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Evaluation of RAPNO criteria in medulloblastoma and other leptomeningeal seeding tumors using MRI and clinical data

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Abstract

Background. Although the Response Assessment in Pediatric Neuro-Oncology (RAPNO) working group has made recommendations for response assessment in patients with medulloblastoma (MBL) and leptomeningeal seeding tumors, these criteria have yet to be evaluated.

Methods. We examined MR imaging and clinical data in a multicenter retrospective cohort of 269 patients with MBL diagnoses, high grade glioma, embryonal tumor, germ cell tumor, or choroid plexus papilloma. Interobserver agreement, objective response (OR) rates, and progression-free survival (PFS) were calculated. Landmark analyses were performed for OR and progression status at 0.5, 1.0, and 1.5 years after treatment initiation. Cox proportional hazards models were used to determine the associations between OR and progression with overall survival (OS). Subgroup analyses based on tumor subgroup and treatment modality were performed.

Results. The median follow-up time was 4.0 years. In all patients, the OR rate was .0.565 (95% CI: 0.505–0.625) by RAPNO. The interobserver agreement of OR determination between 2 raters (a neuroradiologist and a neuro-oncologist) for the RAPNO criteria in all patients was 83.8% (k statistic = 0.815; $P < 0.001$). At 0.5-, 1.0-, and 1.5-year landmarks, both OR status and PFS determined by RAPNO were predictive of OS (hazard ratios [HRs] for 1-year landmark: OR HR = 0.079, $P < 0.001$; PFS HR = 10.192, $P < 0.001$). In subgroup analysis, OR status and PFS were predictive of OS for all tumor subtypes and treatment modalities.

Conclusion. RAPNO criteria showed excellent consistency in the treatment response evaluation of MBL and other leptomeningeal seeding tumors. OR and PFS determined by RAPNO criteria correlated with OS.

Key Points

1. The RAPNO criteria demonstrated interobserver agreement of 83.3% ($k = 0.815$, $P < 0.001$).
2. OR status and PFS determined by RAPNO criteria predicted overall survival ($P < 0.001$).

Importance of the Study

A RAPNO working group recently proposed guidelines for assessment of leptomeningeal seeding pediatric brain tumors. However, the feasibility, accuracy, and applicability of these initial recommendations for clinical trials and practice have yet to be assessed. In the present study, we used MR imaging and clinical data of 269 patients, who were diagnosed with MBL or other leptomeningeal seeding tumors, to evaluate response assessment using RAPNO. We demonstrated that the RAPNO criteria facilitated accurate detection of disease progression, especially for evidence of progression after tumor size has stabilized or disappeared. Moreover, the RAPNO criteria showed good consistency in the response evaluation across tumor subtypes and treatment modalities. Finally, at each landmark point, OR status and PFS determined by RAPNO were predictive of OS for all tumor subtypes and treatment modalities.

Pediatric brain tumors are the second most common childhood malignancy and the leading cause of childhood death from cancer.[1,2] The most common pediatric malignant brain tumor is medulloblastoma (MBL), an embryonal tumor originating from the posterior fossa, with approximately 295 new cases diagnosed in the US annually.[3] MBL's propensity to present with leptomeningeal metastases at diagnosis depends on the tumor's molecular subgroup.[4,5] Other cerebrospinal fluid (CSF) seeding brain tumors, such as pineoblastoma, also exhibit potential for leptomeningeal metastasis.[6]

Importantly, mortality from MBL is primarily due to leptomeningeal metastases at recurrence.[7–9] As such, the standard of care for patients above 3 years of age with leptomeningeal dissemination consists of prophylactic irradiation of the entire brain and spinal cord in addition to maximal safe surgical resection and adjuvant chemotherapy.[10] This treatment strategy comes with the potential for deleterious long-term sequelae, including neurocognitive impairment and secondary neoplasms.[10] The treatment of leptomeningeal metastases is further complicated by lack of agreement on the ideal chemotherapeutic regimen[7] and challenges with drug delivery due to the blood–brain barrier.[11]

These considerations motivate the development and evaluation of standard response assessment measures for pediatric brain tumors with leptomeningeal spreading. Although the Response Assessment in Neuro-Oncology (RANO) criteria have demonstrated good consistency in adult gliomas,[12,13] several challenges hinder the cross-application of these response assessment measures to the pediatric neuro-oncology population, including greater heterogeneity of pediatric brain tumors, disagreement in definition of response in prior clinical trials, and poor correlation between tumor size and survival for MBL and other leptomeningeal seeding tumors.[14] Assessment of leptomeningeal metastases is further complicated by factors like the small and complex geometry of these lesions.[15]

An analogous Response Assessment in Pediatric Neuro-Oncology (RAPNO) working group proposed guidelines for assessment of leptomeningeal seeding pediatric brain tumors.[6] However, the feasibility, accuracy, and applicability of these initial recommendations for clinical trials and practice have yet to be assessed. In the present study, we used the MR imaging and clinical data of 269 patients with diagnosis of MBL or other leptomeningeal seeding tumors to evaluate response assessment using RAPNO criteria.

