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ORIGINAL REPORT

Assessment of Primary Site Response in Children With High-Risk Neuroblastoma: An International Multicenter Study

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ABSTRACT

Purpose

The International Neuroblastoma Response Criteria (INRC) require serial measurements of primary tumors in three dimensions, whereas the Response Evaluation Criteria in Solid Tumors (RECIST) require measurement in one dimension. This study was conducted to identify the preferred method of primary tumor response assessment for use in revised INRC.

Patients and Methods

Patients younger than 20 years with high-risk neuroblastoma were eligible if they were diagnosed between 2000 and 2012 and if three primary tumor measurements (antero-posterior, width, cranio-caudal) were recorded at least twice before resection. Responses were defined as ≥ 30% reduction in longest dimension as per RECIST, ≥ 50% reduction in volume as per INRC, or ≥ 65% reduction in volume.

Results

Three-year event-free survival for all patients (N = 229) was 44% and overall survival was 58%. The sensitivity of both volume response measures (ability to detect responses in patients who survived) exceeded the sensitivity of the single dimension measure, but the specificity of all response measures (ability to identify lack of response in patients who later died) was low. In multivariable analyses, none of the response measures studied was predictive of outcome, and none was predictive of the extent of resection.

Conclusion

None of the methods of primary tumor response assessment was predictive of outcome. Measurement of three dimensions followed by calculation of resultant volume is more complex than measurement of a single dimension. Primary tumor response in children with high-risk neuroblastoma should therefore be evaluated in accordance with RECIST criteria, using the single longest dimension.

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INTRODUCTION

Neuroblastoma is the most common extracranial solid tumor of childhood and is a heterogeneous malignancy. The International Neuroblastoma Staging System (INSS) and the International Neuroblastoma Response Criteria (INRC) were developed to compare results of trials for children with neuroblastoma conducted around the world.[1,2] However, difficulties associated with INSS became apparent over time,[3] and, in 2009, the International Neuroblastoma Risk Group Staging System (INRGSS) was adopted. Whereas INSS was a surgical-pathologic staging system, INRGSS relies upon radiologic characteristics to determine stage. Because INRGSS is imaging-based, and because imaging modalities have changed substantially over time, modernization of the INRC is required. This is particularly true with respect to imaging of primary tumors, as both anatomic imaging (computed tomography [CT] and magnetic resonance imaging [MRI]) and functional imaging (diffusion-weighted MRI, nuclear medicine single-photon emission CT, and positron emission tomography) have evolved.

Determining the method used to assess changes in primary tumor size is a vital step in revising the INRC. INRC requires serial measurement of lesions in three dimensions to compute volume. In contrast, Response Evaluation Criteria in Solid Tumors (RECIST), requires measurement of index lesions in one dimension.[4,5] This study was conducted to determine the best approach for measurement of primary tumors in the updated INRC.

PATIENTS AND METHODS

This study was conducted at seven centers: Texas Children's Hospital, Great Ormond Street Hospital for Children, Children's Hospital of Philadelphia, Universitatsklinikum Koln, Hopital Necker-Enfants Malades, Instituto Giannina Gaslini, and Dr von Hauner Children's Hospital. Medical records and imaging studies were reviewed after ethics board approval. Subjects were eligible if the following criteria were met: younger than 20 years of age at diagnosis; initial imaging studies performed between January 1, 2000, and June 30, 2012; and availability of serial anatomic imaging studies and clinical outcome data. Study radiologists at participating sites measured primary tumors in three dimensions for each subject; central review was not performed. To permit assessment of the relationship between response by imaging and event-free survival (EFS) and overall survival (OS), only patients with high-risk neuroblastoma were included. Because INSS criteria were in use during most of the period in which patients were diagnosed, INSS stage designation was used. For this study, high-risk neuroblastoma was defined as INSS stage 4 neuroblastoma diagnosed at an age greater than 18 months, INSS stage ≥ 2 disease with *MYCN* amplification, and INSS stage 3 disease and unfavorable histology per the International Neuroblastoma Pathology Classification (INPC) system[6,7] diagnosed at an age greater than 18 months. Patients were treated per institutional standards or were enrolled in clinical trials.

