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Association of circulating markers with cognitive decline after radiation therapy for brain metastasis

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Abstract

Background. A recent phase III trial (NCT01372774) comparing use of stereotactic radiosurgery [SRS] versus whole-brain radiation therapy [WBRT] after surgical resection of a single brain metastasis revealed that declines in cognitive function were more common with WBRT than with SRS. A secondary endpoint in that trial, and the primary objective in this secondary analysis, was to identify baseline biomarkers associated with cognitive impairment after either form of radiotherapy for brain metastasis. Here we report our findings on *APOE* genotype and serum levels of associated proteins and their association with radiation-induced neurocognitive decline.

Methods. In this retrospective analysis of prospectively collected samples from a completed randomized clinical trial, patients provided blood samples every 3 months that were tested by genotyping and enzyme-linked immunosorbent assay, and results were analyzed in association with cognitive impairment.

Results. The *APOE* genotype was not associated with neurocognitive impairment at 3 months. However, low serum levels of ApoJ, ApoE, or ApoA protein (all $P < .01$) and higher amyloid beta ($A\beta_{1-42}$) levels ($P = .048$) at baseline indicated a greater likelihood of neurocognitive decline at 3 months after SRS, whereas lower ApoJ levels were associated with decline after WBRT ($P = .014$).

Conclusions. Patients with these pretreatment serum markers should be counseled about radiation-related neurocognitive decline.

Key Points

- Markers can identify those at high risk for neurocognitive impairment following radiotherapy.
- Apolipoproteins and their associated isoforms may confer radiotherapy protective effects.

Importance of the Study

Previous studies have linked apolipoprotein levels with cognitive changes in a variety of diseases; this is, to the best of our knowledge, the first report of their assessment of metastatic cancer. Our findings indicate that lower serum concentrations of selected apolipoproteins (ApoE, ApoA1, and ApoJ), and perhaps higher levels of $A\beta_{1-42}$, may be associated with cognitive decline. Future prospective studies to validate these findings are needed. If our findings are validated, they may be useful for

counseling patients about the likelihood of their experiencing neurocognitive decline after postoperative radiation therapy for brain metastases. We previously found the likelihood of neurocognitive decline to be higher after whole brain radiation therapy (WBRT); however, for patients whose baseline biomarkers suggest that they may be at high risk for neurocognitive decline regardless of radiotherapy regimen, perhaps WBRT should be considered to reduce the risk of intracranial recurrence.

Brain metastases (BrMs) are a key cause of morbidity and mortality for patients with cancer^{1,2}. In the primary analysis of our prospective clinical trial (NCT01372774), postoperative whole-brain radiotherapy (WBRT; 30 Gy in 10 daily 3-Gy fractions or 37.5 Gy in 15 daily 2.5-Gy fractions) to the surgical bed of a single resected BrM was found to be associated with significantly greater declines in cognitive function relative to adjuvant stereotactic radiosurgery (SRS; a 12- to 20-Gy single-fraction dose determined by surgical cavity volume), without appreciable differences in overall survival³. WBRT in this trial was also linked with inferior local control (ie, recurrence of tumor at unresected cranial metastases; 61.8% SRS vs. 89.2% WBRT at 12 months, $P < .00016$), leading to a general shift away from WBRT for patients with single resected BrM³. Nevertheless, large numbers of patients still receive WBRT for intracranial control despite the risk of cognitive toxicity⁴.

The mechanisms underlying radiation-related declines in neurocognitive function remain ill-defined; however, elevated oxidative damage triggered by ionizing radiation has been linked with the pathogenesis of Alzheimer disease (AD)⁵, and ionizing radiation has been linked with increased risks of developing cardiovascular or neurovascular diseases and dementia⁶⁻⁸. Patients carrying the apolipoprotein E epsilon 4 (*APOE4*) allele (present in 16% of the general population) may manifest sporadic AD earlier than non-carriers⁹, and up to 50% of patients with late-onset familial AD also have an *APOE4* allele¹⁰. A large study from the AD Genetics Consortium confirmed that each additional copy of the *APOE4* allele is associated with an increased risk of AD and a younger age at onset¹¹, although carrying the *APOE2* allele conferred considerably lower risk of developing AD¹¹. Moreover, increasing evidence suggests a link between *APOE* genotypes and response to memantine in patients with AD¹². Therefore, although a causal relationship between ionizing radiation to the brain and AD has not been established, whether individuals already carrying risk factors for developing AD may also be more prone to radiation-induced cognitive toxicity is unclear. Here, in an attempt to identify patients who may be at greater risk of cognitive decline after brain radiotherapy, we examined *APOE* genotypes and levels of various apolipoproteins in serum in patients with BrMs who underwent either WBRT or SRS as part of a completed phase III clinical trial.