Materials and Methods

We retrospectively analyzed radiologic and clinical data from 269 patients diagnosed with MBL or other leptomeningeal seeding tumors, admitted to 4 large academic hospitals (Xiangya Hospital, The Second Xiangya Hospital, Hunan Provincial People's Hospital, and Hunan Children's Hospital) in Hunan Province, China from January 2011 to December 2018. Inclusion and exclusion criteria for the study population are detailed in Table 1. The patients received various treatments including surgical resection, radiotherapy, chemotherapy, and chemoradiotherapy. Selected clinical variables are summarized in Table 2. For each patient, we analyzed the baseline of cerebrospinal-MRI, which is defined as the MRI before the patient received the first instance of radiotherapy or chemotherapy, and follow-up MRIs, performed every 2–3 months, until progression or the last follow-up date. Brain MRI included non-enhanced axial T1-weighted turbo spin echo (TSE) and T2-weighted TSE, axial fluid attenuated inversion recovery (FLAIR), and axial as well as coronal contrast-enhanced T1-weighted TSE sequences. Spinal MRI included sagittal T2-weighted TSE and non-enhanced as well as contrast-enhanced T1-weighted TSE sequences, supplemented by axial images as needed. The MRI acquisition settings are summarized in Supplementary Table 1. As outlined by RAPNO recommendations, the preoperative spine MRI

Table 1. Inclusion criteria and exclusion criteria of study population

Inclusion Criteria	Exclusion Criteria
1. Under the age of 18	1. Over the age of 18
2. Definite pathological diagnosis was reported	2. Absence of pathological report
3. Continuous imaging follow-up data were obtained	3. Incomplete image data, missing sequence, etc.
4. Each follow-up record has detailed clinical information such as treatment, CSF, and neurological examination	4. Lack of clinical follow-up information

Table 2. Study population characteristics

Characteristics	
Median age, y, at diagnosis, mean (range)	9.7 (0.1–17.9)
	n **(%)**
Sex	
Male	158 (58.7)
Female	111 (41.3)
HGG group	78
Glioblastoma	40 (14.9)
Anaplastic astrocytoma	38 (14.1)
Non-HGG group	191
Medulloblastoma	87 (32.3)
Embryonal tumor group	
Atypical teratoid rhabdoid tumor	16 (6)
Pineoblastoma	6 (2.2)
Primitive neuroectodermal tumor	19 (7.1)
Germ cell tumor group	
Germinoma	38 (14.1)
Germ cell tumor	4 (1.5)
Yolk sac tumor	1 (0.4)
Choroid plexus papilloma	20 (7.4)
Treatment modalities	
Chemotherapy only	61 (22.7)
Radiotherapy only	44 (16.4)
Chemoradiotherapy	164 (60.9)
Surgical extent	
Biopsy only	53 (19.7)
Partial resection	81 (30.1)
Gross total resection	135 (50.2)
Leptomeningeal seeding or not	
With leptomeningeal seeding	66 (24.5)
Without leptomeningeal seeding	203 (75.5)

was used as the baseline spine evaluation. In this study, complete disappearance of all disease (enhancing and non-enhancing, measurable and unmeasurable) was considered as complete response, while disappearing T1 contrast-enhanced lesion alone did not qualify for response. The study was approved by the institutional review boards of all involved institutions.

Radiological Response Assessment

All patients' imaging data were reviewed by a neuroradiologist (Q.S.) with 10 years of experience, designated as the primary reader. To determine interobserver variability, all imaging data of above patients were independently reviewed by a neuro-oncologist (H.Z.) with 8 years of experience, designated as the secondary reader. The determination of objective response (OR) and progression status was based on evaluation by the primary reader. The MRI studies of each subject were revealed to readers in the order of acquisition dates. In each follow-up MRI study acquired after the patient's initial treatment, the sum of the products of perpendicular diameters of all measurable enhancing lesions and qualitative assessment of T2/FLAIR abnormality were recorded for every available scan. For the RAPNO criteria, the definition of OR was defined as a ≥50% decrease (compared with baseline) in the sum of the products of perpendicular diameters of all measurable lesions sustained for at least 4 weeks, no progression of non-enhanced disease, and negative CSF cytology and extra–central nervous system (CNS) metastases.[6] Progression status was determined by the readers according to both enhancing and T2/FLAIR abnormalities (RAPNO criteria).[6] Disease progression was defined as a ≥25% increase (compared with smallest measurement at any time point) in the sum of the products of perpendicular diameters of all measurable lesions, significant progression of nonmeasurable disease not attributed to prior therapy, or any new tumor, with all lesions suspected to be treatment related confirmed by biopsy.[6]