Patients comprising the analytic cohort included those for whom three primary tumor measurements (antero-posterior, width, and cranio-caudal) were recorded at least twice before tumor resection. Tumor size reduction was the difference in maximum tumor diameter, measured serially in the same orthogonal plane, or the difference in tumor volume observed upon comparison of imaging performed at diagnosis and imaging performed at the time point closest to primary tumor resection. If a primary tumor formed a single conglomerate mass with enlarged regional lymph nodes, the entire mass was measured. If clear separation between the primary tumor and regional nodes became apparent after treatment or regional nodes disappeared, only the primary tumor itself was measured. A complete response was defined as absence of residual tumor. A partial response (PR) on the basis of a comparison of maximum tumor diameters was defined, per RECIST, as a ≥ 30% reduction in longest tumor dimension ($Diam_{30}$). For volume assessment, the formula, volume = (π/6) × antero-posterior (depth) × width × cranio-caudal, was used. A PR on the basis of a comparison of volumes was defined, per INRC, as ≥ 50% reduction in primary tumor volume following treatment (Vol_{50}). Because ≥ 30% reduction in the diameter of a sphere corresponds to a ≥ 65% reduction in volume (Vol_{65}), this definition of PR was also evaluated (Table 1).

Table 1. Measurements of Primary Tumor Response

No. of Dimensions Measured	Definition of Partial Response	Abbreviation Used in Study
Single dimension	≥ 30% reduction in longest diameter	$Diam_{30}$
Three dimensions	≥ 50% reduction in volume*	Vol_{50}
Three dimensions	≥ 65% reduction in volume*	Vol_{65}

*Volume = (π/6) × antero-posterior (depth) × width × cranio-caudal.

Survival plots, life tables, and log-rank tests were used to compare OS and EFS. Risk of relapse was evaluated using known prognostic factors. These included age (< 18 months *v* ≥ 18 months), INSS stage (non–stage 4 *v* stage 4), *MYCN* status (nonamplified *v* amplified), and INPC histology (favorable *v* unfavorable). The Kaplan-Meier method was used to generate survival curves with SEs per Peto et al.[8,9] For EFS, an event was defined as relapse, progression, or death from any cause. For OS, only death was considered. Time to event or death was calculated from time of diagnosis. In the absence of an event or death, survival time was censored at time of last contact.

The sensitivity and specificity of response measures in predicting death were calculated. A χ^2 test was performed for each response measure to determine if a statistically significant relationship existed between tumor reduction and extent of tumor resection, and between maximum diameter or volume reduction and prognostic factors. Patients were classified as having a complete surgical resection if ≥ 90% of the tumor mass was removed, otherwise patients were classified as having an incomplete resection. To determine the independent prognostic strength of response measures for survival in the presence of prognostic factors, multivariable Cox proportional hazards (PH) regression models with the Efron method of handling tied event times were fit. Because INPC histology is confounded with age, models were fit to include these variables separately. Any apparent violations of the PH assumption were tested, and if found significant, were handled by treating the covariate as time dependent, which was accomplished by including a survival-time interaction term in the model.[10] Backward selection was used to determine the most parsimonious model.

Analyses were performed using SAS (SAS/STAT User's Guide, Version 9.2; SAS Institute, Cary, NC). Life tables and survival curves were created using R (R Project for Statistical Computing; https://www.r-project.org/). *P* values less than .05 were considered statistically significant.

RESULTS

Patient Characteristics and Outcome

Data for 252 children with high-risk neuroblastoma were collected. Twenty-three patients were excluded because of the absence of complete tumor measurements. The final analytic cohort consisted of 229 patients. Median time between baseline and presurgical imaging was 110 days (range, 25 to 693 days).