Materials and Methods

Study Design and Participants

Details of randomization, masking, cognitive-decline-free survival (CDFS), cognitive testing, SRS, and WBRT are discussed in the primary report of this trial³. CDFS at 3 months (CDFS3) was defined as being alive and without cognitive decline at 3 months (± 3 weeks) after study enrollment. Cognitive decline at 3 months (CDat3) was defined as a decrease of at least one standard deviation in at least one cognitive test result at 3 months (± 3 weeks) after study enrollment. In the interest of simplifying the analyses, we did not report serum apolipoprotein findings from patients without serum samples at baseline or from those with incomplete cognitive testing.

Genotype Analysis

Genomic DNA was extracted from peripheral blood specimens by using standard protocols. Genotyping for *APOE* isoform-defining alleles (rs429358 C/T and rs7412 C/T) was done with custom TaqMan Allelic Discrimination Assays on an ABI 7900HT Fast Real-Time PCR system (Applied Biosystems, Foster City, CA, USA) according to the manufacturer's instructions. Cluster and genotype calling was done with SDS software v2.2.3 (Applied Biosystems, Foster City, California, USA).

Enzyme-linked Immunosorbent Assay Analysis

Initial-screen ELISA was used to detect interleukin-1 β (DLB50, R&D Systems), β nerve growth factor (EHNGF, ThermoFisher Scientific), tumor necrosis factor α (DTA00D, R&D Systems), tumor growth factor β (DY240, R&D Systems), angiopoietin 1 (DANG10, R&D Systems), angiopoietin 2 (DANG20, R&D Systems), vascular endothelial growth factor (DVE00, R&D Systems), angiopoietin-1 receptor (Tie-2) (DTE200, R&D Systems), monocyte chemoattractant protein-1 (MCP-1/CCL-2) (DCP00, R&D Systems), insulin-like growth factor 1 (DG100, R&D Systems), interferon γ (DIF50C, R&D Systems), amyloid beta 1-42 ($A\beta_{1-42}$) (DAB142, R&D Systems), apolipoprotein J (DCLU00, R&D Systems), apolipoprotein A1 (DAPA10, R&D Systems),

apolipoprotein A2 (ab229423, Abcam), apolipoprotein B (DAPB00, R&D Systems), apolipoprotein C (EHAPOC3, ThermoFisher Scientific), apolipoprotein E (EHAPOE, ThermoFisher Scientific), and apolipoprotein J (DCLU00, R&D Systems), to see if any of these factors were associated with cognitive decline. Human plasma amyloid beta 1-42 ($A\beta_{1-42}$), apolipoprotein J, apolipoprotein A1, and apolipoprotein E concentrations were assayed with the Milliplex MAP corresponding Magnetic Bead Panel (HNABTMAG-68K and APOMAG-62K; MilliporeSigma) according to the manufacturer's guidelines and measured on a Luminex LX200 analyzer. This assay was done in triplicate and the median value was used. This work was supported by the National Cancer Institute, National Institutes of Health under award number P30 CA016672 and the ORION core facility at MD Anderson Cancer Center.

Statistical Analyses

Categorical variables were compared with Fisher's exact tests,¹³ and serum markers were analyzed with unequal-variance *t* tests¹⁴. Recursive partitioning (rpart)¹⁵ Kaplan-Meier¹⁶, and Cox proportional hazards¹⁷ analyses were used to identify optimum cutpoints and analyze subsets of patients with different serum protein levels and CDFS outcomes. The purpose of these analyses was to identify groups at high risk cognitive deterioration or death; both within- and across-arm models were performed. In addition, multivariate Cox proportional hazards models¹⁷ were used to evaluate time to CDFS adjusting for radiotherapy type and baseline serum marker levels or patient genotype. Corrections for multiple comparisons were not used because of the exploratory nature of the analysis. Data collection and statistical analyses were conducted by the Alliance Statistics and Data Management Center. All statistical analyses were done with R version 4.0.3 (R Core Team Vienna, Austria, 2020). Analyses were based on the study database frozen on February 18, 2017.