Statistical Analysis

For each patient, progression-free survival (PFS) was calculated from the date of surgical pathological diagnosis to the date of disease progression or death, whichever occurred first. Patients whose tumor didn't progress were censored using the last scan date. Overall survival (OS) was calculated from the date of surgical pathological diagnosis to the date of death. Patients whose tumor didn't progress were censored according to the last contact date per the clinical data collected.

Interobserver agreement was determined between the primary and the secondary reader (Q.S. and H.Z., respectively) for all studies from all patients. Agreement was quantified as the number of instances where both readers determined the patient had an OR or both determined the patient did not have an OR divided by the number of reads. Likewise, agreement between the readers using RAPNO criteria was calculated as the number of times both readers indicated that a patient had an OR or both indicated the patient did not have an OR divided by the number of patient reads. Cohen's kappa was used to evaluate the concordance between the readers. A k-value of 0 indicated lack of concordance, while a value of $k = 1$ indicated perfect concordance. Correlations between tumor size measurement by different readers and between progression times were summarized with the Spearman rank coefficient.

In landmark analyses, evaluation by the primary reader was used. We excluded patients who died prior to the specified landmark time from the analysis. We analyzed landmark times at 0.5, 1.0, and 1.5 years. At the specified landmark time, patients were classified as positive or negative for OR if they were classified as a confirmed response at that time or not. For patients with a confirmed response at the landmark time, the response time was determined to be the first scan at which the tumor exhibited a response. A Cox proportional hazards model was used to assess residual survival time, which was defined as time from specified landmark time to death or last follow-up. Finally, the concordance index (C-index) was used to assess the predictive effects of OR and PFS on OS. The choroid plexus tumors and germ cell tumor subgroups were excluded from landmark analysis, due to all cases in these groups reaching complete/partial response before the shortest landmark time (0.5 y).

For all statistical analyses, we accounted for multiple testing using the Bonferroni correction method, with a predetermined alpha level of 0.05 and the number of independent comparisons at 10, as determined by the number of subgroup analyses in our study. Consequently, statistical significance was maintained at $P = 0.05/10$ or $P = 0.005$.

Results

Study Population

A total of 269 pediatric patients treated for MBL or other leptomeningeal seeding tumors were analyzed. The flow diagram of the study detailing the patient cohort is shown in Supplementary Figure 1. Demographics for the study population are summarized in Table 2. The median age at diagnosis was 9.7 years (range = 0.1–17.9 y) and 58.7% of patients were male—87 patients (32.3%) were diagnosed with MBL. Other patients were characterized into a tumor type subgroup of glioma, embryonal tumor, germ cell tumor, or choroid plexus papilloma. Glioma was the largest tumor type subgroup at 78 patients (29.0%). For treatment modalities, 50.2% ($n = 135$) of the patients underwent gross total resection and 60.9% received chemoradiotherapy ($n = 164$). The median follow-up time for the entire cohort was 4.0 years.

Interobserver Agreement of Objective Response

Agreement of OR determination between the primary reader and the secondary reader for the RAPNO criteria was 83.8% (k statistic = 0.815; $P < 0.001$). The rest of the results calculated by subgroups are listed in Table 3. The Spearman rank correlations between the primary reader and the secondary reader were 0.612 and 0.574 for the measurements of enhancing and T2/FLAIR abnormalities, respectively.

Objective Response Rates

On the basis of evaluation by the primary reader, the OR rate in all patients was 152/269 (56.5%; 95% CI: 50.5%–62.5%) by RAPNO criteria. The median PFS calculated by RAPNO criteria for the entire cohort was 1.8 years (range, 0.1–14.9 y). OR rates and median PFS from subgroups are shown in Table 3. The detailed results of complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) within each tumor subtype are shown in Supplementary Table 2.

Ninety-five patients progressed per RAPNO criteria by the last available scan date. There were 15 patients who only had progression by T2/FLAIR, and 5 patients remained positive in CSF cytology temporarily when the tumor size became stable or disappeared. Three patients developed bone marrow metastases, one of whom developed a single bone marrow metastasis without imaging progression. Abnormal serum or CSF levels of alpha-fetoprotein (AFP) and beta human chorionic gonadotropin (βhCG) were only found in germinoma, but almost all became normal soon after treatment.

