ON-LINE APPENDIX

Accounting for Differential Volume Changes with Weighted PRMs

We were concerned that choice of tumor ROI affected group differences in PRM measures. The selected ROI was voxels containing tumor tissue at any time point. For rapidly growing tumors, this choice of ROI will result in inclusion of healthy tissue in analyses involving earlier time points. We therefore applied a weighted-PRM approach, in which the contribution of each voxel to the extracted PRM metrics was weighted by the proportion of time points in which that voxel was classified as tumor tissue (ie, a voxel in the center of the tumor present in all time points receives a weight of 1, and a voxel in the tumor margin only present in the later 30% of scans receives a weight of 0.3). WGEE results were not substantively different by using the weighted-PRM approach (for example, the expected fiADC/fdADC ratio was 0.5 for patients without pseudoprogression [compared with 0.4 for the primary analysis] and 4.4 for patients with pseudoprogression [compared with 3.7], $P = .01$ [compared with $P = .01$]). On-line Fig 2 shows a comparison among the patient PRM metric time courses by using these approaches. We conclude that results were not substantively different from the primary analysis in the article, which featured an inclusive, unweighted ROI.

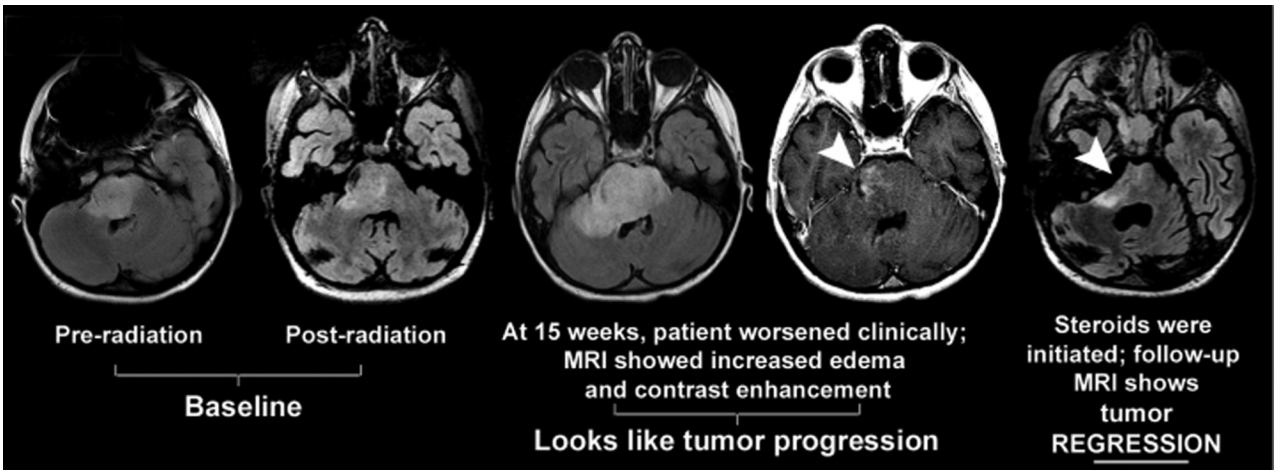
Of note, when given concomitantly with radiation, bevacizumab has been shown to reduce the postradiation necrosis rate. A small number ($n = 4$) did undergo chemoradiation with bevacizumab before the beginning of the vaccine treatment, but excluding these patients did not change our results. Prior treatment with the antiangiogenic agent bevacizumab could potentially affect study ADC measures (especially at the prevaccine baseline), confounding the use of ADC to assess the effects of vaccine therapy. We conducted an additional sensitivity analysis, removing the 4 patients with brain stem glioma treated with radiation therapy with concurrent bevacizumab. The WGEE parameter estimates did not change substantially, and the statistical significance for differences between pseudoprogression and other cases was maintained ($P = .001$ for fiADC, $P = .17$ for fdADC, and $P = .02$ for PRMratios, compared with .0004, .12, and .01 in the full sample).