Data Availability

The data generated in this study are available upon request from the corresponding author.

Results

Of the initial 194 patients, 175 had samples available for genotype analysis (93 who received SRS to the surgical bed and 82 WBRT). Baseline characteristics were well balanced between the groups, including the primary tumor histologies, ie, lung (SRS 60% vs. WBRT 58%), radioresistant (melanoma, sarcoma, and renal cell carcinoma) (SRS 11% vs. WBRT 11%), and other (SRS 29% vs. WBRT 31%) (Table 1). The frequency and distribution of *APOE* genotypes (E2E2, E2E3, E2E4, E3E3, E3E4, and E4E4) resembled those in the general population. Baseline serum protein levels were not statistically different by *APOE* genotype, sex, age, or combined sex and age (Supplementary Figure S1-2). Similar to the overall study results, among

patients with available genotype data, median CDFS was longer after SRS than after WBRT³ (Supplementary Figure S3). CDFS3 was significantly lower after WBRT than after SRS, but only for patients with the E3E3 or heterozygous E3 genotypes (E3E3: 9 of 51 [18%] WBRT vs. 27 of 52 [52%] SRS, $P < .001$; and E3: 16 of 74 [22%] WBRT vs. 41 of 79 [52%] SRS, $P < .001$) (Supplementary Table S1). On the other hand, when the treatment groups were analyzed separately, the proportions of patients with CDFS3 (vs. without CDFS3) were no different for those with the E3E3 or E3E4 genotypes (Supplementary Table S2). Within-group analyses of specific genotypes indicated that no other genotypes were associated with different CDFS3 rates (all $P \geq .24$) (Supplementary Table S3). Similarly, results of within-arm Cox proportional hazard analyses suggested that *APOE* genotype did not influence risk of cognitive deterioration or death (Supplementary Table S4).

Regarding the serum protein analyses, 73 patients (44 SRS, 29 WBRT) had baseline serum samples and cognitive decline data available for analysis (Table 1). SRS patients with CDat3 had lower mean serum ApoE, ApoA1, and ApoJ concentrations (all $P < 0.01$), and higher amyloid β -protein ($A\beta_{1-42}$) concentrations ($P = .048$), than did SRS patients without CDat3. WBRT patients with CDat3 had significantly lower ApoJ concentrations ($P = .014$) than did WBRT patients without CDat3 (Table 2). Analysis of within-arm subgroup differences in CDFS using information from recursive partitioning models revealed that SRS patients with high ApoJ and high ApoA1 levels (12/44, 27%) had a median CDFS interval of 12.4 months (95% confidence interval [CI] 11.2–NA), which was longer than for patients with high ApoJ + low ApoA1 (11/44, 25%) (median 6.5 months [95% CI 6.5–NA]; hazard ratio [HR] 8.6 [95% CI 2.3–32.6], $P < .01$); SRS patients with low ApoJ (21/44, 47%) had the shortest CDFS time (median 3.3 months [95% CI 3.1–3.7]; HR 51.3 [95% CI 11.7–224], $P < .01$) (Fig. 1a, Supplementary Figure S4.2). Similarly, WBRT patients with high ApoJ values (12/29, 41%) had slightly—but significantly—longer CDFS (median 3.3 months [95% CI 3.3–NA]) than did WBRT patients with low ApoJ levels (17/29, 59%) (median 2.8 months [95% CI 2.8–3]; HR 2.7 [95% CI 1.2–6.2], $P = 0.02$) (Figure 1b, Supplementary Figure S4.4). Furthermore, in the Cox proportional hazards model with all serum markers and treatment arm ($n = 73$), the estimated risk of cognitive deterioration or death in patients receiving WBRT was 2.9 times that of SRS patients (HR 2.9 [95% CI 1.6–5.3], $P < .001$). Also, an increase of one unit of ApoE resulted in an estimated 4.2% decrease in the estimated risk of CDFS (relative risk –4.2% [95% CI –1.6 to –6.7%], $P = 0.001$). Similarly, an increase of one unit of ApoJ resulted in an estimated 2.7% decrease (relative risk –2.7% [95% CI –1.7 to –3.7%], $P < .001$) in the estimated risk of CDFS (Supplementary Table S4).

