	2.43	0.71	0.794	0.775	0.582	0.412	1.025	1.151	72
5	4.62	6.16	0.698	0.902	0.496	0.682	0.863	1.308	39
6	0.53	0.64	0.750	0.711	-	-	-	-	27
7	10.70	9.72	0.951	1.009	0.715	0.691	1.174	1.476	37
8	5.54	5.54	0.959	0.935	0.767	0.744	1.189	1.134	49
9	1.31	1.16	1.267	0.880	0.731	0.813	1.328	1.412	37
10	0.88	0.74	1.025	1.036	0.801	0.727	1.422	1.362	41
11	1.43	1.14	1.247	1.295	1.008	1.050	1.500	1.612	35
12	3.45	3.60	1.131	1.073	0.945	0.792	1.325	1.284	17
13	5.15	2.32	1.179	0.982	0.930	0.753	1.489	1.327	44
14	3.21	1.01	0.968	1.313	0.706	0.878	1.256	1.738	37
15	0.58	0.58	0.929	0.774	0.503	0.620	1.213	1.023	13
16	2.02	0.22	1.000	1.174	0.538	0.876	1.271	1.525	12
17	3.28	2.78	1.610	1.753	1.153	1.400	1.990	2.029	11
18	0.63	0.63	0.620	1.071	0.331	0.545	0.978	1.724	13
19	0.85	0.70	0.833	1.041	0.627	0.756	1.221	1.604	17
20	0.41	0.73	0.760	0.830	0.527	0.628	0.984	1.070	17
21	1.87	1.39	1.172	1.200	0.783	0.833	1.719	1.772	15
22	0.85	0.85	1.371	1.402	0.577	0.578	2.235	2.258	14
23	10.30	10.30	0.826	0.857	0.617	0.671	1.023	1.134	13
24	3.56	3.56	0.947	0.951	0.867	0.789	1.113	1.171	11
25	4.19	3.22	1.203	1.162	0.962	0.783	1.537	1.557	15
mean ± SD	3.04 ± 2.82	2.58 ± 2.77	1.007 ± 0.235	1.046 ± 0.241	0.732 ± 0.207	0.772 ± 0.210	1.313 ± 0.335	1.438 ± 0.327	28 ± 17

ADC apparent diffusion coefficient, $ADC_{min10\%}$ minimum 10th percentile, $ADC_{max90\%}$ maximum 90th percentile, *f.u.* follow-up, *M* months

11 years, 18 female) and were conservatively managed whereas 25 were treated with radiosurgery (mean age 57 ± 13 years, 19 female). The follow-up data ranged between 1 and 10 years. One patient was treated with a hypofractionated scheme (5 × 5 Gy); all other patients underwent a single-dose radiosurgery treatment.

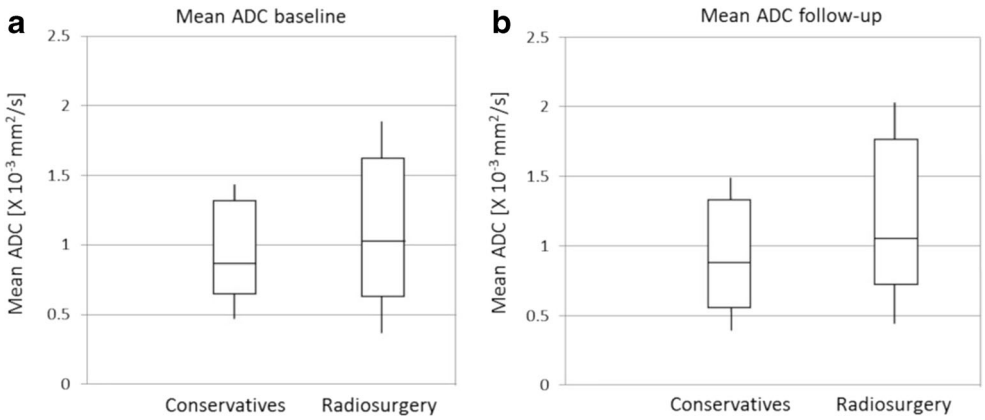

Fig. 2 Statistically significant difference (*$p < 0.01$) was observed when comparing the baseline mean ADC of untreated and radiosurgically treated meningiomas, as well as mean ADC at follow-up. The mean ADC values within the groups did not show any significant changes