On-line Table: Demographic, clinical, and imaging data (tumor volume and diffusion measurements) for each patient, sorted by decreasing overall survival from diagnosis

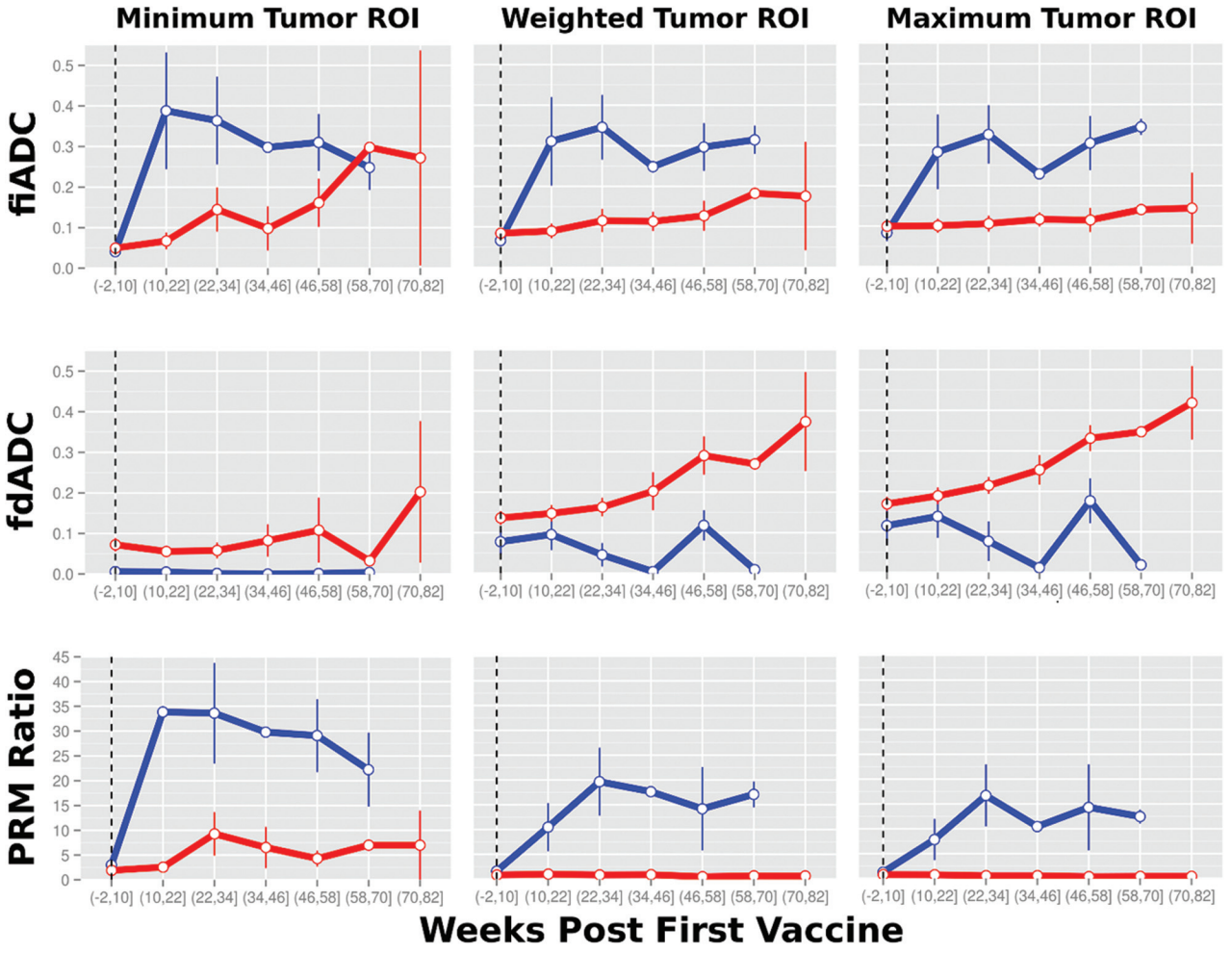
Study ID	Age (yr)	Chemotherapy	Radiation Therapy	Total No. of Vaccines	Time between First and Last Vaccine Dose (wk)	Psuedo-progression	Overall Survival (wk)	Total No. of Scans in fDM Analysis	Baseline Tumor Volume (mm^3)	Greatest % Change in Volume from Baseline Scan $[(V-V_0)/V_0]$	Baseline Mean ADC × $10^{-3}mm^2/s$	Greatest % Change in Mean ADC from Baseline Scan $[(M-M_0)/M_0]$
16	5	Bevacizumab	XRT total dose, 54 Gy in 30 fractions	10	37	No	107	7	18,093	98%	1218	16%
15	5	Temozolomide	6-MV photons, 1.8 Gy per fraction ×30 fractions for a total of 54 Gy to the boost PTV (45 Gy in 30 fractions to the PTV)	11	41	No	100	8	19,891	121%	1045	26%
11	11		5400 cGy/30 fractions of 18 Gy per fractionation (5 fractions/wk) via 6-MV protons; tumor volume, 73.6 mL; max dose, 5620 cGy	10	45	Yes	85	8	11,186	196%	1002	43%
10	11		Total dose, 5400 cGy	4	12	Yes	85	3	14,840	192%	1014	23%
4	10		Total dose, 5400 cGy; 30 fractions total, 180 cGy per day	11	38	Yes	79	8	14,805	222%	1142	−24%
21	6		XRT, IMRT w/6-MV photons, 5940 cGy in 33 fractions of 180 cGy each	8	23	No	72	7	25,490	47%	1061	12%
27	12	Bevacizumab	180 cGy per day for total dose of 54 cGy	7	19	No	73	4	10,075	141%	1058	34%
7	10		Total dose, 5600 cGy in 28 fractions	3	6	No	68	3	15,672	35%	1273	−13%
23	11		6 MV; dose, 54 Gy; 180 cGy/day, 30 fractions total	9	28	No	59	6	46,236	−27%	1141	16%
17	4	Bevacizumab	Total dose, 5400 cGy; 30 fractions	8	24	No	58	4	20,488	53%	1319	−9%
5	9		Total dose, 5400 cGy; 180 cGy daily; dose, 30 fractions	6	13	No	56	3	27,136	−9%	1267	−25%
22	7		RapidArc[a] technique to 54 Gy at 1.8 Gy per fraction in 30 fractions	7	26	No	54	5	60,697	27%	1389	2%
12	18		Modulated 7 fields (M–F), 30 fractions/daily fraction of 180 cGy; target volume dose, 5400 cGy	9	29	Yes	49	5	34,213	−39%	557	86%
9	6		55.8 Gy in 31 fractions with IMRT-planned radiotherapy	8	21	No	47	5	29,376	64%	1219	10%
24	17		6-MV photons; IMRT, 5580 cGy; 180 cGy per fraction, 31 fractions	7	19	No	43	3	20,147	63%	1058	3%
3	9		Total dose, 5400 cGy for a 6-wk course	5	13	No	42	2	27,832	2%	1131	−5%
28	7		6 MV, 54 Gy, 1.8 fraction/dose, 5 fractions/wk, total of 30 fractions	2	6	No	41	3	16,955	74%	908	36%
2	17		Total dose, 5400 cGy	2	3	No	38	2	46,784	6%	1114	−4%
18	11	Temozolomide	900 cGy in 5 fractions of 180 cGy each; then 4500 cGy in 25 fractions of 180 cGy each	4	8	No	37	5	21,467	126%	1035	5%
1	13		1.8 Gy/daily for 5 days per wk; total dose, 5400 cGy	2	3	No	36	2	22,518	134%	1240	7%
20	9	Bevacizumab	Daily dose, 180 cGy; total dose, 5580 cGy in 31 fractions	4	10	No	27	3	25,880	67%	1233	−3%