Discussion

Previous prospective studies have shown that patients undergoing non-hippocampal-sparing WBRT for BrMs after either SRS or surgery were at higher risk of decline in cognitive function at 3–4 months after treatment than

Table 1. Baseline Patient Characteristics

Value or no. of patients (%)	WBRT group (n = 82)	SRS group (n = 93)	All patients (n = 175)	P value
Age, years				.292
Mean (SD)	61.8 (9.0)	60.3 (9.4)	61.0 (9.2)	
Range	41–81	26–83	26–83	
Age group				.456
<60 years	29 (35)	38 (41)	67 (38)	
≥60 years	53 (65)	55 (59)	108 (62)	
Sex				.606
Female	42 (51)	44 (47)	86 (49)	
Male	40 (49)	49 (53)	89 (51)	
Duration of extracranial disease control before study entry *				.883
≤3 months	45 (55)	50 (54)	95 (54)	
>3 months	37 (45)	43 (46)	80 (46)	
No. of brain metastases				.643
1	65 (79)	71 (76)	136 (78)	
2–4	17 (21)	22 (24)	39 (22)	
Histology of primary disease				.973
Lung	48 (58)	56 (60)	104 (59)	
Other	25 (31)	27 (29)	52 (30)	
Radioresistant (melanoma, sarcoma, and renal cell carcinoma)	9 (11)	10 (11)	19 (11)	
Resection cavity diameter				.821
≤3 cm	48 (58)	56 (60)	104 (59)	
>3 cm	34 (42)	37 (40)	71 (41)	
ELISA findings available at baseline*				.110
Yes	29 (35)	44 (47)	73 (42)	
No	53 (65)	49 (53)	102 (58)	
Baseline ApoA1				
n	29	44	73	
Median (IQR)	108.9 (97.3–122.1)	130.6 (105.6–158.5)	116.2 (98.8–138.9)	
Range	82.5–138.1	84.1–220.3	82.5–220.3	
Baseline ApoE				
n	29	44	73	
Median (IQR)	17.0 (12.4–25.0)	29.4 (20.7–36.9)	24.7 (15.0–34.1)	
Range	3.4–52.7	10.7–47.4	3.4–52.7	
Baseline ApoJ				
n	29	44	73	
Median (IQR)	115.8 (94.6–145.2)	134.9 (98.9–158.4)	130.3 (97.8–150.0)	
Range	84.5–194.6	82.8–218.9	82.8–218.9	
Baseline amyloid beta				
n	29	44	73	
Median (IQR)	66.5 (65.3–80.7)	65.3 (40.7–78.9)	65.3 (48.3–80.6)	
Range	40.7–107.5	39.1–102.9	39.1–107.5	
APOE genotype				.178
E2E2	1 (1)	0 (0)	1 (1)	
E2E3	3 (4)	12 (13)	15 (9)	

Table 1. Continued

Value or no. of patients (%)	WBRT group (n = 82)	SRS group (n = 93)	All patients (n = 175)	P value
E2E4	2 (2)	3 (3)	5 (2)	
E3E3	51 (62)	52 (56)	103 (59)	
E3E4	20 (25)	15 (16)	35 (20)	
E4E4	1 (1)	2 (2)	3 (2)	
Not measured	4 (5)	9 (10)	13 (7)	
ECOG performance status score				.363
0	28 (34)	36 (39)	64 (36)	
1	49 (60)	47 (50)	96 (55)	
2	5 (6)	10 (11)	15 (9)	
Extent of surgery				.132
Subtotal resection	12 (15)	7 (7)	19 (11)	
Total (gross) resection	70 (85)	86 (93)	156 (89)	
Surgical approach				.295
Not reported	0	1	1	
En-Bloc	51 (62)	50 (54)	101 (58)	
Piecemeal	31 (38)	42 (46)	73 (42)	

Values are mean pg/mL (SD) for ApoE and amyloid beta, and mg/dL (SD) for ApoA and ApoJ. **Abbreviations:** ECOG, Eastern Cooperative Oncology Group; ELISA, enzyme-linked immunosorbent assay; SD, standard deviation; SRS, stereotactic radiosurgery; WBRT, whole-brain radiotherapy

*Defined as months of systemic disease control before study entry.

**In the interest of simplifying the analyses, we did not report ELISA (i.e., serum apolipoprotein) findings from patients without serum samples at baseline or from those with incomplete cognitive testing.

Table 2. Mean Marker Levels by Treatment Groups Versus Cognitive Decline Status.