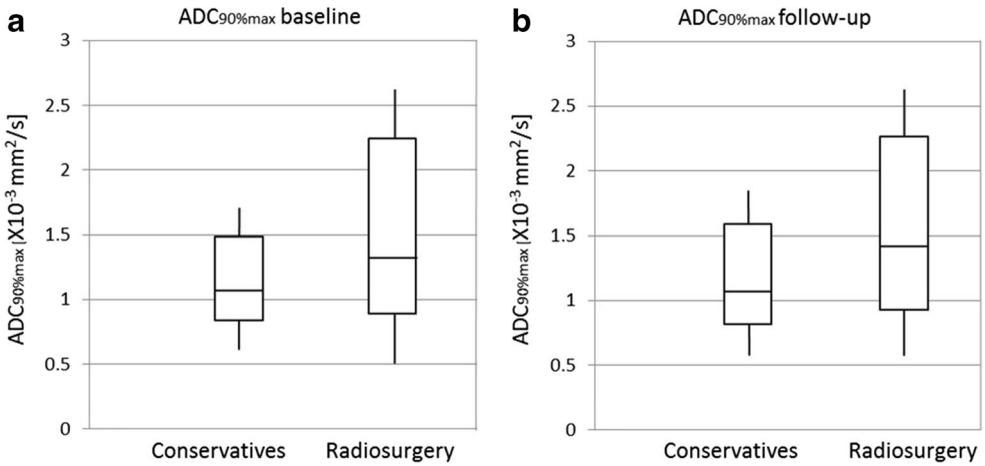

Fig. 3 $ADC_{90\%max}$ values revealed a statistically significant difference between the ADC values in conservatively treated meningiomas and radiosurgically treated meningiomas at **a** baseline (*$p < 0.01$) and at **b** follow-up (**$p < 0.0001$). When comparing the $ADC_{90\%max}$ values from baseline to follow-up, no significant changes within the groups were detected

ADC

The mean ADC values, $ADC_{10\%min}$, and $ADC_{90\%max}$ within the different groups did not show any significant changes during the follow-up times in the untreated (over 10 years period, Table 1) and radiosurgically treated (over 4 years period, Table 2) group when comparing baseline to follow-up values. However, statistically significant difference was observed when comparing the baseline mean ADC of untreated and radiosurgically treated meningiomas ($p < 0.01$), as well as mean ADC at follow-up ($p < 0.01$) (Fig. 2). $ADC_{90\%max}$ values revealed statistically significant difference between the groups at baseline ($p < 0.01$) as well as at follow-up ($p < 0.0001$) (Fig. 3). $ADC_{10\%min}$ showed no changes either at baseline or at follow-up.

Tumor volume

Tumor volume remained stable in 8 (31%) and increased in 18 (69%) patients on the conservatively managed meningiomas (Table 1). Of those meningiomas which underwent radiosurgery, 14 revealed a reduced tumor volume in the last follow-up (56%) whereas 4 increased slightly in size (16%, Table 2). The remaining ten radiosurgically treated meningioma volumes stayed stable over time ($n = 7$, 28%).

Discussion

With DWI water diffusion in tissue can be measured and quantified by ADC [13]. ADC_{mean}, $ADC_{10\%min}$, and $ADC_{90\%max}$ have been widely examined in several types of tumors with varying results [6, 7, 26–29]. ADC values may be influenced by cellularity, proliferation, nucleic volume and size, permeability of cell membrane, cell size, composition of extracellular matrix, microvessel density, cell density, and tumor grade [1, 23, 28]. This allows to distinguish between brain tissue, edema, and tumor and provides information about cell density [7]. Within the last years, ADC has been increasingly shown to be a useful biological marker for treatment response in neuro-oncology, mainly in gliomas [8, 11, 16, 18].