Table 3. Results of OR rate and interobserver agreement in different study population subgroups

Study Population Subgroup	OR Rate		Median PFS, y	Interobserver Agreement of OR		*P*
	Percent	95% CI (%)		Percent	*k* statistic	
HGG ($n = 78$)	12.8	5.2–20.4	0.8	66.7	0.771	<0.001
Non-HGG ($n = 191$)	74.9	68.7%–81.1	2.5	84.6	0.734	<0.001
MBL ($n = 87$)	72.4	62.8–82	2.1	88.9	0.815	<0.001
Embryonal tumors ($n = 41$)	53.7	37.7–69.6	1.6	72.7	0.712	<0.001
Germ cell subtypes ($n = 43$)	88.4	78.4–98.4	4.4	76.3	0.428	<0.001
Chemotherapy only ($n = 61$)	62.3	49.8–74.8	1.8	92.1	0.898	<0.001
Radiotherapy only ($n = 44$)	61.4	46.4–76.3	1.7	77.8	0.730	<0.001
Chemoradiotherapy ($n = 164$)	53.7	45.9–61.4	1.9	81.1	0.794	<0.001
With leptomeningeal seeding ($n = 66$)	22.7	12.3–33.1	1.0	66.7	0.756	<0.001
Without leptomeningeal seeding ($n = 203$)	67.5	61.0–74.0	2.1	85.6	0.789	<0.001
All ($N = 269$)	56.5	50.5–62.5	1.8	83.8	0.815	<0.001

Landmark Analysis: Objective Response versus Residual Survival

The stratifications of patients at 0.5, 1, and 1.5 years by OR status, as determined by the RAPNO criteria, are listed in Table 4 (including other subgroups). The numbers of patients who were alive at the 3 landmarks were 251, 219, and 190, respectively. Cox proportional hazards models confirmed the association of OR and residual survival at each landmark. At the 1-year landmark, responders and nonresponders in the overall study population exhibited significant differences in OS (HR = 0.079, $P < 0.001$) (Table 5). This was also validated at the 0.5- and 1.5-year landmarks (Fig. 1). Subgroup analyses also confirmed association between OR and residual survival for gliomas (Supplementary Figure 2), MBL (Supplementary Figure 3), embryonal tumors (Supplementary Figure 4) and patients treated by chemotherapy only (Supplementary Figure 5), radiotherapy only (Supplementary Figure 6), and chemoradiotherapy (Supplementary Figure 7), patients with (Supplementary Figure 8) or without leptomeningeal seeding (Supplementary Figure 9) as well as for non–high-grade gliomas (HGGs) (Supplementary Figure 10).

Landmark Analysis: Progression versus Residual Survival

Progression status as determined by the RAPNO criteria was used to stratify patient groups at 0.5, 1, and 1.5 years (data from 0.5-, 1-, and 1.5-y landmark times as shown in Table 4). Kaplan–Meier curves were generated by groups, comparing those who had experienced disease progression by the landmark time and those who had not; Cox proportional hazards models confirmed the association between the progression status and OS at each landmark. Landmark analysis at 1 year demonstrated that progressors and nonprogressors in the overall study population had significant differences in OS (HR = 10.192, $P < 0.001$) (Table 5). Like objective response, these findings were also significant at the 0.5- and 1.5-year landmarks (Figure 1). Subgroup analyses also validated association between progression and residual survival for gliomas (Supplementary Figure 2), MBL (Supplementary Figure 3), embryonal tumors (Supplementary Figure 4) and patients treated by chemotherapy only (Supplementary Figure 5), radiotherapy only (Supplementary Figure 6), and chemoradiotherapy (Supplementary Figure 7), patients with (Supplementary Figure 8) or without leptomeningeal

Table 4. Landmark analysis for confirmed response and progression at each landmark time