Patient group	No cognitive decline	Cognitive decline	P value
SRS group	No CDat3, n = 25	CDat3, n = 19	
ApoE	32.696 (9.986)	24.305 (9.406)	.007
Amyloid beta	58.840 (17.927)	69.916 (17.853)	.048
ApoA1	150.644 (32.367)	113.147 (23.257)	<.001
ApoJ	151.772 (30.032)	111.411 (23.872)	<.001
WBRT group	No CDat3; n = 3	CDat3; n = 26	
ApoE	22.233 (12.626)	19.811 (11.544)	.735
Amyloid Beta	59.867 (17.110)	70.246 (18.547)	.364
ApoA1	102.467 (7.557)	110.535 (15.774)	.395
ApoJ	162.467 (30.266)	118.938 (26.822)	.014

Values are mean pg/mL (SD) for ApoE and Amyloid beta, and mg/dL (SD) for ApoA and ApoJ.

For each marker, means and standard deviations were calculated separately for each treatment group for patients without cognitive decline (NoCDat3) versus with cognitive decline at 3 months (CDat3).

*Means were compared with unequal variance *t* tests within each marker.

were patients undergoing SRS only^{3,18}. Here we attempted to determine whether a patient's *APOE* genotype or serum apolipoprotein levels was associated with their risk of neurocognitive decline after radiation. We found that *APOE* genotype was not associated with cognitive decline

at 3 months after radiation therapy. However, patients in both arms with low baseline serum ApoJ were more likely to experience cognitive decline at 3 months. Recursive partitioning analysis done internally within each arm also suggested that patients in both arms with low ApoJ had