Note:—ID, indicates identification; fDM, functional diffusion mapping; XRT, external beam radiation therapy; MV, megavolt; PTV, planning tumor volume; V, volume of greatest change; V_0, baseline volume; M, mean ADC at greatest change; M_0, mean ADC at baseline; max, maximum; IMRT, intensity-modulated radiation therapy; M–F, modulated fields; w/6, with 6-MV photons.

[a] Varian Medical Systems, Palo Alto, California.



ON-LINE FIG 1. Series of conventional MR images showing the development of true pseudoprogression in a pediatric patient with DIPG treated with a peptide-based vaccine. This matches the pseudoprogression case in Fig 1.



ON-LINE FIG 2. Evaluation of 3 approaches to PRM analysis. Fractional increased ADC, fractional decreased ADC, and PRMratio for 3 different methods of calculation. Minimum tumor ROI calculates PRM metrics only within voxels classified as tumor tissue present in all time points. Weighted-tumor ROI calculates PRM metrics within all voxels classified as tumor tissue at any time point, weighting the contribution of each voxel by the proportion of time points that classify it as tumor tissue. Maximum tumor ROI calculates each metric, giving equal weight to all voxels classified as tumor tissue at any time point. Groups are divided into true tumor progression (red) and pseudoprogression (blue). Error bars indicate the standard error of the mean at each time point.