Of the 229 patients, 189 (83%) had INSS stage 4 disease. Eighty-two percent (187 of 229 patients) were age ≥ 18 months at diagnosis. Fifty-two percent of patients had *MYCN* amplified tumors, and 87% had tumors with unfavorable histology (Table 2). Patients without an event (n = 101) had a median follow-up time of 2.9 years (range, 88 days to 12.6 years). Patients with an event (n = 128) had a median time to event of 1.1 years (range, 81 days to 12.1 years). Patients who remained alive (n = 134) had a median follow-up time of 2.8 years (range, 88 days to 12.6 years). Patients who died (n = 95) had a median time to death of 1.2 years (range, 96 days to 10.9 years).

The 3-year EFS and OS for all 229 patients was 44.4% ± 4.3% and 58.2% ± 4.4%, respectively (Fig 1). Three-year EFS and OS for patients with non–stage 4 disease were significantly higher than the EFS and OS for patients with stage 4 disease (67.0% ± 9.9% *v* 39.4 ± 4.6%; *P* = .002; and 76.4% ± 9.0% *v* 54.0% ± 4.9%; *P* = .023, respectively). Patients whose tumors were *MYCN* nonamplified fared better than those whose tumors were *MYCN* amplified (3-year EFS 52.4% ± 7.0% *v* 37.0 ± 5.4%; *P* = .006; 3-year OS 70.5% ± 6.5% *v* 45.7% ± 5.8%; *P* < .001, respectively).

Table 2. Patient Characteristics and Outcome

Patient Cohort	No. (%)	3-Year EFS ± SE (%)	*P* (EFS Log-Rank)	3-Year OS ± SE (%)	*P* (OS Log-Rank)
Overall	229	44.4 ± 4.3	N/A	58.2 ± 4.4	N/A
Age at diagnosis, months					
< 18	42 (18)	53.1 ± 9.7	.284	60.7 ± 9.8	.943
≥ 18	187 (82)	42.4 ± 4.7		57.6 ± 4.9	
INSS stage					
Non–stage 4	40 (17)	67.0 ± 9.9	.002	76.4 ± 9.0	.023
Stage 4	189 (83)	39.4 ± 4.6		54.0 ± 4.9	
MYCN status					
Nonamplified	105 (48)	52.4 ± 7.0	.006	70.5 ± 6.5	< .001
Amplified	112 (52)	37.0 ± 5.4		45.7 ± 5.8	
Histology					
Favorable	18 (13)	81.3 ± 12.4	.035	80.8 ± 12.5	.133
Unfavorable	107 (87)	48.9 ± 6.3		60.1 ± 6.5	

Abbreviations: EFS, event-free survival; INSS, International Neuroblastoma Staging System; N/A, not applicable; OS, overall survival.

Response Measures and Outcome

Sensitivity and specificity of response measures with respect to life status (alive *v* dead) are shown in Table 3. The sensitivity of each measure reflects the ability of that measure to detect a PR or greater in patients who go on to survive. The specificity of each measure reflects the ability of that measure to identify less than a PR among patients who ultimately die. The sensitivity of Vol_{50} was 79% and the sensitivity of Vol_{65} was 72%; both were greater than the sensitivity associated with $Diam_{30}$. However, the specificity of all three measures was low: $Diam_{30}$, 23%; Vol_{50}, 17%; and Vol_{65}, 28%. None of the methods of response assessment was significantly associated with extent of resection.

EFS and OS on the basis of response to initial therapy are shown in Figures 2A to 2F. Because survival curves cross, PH assumptions were tested; however, no statistically significant results were found, indicating that PH may be assumed and that log-rank *P* values are valid. In both EFS and OS multivariable Cox models, only INSS stage and *MYCN* status were predictive of outcome; neither a change in the single longest diameter nor changes in tumor volume were retained in the respective models.