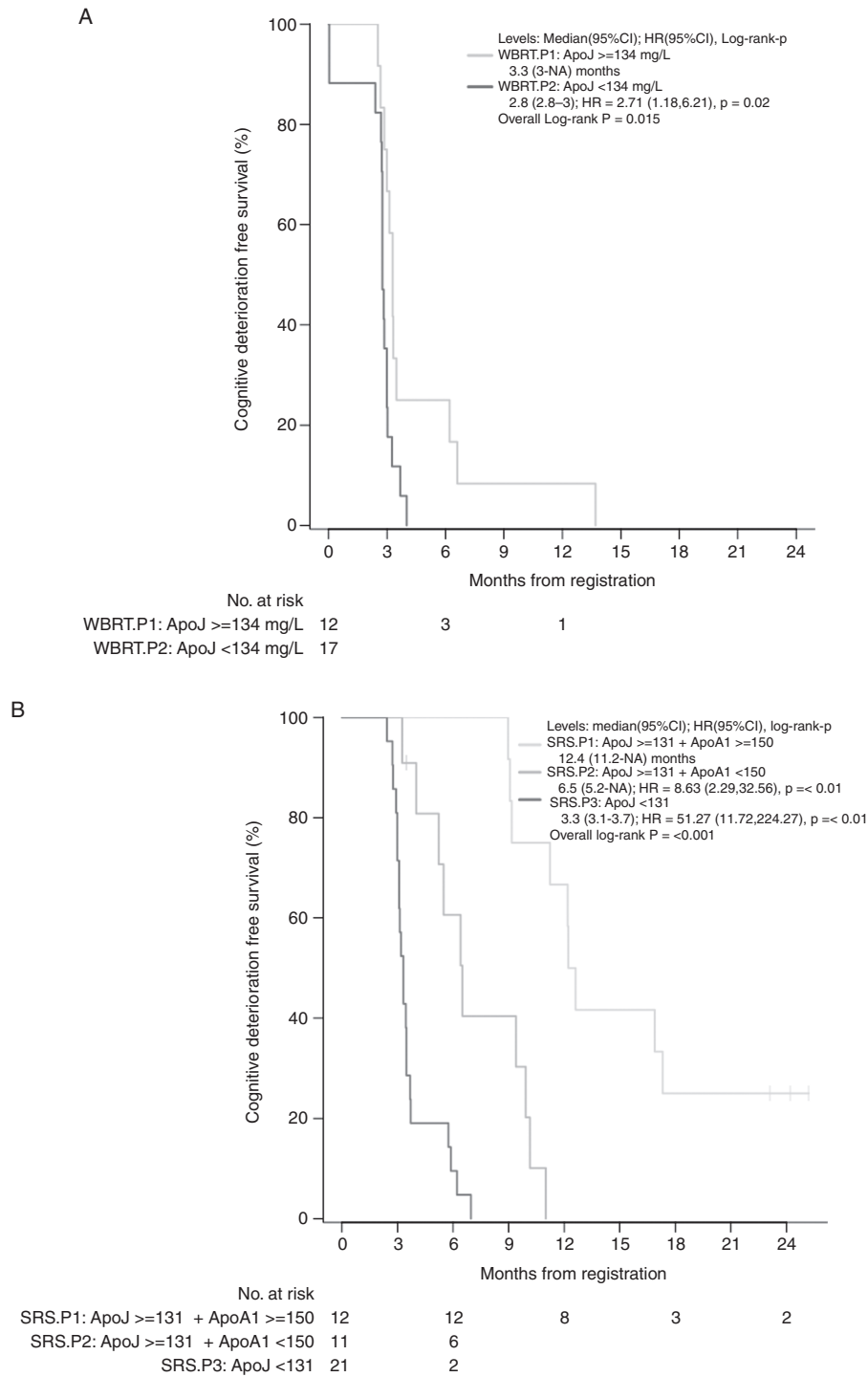


Fig. 1 Kaplan–Meier plot of cognitive decline-free survival by recursive partitioning analysis among patients treated with (a) stereotactic radiosurgery (SRS) or (b) whole-brain radiation therapy (WBRT). Recursive partitioning analysis (rpart) was performed separately within each treatment group using all 4 serum markers (measured at baseline by enzyme-linked immunosorbent assay) to determine if groups (partitions) of patients could be identified who had different median times to cognitive decline-free survival (CDFS).

SRS.P1: ApoJ \geq 131 mg/L + ApoA1 \geq 150 mg/dL.

SRS.P2: ApoJ \geq 131 mg/L + ApoA1 <150 mg/dL.

SRS.P3: ApoJ <131 mg/L.

WBRT.P1: ApoJ \geq 134 mg/L.

WBRT.P1: ApoJ <134 mg/L.

lower median CDFS (SRS, ApoJ <131 mg/L; WBRT, ApoJ <134 mg/L). In addition, two potential lower-risk groups were observed among patients treated with SRS: ApoJ \geq 131 mg/L + ApoA1 \geq 150, and ApoJ \geq 131 mg/L + ApoA1 < 150. These groups seemed to have much longer median time to cognitive decline or death (median 12.4 months and 6.5 months, compared with 3.3 months in the highest-risk SRS group). The impact of this high-ApoA1 group could not be assessed in the WBRT group because the maximum observed ApoA1 level in the WBRT group was 138 (Table 1). The mechanism of neurocognitive decline in these patients seems to be independent of that underlying AD but may have a similar overlap with changes observed in apolipoproteins that are not specific to AD in dementia and other neurocognitive diseases.

ApoJ, also known as clusterin, is an acidic glycoprotein and the second major apolipoprotein in the brain¹⁹. ApoJ is also referred to as an extracellular chaperone because of its function in preventing the aggregation of non-native proteins²⁰. In one study, *in situ* hybridization of human brain specimens detected ApoJ mRNA in astrocytes and in a subset of hippocampal neurons²¹. ApoJ-containing lipoproteins were first isolated from human plasma and are associated with lipid-poor, protein-rich apoA1-containing high-density lipoprotein in addition to other plasma lipoproteins²². Numerous functional properties have been attributed to ApoJ, including roles in innate immune responses such as complement-mediated lysis and complement lysis inhibitor²³. It also acts as an extracellular chaperone with increased expression in response to cellular stress²⁴ and displays anti-apoptotic properties²⁵. ApoJ is also capable of interacting with $A\beta_{1-42}$, which alters its aggregation²⁶ and seems to promote $A\beta_{1-42}$ clearance²⁷. In a prospective study of 196 subjects with mild cognitive impairment, the authors found, after adjustment for potential confounders, a two-fold increase in the risk of conversion to dementia in subjects with low ApoJ serum levels²⁸. This finding is in agreement with a previous study showing that plasma ApoJ levels were higher in patients with mild cognitive impairment than in patients with AD²⁹. In the current study, having low baseline levels of ApoJ seems to indicate susceptibility to neurocognitive decline, and having higher serum baseline levels of ApoJ predict the more favorable situation of not having cognitive decline. These findings mirror those of the previous study, in which the follow-up time was nearly 9 years²⁸. In the future, radiation oncologists may want to consider withholding radiotherapy in patients with low baseline serum levels of ApoJ, reserving it for later in the course of the disease.