Study Population Subgroup	Landmark Time (Alive/Total)	Assessment, *n*			
		Nonresponder	Responder	Nonprogressor	Progressor
HGG (*n* = 78)	0.5 y (73/78)	53	20	42	31
	1.0 y (55/78)	33	22	35	20
	1.5 y (43/78)	25	18	26	17
Non-HGG (*n* = 191)	0.5 y (179/191)	36	143	162	17
	1.0 y (165/191)	27	138	148	17
	1.5 y (148/191)	26	122	133	15
MBL (*n* = 87)	0.5 y (80/87)	15	65	72	8
	1.0 y (73/87)	13	60	63	10
	1.5 y (66/87)	13	53	58	8
Embryonal tumors (*n* = 41)	0.5 y (40/41)	15	25	31	9
	1.0 y (36/41)	11	25	29	7
	1.5 y (31/41)	10	21	24	7
Chemotherapy only (*n* = 61)	0.5 y (55/61)	18	37	47	8
	1.0 y (45/61)	10	35	37	8
	1.5 y (42/61)	9	33	36	6
Radiotherapy only (*n* = 44)	0.5 y (41/44)	15	26	32	9
	1.0 y (34/44)	11	23	29	5
	1.5 y (31/44)	9	22	27	5
Chemoradiotherapy (*n* = 164)	0.5 y (156/164)	56	100	125	31
	1.0 y (141/164)	39	102	117	24
	1.5 y (118/164)	33	85	97	21
With leptomeningeal seeding (*n* = 66)	0.5 y (61/66)	37	24	41	20
	1.0 y (52/66)	29	23	34	18
	1.5 y (44/66)	27	17	27	17
Without leptomeningeal seeding (*n* = 203)	0.5 y (191/203)	52	139	163	28
	1.0 y (168/203)	31	137	149	19
	1.5 y (147/203)	24	123	132	15
All (*N* = 269)	0.5 y (251/269)	88	163	203	48
	1.0 y (219/269)	59	160	182	37
	1.5 y (190/269)	50	140	158	32

Table 5. Results of Cox proportional hazards models and C-index (standard error) in different groups

Group	Landmark Time, y	Responder or Nonresponder			*P*	Progressor or Nonprogressor			*P*
		HR	95% CI (%)	C-index (SE)		HR	95% CI (%)	C-index (SE)	
HGG ($n = 78$)	0.5	0.147	0.063–0.343	0.625 (0.035)	<0.001	4.128	2.246–7.588	0.579 (0.064)	<0.001
	1.0	0.204	0.091–0.460	0.637 (0.048)	<0.001	7.783	3.398–17.826	0.540 (0.046)	<0.001
	1.5	0.207	0.080–0.535	0.667 (0.047)	0.001	14.166	4.218–47.574	0.597 (0.066)	<0.001
Non-HGG ($n = 191$)	0.5	0.112	0.054–0.231	0.516 (0.017)	<0.001	14.844	6.969–31.619	0.500 (0.010)	<0.001
	1.0	0.076	0.034–0.172	0.502 (0.016)	<0.001	8.691	3.794–19.910	0.509 (0.014)	<0.001
	1.5	0.101	0.044–0.236	0.511 (0.019)	<0.001	15.312	6.483–36.162	0.500 (0.012)	<0.001
MBL ($n = 87$)	0.5	0.121	0.047–0.308	0.517 (0.025)	<0.001	8.485	3.150–22.861	0.507 (0.019)	<0.001
	1.0	0.126	0.045–0.353	0.512 (0.025)	<0.001	5.798	1.929–17.426	0.511 (0.021)	0.002
	1.5	0.137	0.045–0.414	0.505 (0.029)	<0.001	12.910	3.614–46.111	0.508 (0.016)	<0.001
Embryonal tumors ($n = 41$)	0.5	0.176	0.054–0.574	0.532 (0.052)	0.004	9.355	2.706–32.336	0.517 (0.033)	<0.001
	1.0	0.085	0.021–0.338	0.529 (0.053)	<0.001	4.194	1.173–14.998	0.517 (0.046)	0.027
	1.5	0.218	0.061–0.776	0.541 (0.048)	0.019	6.897	1.927–24.684	0.515 (0.046)	0.003
Chemotherapy only ($n = 61$)	0.5	0.030	0.006–0.136	0.537 (0.041)	<0.001	43.242	7.901–236.665	0.533 (0.031)	<0.001
	1.0	0.051	0.011–0.243	0.540 (0.038)	<0.001	20.989	5.065–86.982	0.518 (0.032)	<0.001
	1.5	0.113	0.027–0.473	0.544 (0.045)	0.003	12.108	3.065–47.827	0.534 (0.024)	<0.001
Radiotherapy only ($n = 44$)	0.5	0.042	0.005–0.329	0.500 (0.019)	0.003	60.979	7.258–512.318	0.518 (0.025)	<0.001
	1.0	0.049	0.006–0.429	0.545 (0.048)	0.006	15.096	2.388–95.437	0.533 (0.032)	0.004
	1.5	0.046	0.005–0.408	0.571 (0.050)	0.006	20.121	3.641–111.182	0.528 (0.036)	0.001
Chemoradiotherapy ($n = 164$)	0.5	0.141	0.079–0.252	0.500 (0.026)	<0.001	6.601	3.785–11.511	0.506 (0.018)	<0.001
	1.0	0.112	0.058–0.213	0.528 (0.024)	<0.001	7.636	4.034–14.453	0.500 (0.015)	<0.001
	1.5	0.175	0.087–0.351	0.538 (0.028)	<0.001	8.136	3.853–17.177	0.532 (0.022)	<0.001
With leptomeningeal seeding ($n = 66$)	0.5	0.205	0.092–0.455	0.531 (0.061)	<0.001	4.764	2.122–10.694	0.596 (0.053)	<0.001
	1.0	0.165	0.068–0.403	0.540 (0.065)	<0.001	3.079	1.416–6.695	0.547 (0.061)	0.005
	1.5	0.301	0.125–0.726	0.579 (0.062)	00.007	4.820	2.124–10.941	0.516 (0.062)	<0.001
Without leptomeningeal seeding ($n = 203$)	0.5	0.067	0.033–0.132	0.504 (0.019)	<0.001	17.827	9.613–33.061	0.510 (0.011)	<0.001
	1.0	0.077	0.036–0.162	0.514 (0.016)	<0.001	21.048	9.803–45.196	0.500 (0.008)	<0.001
	1.5	0.097	0.040–0.231	0.528 (0.018)	<0.001	23.644	8.945–62.497	0.529 (0.014)	<0.001
All ($N = 269$)	0.5	0.088	0.053–0.148	0.500 (0.020)	<0.001	10.539	6.594–16.843	0.510 (0.014)	<0.001
	1.0	0.079	0.045–0.140	0.521 (0.019)	<0.001	10.192	5.954–17.447	0.503 (0.013)	<0.001
	1.5	0.106	0.058–0.195	0.527 (0.021)	<0.001	14.490	7.787–26.965	0.520 (0.015)	<0.001