Primary Site Response in MYCN *Amplified Neuroblastoma*

Three-year EFS and OS for patients with *MYCN* amplified tumors (n = 112) were 37.0% ± 5.4% and 45.7% ± 5.8%, respectively (Table 4). The majority of patients with *MYCN* amplified tumors responded to initial treatments; 87% were classified as responders by $Diam_{30}$, 92% were responders using Vol_{50}, and 87% were responders using Vol_{65} as the response benchmark. Within this subgroup, the sensitivity of all measures in detecting response among survivors was high (Table 3). However, the specificity of all measures was low, which indicated that a lack of a PR did not identify patients who would go on to die of disease, regardless of method of assessment used. In this subgroup, as in the cohort as a whole, none of the response measures was significantly associated with extent of tumor resection.

In contrast with the finding for the overall cohort, however, a statistically significant association between volume-based response assessment and survival was observed in the *MYCN* amplified subgroup (Table 4). $Diam_{30}$ was not associated with a statistically significant difference in EFS or OS in this subgroup. Differences in outcome related to volume response measures were further explored by fitting Cox PH regression models that included age, histology, and INSS stage. Vol_{50} or Vol_{65} remained predictive of both EFS and OS. Patients with *MYCN* amplified neuroblastoma who did not have a ≥ 50% reduction in tumor volume in response to initial systemic therapy were at more than three times greater risk for an event and for death than were patients who had such a reduction in volume. The hazard ratios associated with a 65% volume reduction were 2.79 and 2.73 for EFS and OS, respectively.

Primary Site Response in Stage 4 Neuroblastoma

The 3-year EFS and OS for patients with stage 4 disease (n = 189) were 39.4% ± 4.6% and 54.0% ± 4.9%, respectively (Table 3). The majority of stage 4 patients responded to initial therapy; 71% were responders using $Diam_{30}$, 81% were responders using Vol_{50}, and 75% were responders using Vol_{65}. In this group,

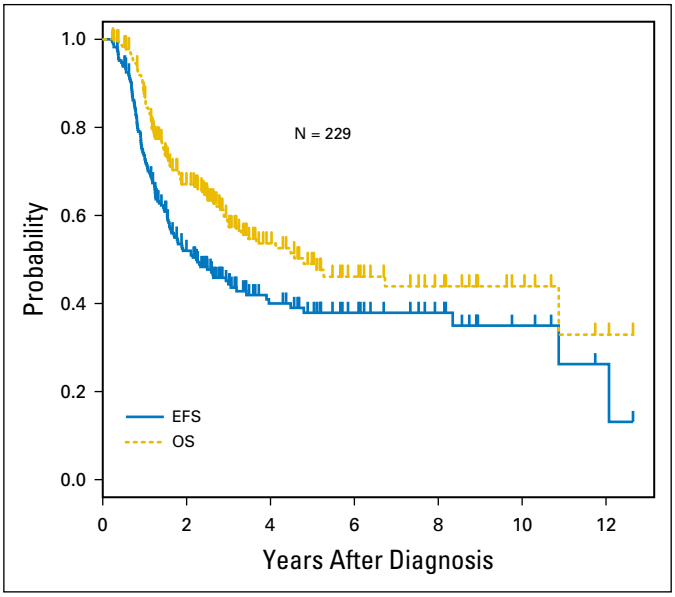

Fig 1. Event-free survival (EFS) and overall survival (OS) for all patients (n = 229).