ApoE is the most abundant apolipoprotein in the brain and has been extensively studied in the context of AD and dementia. ApoE was initially characterized in the context of human hyperlipidemia³⁰. The liver is the largest production site for ApoE, and the brain is the second largest³¹. Immunohistochemical staining for ApoE in brains shows that this protein is present in astrocytes³², choroid plexus³³, and microglia³⁴, particularly reactive microglia³³. ApoE expression has also been detected, albeit to a lesser extent, in pericytes and oligodendrocytes³⁵, and neurons have also been reported to produce ApoE in response to injury³³. The neuronal uptake of ApoE lipoprotein particles via ApoE receptors has been implicated in brain homeostasis, synaptic

integrity, and synaptic function³⁶. ApoE, like ApoJ, also has known functions related to immune response. ApoE has been shown to suppress T-cell proliferation³⁷ and neutrophil activation³⁸, regulate macrophage functions³⁹, facilitate the presentation of the lipid antigen by CD1 molecules to natural killer T cells^{40,41}, and modulate inflammation⁴². A recent epidemiologic analysis showed an association between low plasma ApoE levels and increased risk of future dementia in the general population; this association was independent of APOE genotype and has been confirmed in different patient populations⁴³.

ApoA1 is one of the most abundant apolipoproteins in the cerebrospinal fluid. Because ApoA1 is thought to be produced mainly in the liver and intestines, the presence of ApoA1 in the CNS is thought to originate from the periphery⁴⁴. *In vivo* models have shown that ApoA1 can enter the CNS via the choroid plexus, and it can be taken up by human epithelial and endothelial cells in *in vitro* models of the blood-brain barrier⁴⁵. However, prospective studies of plasma ApoA1 concentrations and the risk of dementia or cognitive decline are sparse and have produced inconsistent results. However, in the large-scale Honolulu-Asia Aging Study, higher concentrations of plasma ApoA1 were found to be associated with a lower risk of dementia⁴⁶.

We acknowledge that the current study had limitations. First, the results were derived from analyses of serum samples from a heterogeneous group of patients, and we could not fully control for cancer type, extent of systemic disease, comorbidities, and systemic cancer treatments that may have affected baseline levels of the measured variables. Second, the relatively small number of patients in specific subgroups also limited our power to make formal comparisons between groups within the Cox proportional hazard models. Third, the numbers of patients with complete data on cognitive decline and serum apolipoproteins were not equal between arms, which led to unbalanced distribution of potential confounding or prognostic factors. In addition, we observed significant differences in distribution of baseline characteristics of ApoA1 and ApoE between study arms, which limited our ability to make cross-arm conclusions about the influence of recursive partitioning-identified groups on overall CDFS. Finally, the choice to remove patients without complete cognitive testing allows easier interpretation of results but limits full determination of the relationship between biomarker serum profile and cognitive decline-free survival for this study. Further study is warranted before implementing these cutoffs in clinical practice.

In sum, although previous studies have linked levels of ApoE⁴⁷, ApoA1⁴⁸, ApoJ²⁸, and $A\beta_{1-42}$ ⁴⁹ with cognitive changes in a variety of diseases, this is, to the best of our knowledge, the first report of their assessment in metastatic cancer⁵⁰. Our findings indicate that lower serum concentrations of selected apolipoproteins, and perhaps higher levels of $A\beta_{1-42}$, may be associated with cognitive decline. Future prospective studies to validate these findings are needed. If our findings are validated, they may be useful for counseling patients about the likelihood of their experiencing neurocognitive decline after postoperative radiation therapy for BrMs. This analysis allowed us to identify observable differences in CDFS among different biomarker-driven subsets. Because of limitations in study design and

availability of lab data and complete cognitive test results, our results should not be extrapolated beyond scope of this study. However, this is sufficient evidence to continue to collect serum samples for biomarker analyses in these patients and to analyze their association with CDFS in a larger study.

Supplementary material

Supplementary material is available online at *Neuro-Oncology* (<http://neuro-oncology.oxfordjournals.org/>).

Keywords

amyloid beta | apolipoproteins | brain metastases | cognitive decline | radiation therapy

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Conflicts of Interest: The authors declare no potential conflicts of interest.

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Author Contributions

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