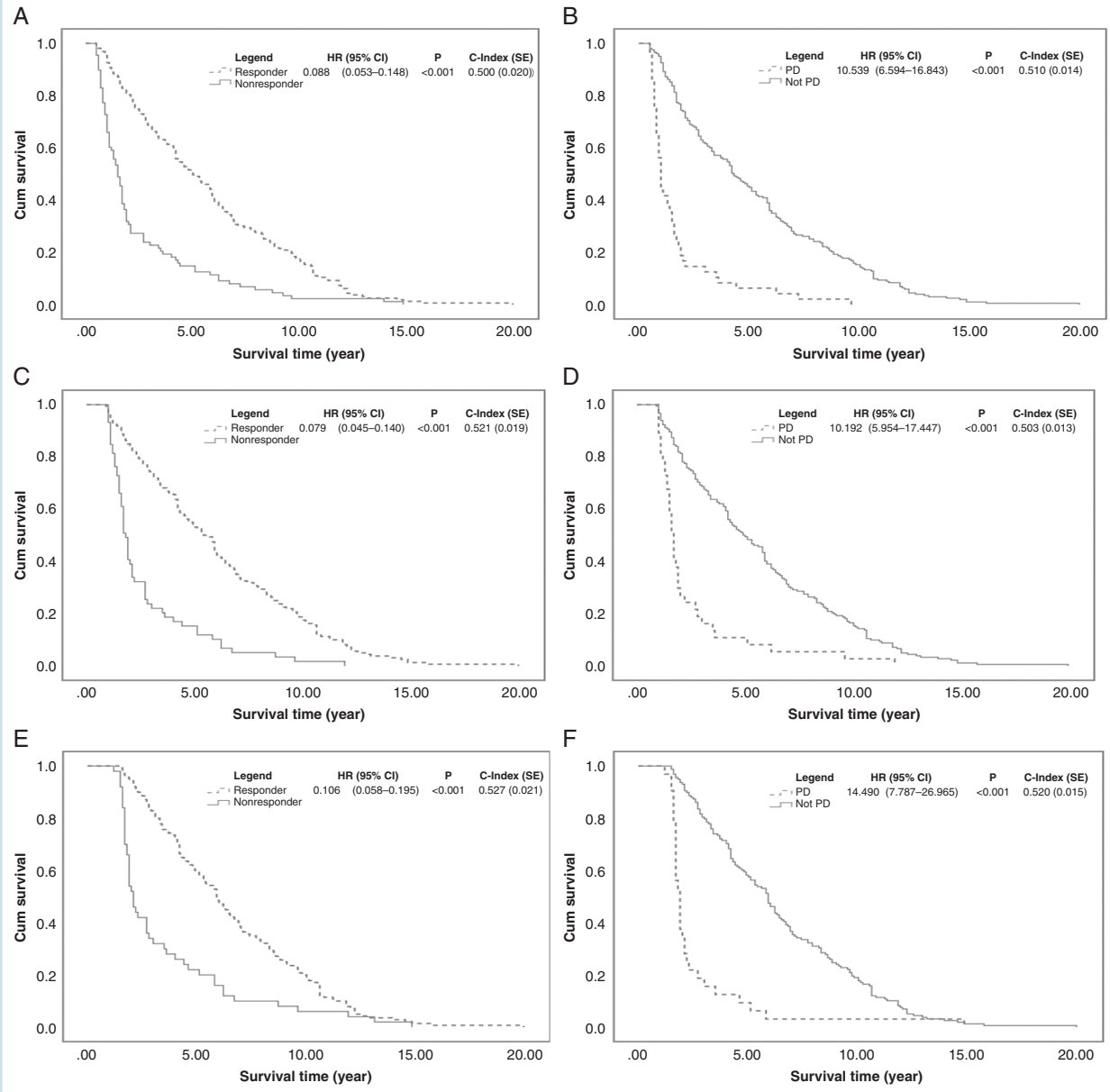

Fig. 1 Landmark analyses of entire cohort ($N = 269$). (A) Kaplan–Meier analysis of OR at 0.5 years, (B) Kaplan–Meier analysis of progression at 0.5 years, (C) Kaplan–Meier analysis of OR at 1 year, (D) Kaplan–Meier analysis of progression at 1 year, (E) Kaplan–Meier analysis of OR at 1.5 years, (F) Kaplan–Meier analysis of progression at 1.5 years.

seeding (Supplementary Figure 9) as well as for non-HGGs (Supplementary Figure 10).

Discussion

In the present study, radiological and clinical data from 269 patients with MBL and other leptomeningeal seeding tumors were collected from 4 hospitals to evaluate response assessment using the RAPNO criteria. MBL constituted the largest tumor subtype of our cohort (32.3%). Compared with the study population's median PFS of 1.8 years, each of the 3 treatment groups did not have significantly different median PFS. Among tumor subtypes, the median PFS for low-grade germ cell tumors (4.4 y) was significantly higher than the PFS for higher-grade tumors, including glioma (0.8 y), MBL (2.1 y), and embryonal tumors (1.6 y). Similar to the median PFS, OR rate was also associated with tumor malignancy, with the lowest in the glioma group (12.8%) and the highest in the germ cell tumor group (88.4%). These results were not surprising, due to the poorer documented survival rates for higher-grade tumors, such as glioma, compared with lower-grade ones, such as germ cell tumors.[3] Thus, OR rates predicted by the

RAPNO criteria reflect known differences among the pediatric brain tumor subtypes in response to treatment. Of note, the OR rate for HGG (12.8%) is extraordinarily low per RAPNO criteria in our study. It is also known that HGG is significantly different from the non-HGG in evaluation and prognosis. As such, our results lend support to separating out HGG in the next version of RAPNO response criteria, although the current RAPNO criteria achieved favorable results in landmark analysis of the HGG subgroup as well.