Table 3. Sensitivity and Specificity of Response Measures

Response Measure	Overall Cohort (N = 229)		*MYCN* Amplified (n = 112)		Stage 4 (n = 189)	
	Sensitivity, % (95% CI)	Specificity, % (95% CI)	Sensitivity, % (95% CI)	Specificity, % (95% CI)	Sensitivity, % (95% CI)	Specificity, % (95% CI)
> 30% maximum diameter reduction	61.9 (53.7 to 70.2)	23.2 (14.7 to 31.6)	89.1 (80.9 to 97.3)	15.8 (6.3 to 25.3)	65.4 (56.2 to 74.5)	21.2 (12.5 to 29.9)
> 50% volume reduction	79.1 (72.2 to 86.0)	16.8 (9.3 to 24.4)	96.4 (87.5 to 99.6)	12.3 (3.8 to 21.0)	82.7 (74.0 to 89.4)	15.3 (7.6 to 23.0)
> 65% volume reduction	72.4 (64.8 to 80.0)	28.4 (19.4 to 37.5)	92.7 (82.4 to 98.0)	19.3 (9.1 to 29.5)	76.9 (67.6 to 84.6)	28.2 (18.7 to 37.8)

the sensitivities of all measures were lower ($Diam_{30}$, 65.4%; Vol_{50}, 82.7%; and Vol_{65}, 76.9%) than the sensitivities observed in the *MYCN* amplified subgroup. The specificity of Vol_{50} was the lowest of the measures evaluated (15.3%). The specificity of Vol_{65} and $Diam_{30}$ were 28.2% and 21.2%, respectively (Table 2). Again, none of the response measures was significantly associated with extent of resection.

EFS and OS in this subgroup were also evaluated in light of method of response assessment. Cox models for EFS and OS did not reveal a statistically significant violation of the PH assumption for volume response measures; the log-rank test remains valid for these analyses. However, PH assumptions were violated for the longest diameter response measure, and Cox models were therefore used for additional analyses. The final backward-selected Cox model showed that only *MYCN* status was predictive of EFS. Among patients with INSS stage 4 disease, those with *MYCN* amplified tumors had an increased risk of event of 1.473. $Diam_{30}$ was dropped from the EFS model as a result of a lack of statistical significance. For OS, stage 4 patients whose tumors decreased by greater than 30% in longest diameter unexpectedly seemed to have a higher risk of death, with all other prognostic factors dropping out of the final backward-selected model. Within the stage 4 subgroup, *MYCN* status and response as assessed by diameter reduction are highly correlated ($P < .001$), which could explain, in part, this finding. Of 127 patients with stage 4 disease who had a PR by $Diam_{30}$, 82 (65%) had *MYCN* amplified tumors. Of 93 patients with stage 4 disease with *MYCN* amplified tumors, 82 (88%) had a greater than 30% reduction in maximum tumor diameter.

DISCUSSION

This study was undertaken to build international consensus regarding measurement of primary tumor response using current imaging technology. When the INRC were published in 1988, recommended modalities for primary site imaging included ultrasound, CT, and MRI.[1] By 1993, ultrasound was no longer recommended for volume assessment.[2] Since the last INRC revision, there have been dramatic changes in imaging techniques. Multidetector CT has made submillimeter section thickness scanning routine, and isovolumetric resolution allows rapid measurement of regions of interest in all three orthogonal planes. Increased availability of MRI with sequences in all planes has also greatly improved accuracy of depiction. To our knowledge, the present cohort represents the largest group of patients with high-risk neuroblastoma in whom current approaches to primary tumor response have been evaluated. In the cohort as a whole, no clear advantage for use of three-dimensional rather than one-dimensional measurement was observed, and neither change in volume nor change in longest diameter was predictive of outcome.

Use of one versus three dimensions for assessment of response in pediatric tumors has been studied previously in patients with rhabdomyosarcoma. Two studies showed that use of volume in assessment of response to initial therapy did not more accurately predict outcome than did use of single dimension measurements.[11,12] In children with neuroblastoma, Yoo et al[13] evaluated the relationship between primary tumor response and outcome, but did not compare methods of response assessment. Our study, to our knowledge, is the first to compare reduction in volume versus reduction in longest diameter as response measures in children with neuroblastoma.