Different studies have looked whether ADC values correlate with the tumor grading in meningiomas [1, 17, 31]. Others studied if ADC could differentiate fibrous tumor/hemangiopericytoma from angiomatous meningioma [14] or if ADC could be used as a preoperative predictor for progression or recurrence in meningiomas [12]. They found that parasagittal and parafalcine meningiomas with preoperative high DWI signal and lower ADC values had higher risks for progression or recurrence.

In our study, we analyzed if ADC values change in meningiomas over time and therefore compared a series of conservatively managed versus radiosurgically treated meningiomas. Since we hypothesize that a change in cell density highly corresponds with a change in ADC values [29], either an increase or decrease in ADC values would reflect a change in the biological tumor behavior. To evaluate this, we measured mean ADC values as well as $ADC_{10\%min}$ and $ADC_{90\%max}$ values in untreated and treated meningiomas. In our series, ADC_{mean} values increased after radiosurgery. These results are in line with the existing literature possibly indicating that ADC could be used as a marker for treatment response and used to distinguish tumor recurrence versus treatment related (radiogenic) changes [2, 10, 32]. In the future, it would be interesting to evaluate the ADC values of those treated meningiomas that grew in the follow- up period, decreased in size, or remained in their original size. Due to our small series in our study, this subgroup analysis could not be carried out; however, further studies are planned to address this question.

Conclusion

Radiosurgically treated meningiomas reveal significant change of the mean ADC values over time whereas ADC values in conservatively treated meningiomas remain stable

during follow-up, suggesting that ADC may reflect a change in the biological behavior of the tumor. Thus, especially in meningiomas where volume change after radiosurgery is not frequent, ADC analysis could be a useful tool to measure early treatment response; however, additional long-term studies are needed to address this issue.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in this study were in accordance with the ethical standards of the institutional and national research committee (EKNZ 2016-00854) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Due to the retrospective nature of this study, informed consent was not required.

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Comments

Berberat et al are addressing a key issue in Radiosurgery (SRS). We know from large series with long term follow up that Radiosurgery in small WHO I Meningiomas is providing a very advantageous safety efficacy ratio on the long term [2,5]. However, meningiomas are indolent slowly growing tumors. Thus, for years, the stability of the MRI T1 contrast enhanced image is not a convincing demonstration of the capability of radiosurgery to control on the very long term the individual tumor.

Neurosurgeons are lacking a marker of response. In this perspective the contribution of Berberat et al is of interest for intracranial meningiomas management. At the difference of meningiomas managed conservatively meningiomas treated by radiosurgery are revealing "significant change of the mean apparent diffusion coefficient (ADC) values over time". The authors are speculating that this change of ADC over time "may reflect a change in the biological behavior of the tumor" and "might suggest the value of ADC changes as an indicator of treatment response". However, till now the authors data are not supporting this hypothesis. Only long-term follow-up of patients presenting with meningiomas treated by radiosurgery with ADC on the occasion of each MR follow up could demonstrate if the change of the ADC over time is, or not, a predictor of long-term control! For future studies we recommend to separate skull meningiomas and convexity meningiomas who have clearly not the same biological behavior after SRS. We also recommend not to mix radiosurgery with stereotactic radiotherapy as long as nowadays the radiobiology of these two approaches are demonstrated to induce different biological responses specially at the level of the microvasculature and immune system. This is an important field of research for the future of SRS in general as long as the same question exists for other tumors like vestibular schwannomas or brain metastases with the additional difficulty of pseudo progression phenomenon which is even making more difficult the assessment of tumor response [1,3,4]!

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