For our patient cohort, RAPNO criteria showed good consistency in the evaluation responses. For subgroup analysis based on tumor subtypes and treatment modality, most subgroups also exhibited similarly high interobserver agreement. Only germ cell tumors had relatively poor results. Challenges in imaging diagnosis of germ cell tumors have been previously documented, with 17 out of 181 patients in a case series of intracranial germ cell tumors receiving a delayed diagnosis of over 3 months after initial MR imaging.[16] This is attributed to more subtle abnormalities and delayed appearance of contrast-enhancing lesions.

For both the analysis of the entire study population and subgroup analyses, our landmark analyses demonstrate that progression determined by RAPNO criteria at 0.5, 1.0, and 1.5 years following pathological diagnosis correlated with OS. We also found an association between OR status and OS, as demonstrated by our landmark analysis per RAPNO criteria. The successful stratification of OS by OR status was consistent across all 3 tumor subtypes and all 3 treatment modalities studied. Of note, correlations for embryonal tumors and radiotherapy were worse than those for other subgroups. While this may be explained by these groups being the least frequent tumor subtype and treatment modality, respectively, certain subgroup-specific traits may also explain this. For example, heterogeneous imaging characteristics present in embryonal tumors, such as lack of consistent imaging patterns for pineal tumors like pinealoma, may complicate response assessment for these malignancies, and this is reflected by the lower interobserver agreement in response assessment compared with other subgroups.[17]