Early response in sites of metastatic disease is predictive of outcome in patients with high-risk neuroblastoma[14-16]; however, the fact that primary tumor response after initial chemotherapy did not predict outcome in our study is not surprising given the nature of modern-era therapy. Multiagent chemotherapy remains a cornerstone of treatment, but primary tumor control includes use of other therapeutic modalities. Although there is debate regarding the extent to which aggressive surgery alters outcome in patients with metastatic disease,[17-19] surgery remains a key component of primary tumor treatment. Radiation of the primary tumor bed in all patients[20,21] or those with residual disease at end induction is also standard.[22] Because of local tumor control measures and addition of effective postconsolidation therapy (isotretinoin and immunotherapy), chemoresponsiveness is not the sole determinant of outcome. Indeed, 5-year local relapse-free survival in the Children's Oncology Group A3973 trial was 87.3%, whereas overall EFS at 5 years was 43.5%.[19] Thus, although control of primary tumors is important, control of other sites of disease is also essential.

Yoo et al[13] have reported that more favorable primary tumor response is associated with improved relapse-free survival in patients with high-risk neuroblastoma. The discrepancy between those findings and the results of the current study may in part be a result of differences in treatment. Children described by Yoo et al received postconsolidation therapy (isotretinoin and interleukin-2), but GD2-directed antibody therapy was not included. Dose-intensified chemotherapy was the central component of treatment of the Yoo et al cohort, and the majority of patients underwent two cycles of high-dose chemotherapy with stem cell rescue. Therefore, an early measure of chemoresponsiveness might be expected to have greater predictive value in the context of treatment that is chemotherapy focused.

Differences in response assessment methodology may also explain differences between the current results and those reported by Yoo et al.[13] In the latter study, a good response to initial therapy