The strong correlation between OR and PFS with OS may be explained by the incorporation of the non-enhanced lesions, extra-CNS disease assessment, and other clinical metrics, such as CSF cytology as well as serum or CSF levels of AFP and βhCG into the RAPNO criteria, which increased the stringency of the evaluation process. For example, there were 15 patients who had only T2/FLAIR progression, 1 patient who developed a single bone marrow metastasis, and 5 patients who remain CSF cytology positive temporarily when the tumor size became stable or disappeared. These findings suggest that the decreased tumor size may not always correlate with improved survival for pediatric CNS tumors.[18–20]

A RANO working group with expertise in leptomeningeal metastases disease (LMD) developed a consensus proposal in 2017 for evaluating patients treated for this disease. Three elements, including neurologic examination, cerebrospinal imaging, and CSF cytology, were used in the RANO-LMD criteria for diagnosis and response assessment during follow-up. For imaging evaluation, a scorecard to evaluate MRI findings during the course of LMD was designed and recommended.[15] However, there are several main differences of response criteria pertaining to LMD between RANO-LMD and RAPNO. First, the RANO-LMD criteria do not account for all aspects of metastatic complication (for example, the response of systemic cancer), while extra-CNS disease is incorporated into the RAPNO response criteria. Second, presence or absence of hydrocephalus contributes to response assessment in the RANO-LMD criteria but not in the RAPNO criteria. In addition, persistently positive CSF cytology in isolation is insufficient to define progressive disease per RANO-LM but positive CSF tumor cells in isolation are sufficient to define progressive disease in the RAPNO criteria. Most notably, the RAPNO criteria were developed for application specifically for pediatric LMD, while the RANO-LM criteria are for the adult population. Despite excellent performance that RAPNO criteria achieved among patients with leptomeningeal seeding in our study, it should be noted that only 66 patients were included for analyses. Assessing response of leptomeningeal metastasis patients remains challenging, and further studies with a larger cohort size are needed to better validate the feasibility and utility of RAPNO criteria in this subgroup.

There are several limitations to our study. First, because all analyses were performed on imaging and clinical data from a retrospective cohort of 269 patients, there were inevitably areas of incompleteness and potential errors in the medical records. For example, a small number of patients with germ cell tumors were not examined for AFP and βhCG, and very few patients underwent bone marrow examination for biopsy data. Second, many patients were excluded to loss of follow-up or unavailable imaging, which may have resulted in selection bias. Third, because response assessment in our study focused primarily on imaging data and a few laboratory values according to RAPNO, the evaluator was unaware of other clinical data during the assessment. We do not believe that this approach affected our assessment because there was no clinical progression prior to imaging progression. Finally, we were unable to perform landmark analysis for the choroid plexus tumors or germ cell tumor subgroups, because all the cases in our study population had reached complete/partial response before our shortest landmark time (0.5 y) due to the favorable outcomes of these tumors.

In conclusion, due to its incorporation of non-enhanced lesions and other clinical results, we demonstrated in a cohort of 269 pediatric patients with MBL and other leptomeningeal seeding tumors that the RAPNO criteria facilitated accurate detection of disease progression, especially for evidence of progression after tumor size has stabilized or disappeared. Moreover, the RAPNO criteria showed good consistency in the response evaluation across tumor subtypes and treatment modalities. Finally, at each landmark point, OR status and PFS determined by RAPNO were predictive of OS for all tumor subtypes and treatment modalities.

Supplementary Material

Supplementary data are available at *Neuro-Oncology* online.

Keywords

interobserver agreement | objective response | overall survival | progression-free survival | RAPNO

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Authorship statement

Conception and design: H. X. Bai, R. Y. Huang, L. Yang, J. Peng, H. Zhou, O. Tang, P. Y. Wen, X. Gao, K. Chang. Development of methodology: H. X. Bai, R. Y. Huang, S. H. Patel, J. Boxerman, P. Y. Wen. Acquisition of data: J. Peng, P. Wang, X. Zeng, J. Wu, C. Hu, K. Jin. Analysis and interpretation of data: J. Peng, H. Zhou, Q. Shen, Y. Xiao. Writing, review, and/or revision of the manuscript: J. Peng, O. Tang, H. Zhou, H. X. Bai, R. Y. Huang, P. Y. Wen, K. Chang. Administrative, technical, or material support (ie, reporting or organizing data, constructing databases): B. Xiao, L. Yang, K. Jin, C. Hu, X. Gao. Study supervision: H. X. Bai, L. Yang, R. Y. Huang, B. Xiao.

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