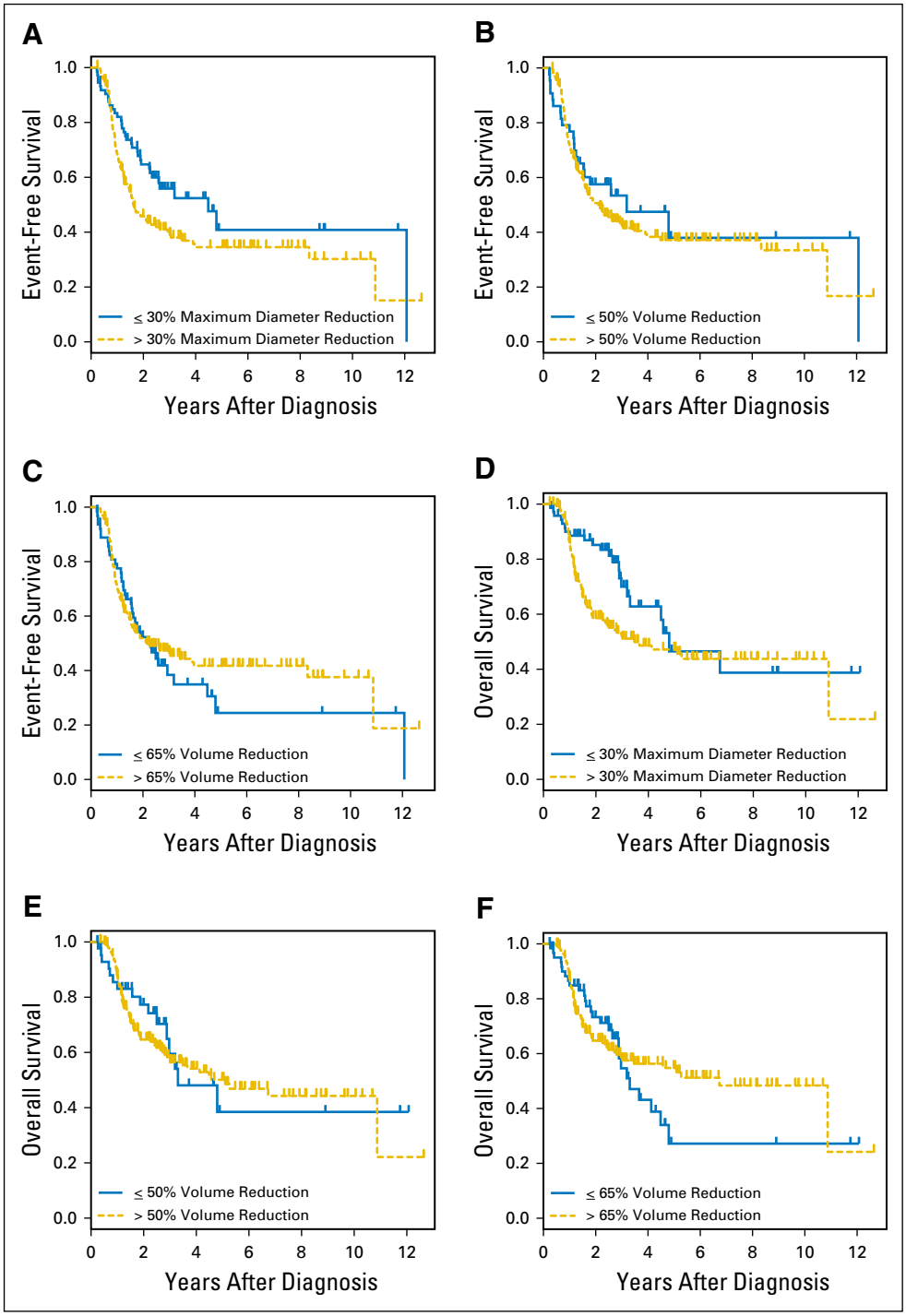

Fig 2. Event-free survival and overall survival by method of response assessment. (A to C) Event-free survival and (D to F) overall survival on the basis of response as defined by a (A, D) greater than 30% reduction in longest diameter, (B, E) greater than 50% reduction in volume, (C, F) greater than 65% reduction in volume.

was defined as a $\geq$ 60% reduction in volume. In contrast, our study used standard response definitions including the RECIST definition of PR ($Diam_{30}$), a corresponding reduction in volume (Vol_{65}), and the INRC definition of PR (Vol_{50}). Finally, Yoo et al computed tumor volume by outlining regions of interest in each slice of stacked CT or MRI images. Areas of interest were summed and multiplied by slice thickness to determine volume. In our study, the formula for volume of a spheroid was used to estimate tumor volume, as is more typically done in everyday radiology practice. Although this strategy is more accurate than the use of formulae for cubes or spheres, volumes calculated are approximations of the irregularly shaped lesions commonly encountered in children with neuroblastoma. Volumetric approaches, rather than formula-based approximations, have been used in other pediatric studies[23-26] but volumetrics have not been broadly incorporated into clinical practice. Because our study was designed to facilitate a common approach to response assessment internationally, we focused on measurement methods that can be used around the globe today, acknowledging that volumetric techniques may be used more widely in the future.

Table 4. Response Measures

Response Measure	No. (%)	3-Year EFS ± SE, %	*P* (EFS)	3-Year OS ± SE, %	*P* (OS)
Overall cohort					
Maximum diameter reduction					
≤ 30%	73 (32)	55.9 ± 8.5	.023*	70.0 ± 8.0	.016*
> 30%	156 (68)	39.0 ± 4.8		52.2 ± 5.1	
Volume reduction					
≤ 50%	44 (19)	53.4 ± 12.2	.648*	59.5 ± 11.4	.664*
> 50%	185 (81)	42.4 ± 4.5		57.4 ± 4.7	
Volume reduction					
≤ 65%	64 (28)	38.4 ± 9.1	.791*	54.6 ± 9.5	.899*
> 65%	165 (72)	46.4 ± 4.9		58.5 ± 4.9	
MYCN amplified					
Overall	112	37.0 ± 5.4	N/A	45.7 ± 5.8	N/A
Maximum diameter reduction					
≤ 30%	15 (13)	26.7 ± 13.2	.254	40.2 ± 15.5	.335
> 30%	97 (87)	38.9 ± 5.6		47.0 ± 6.3	
Volume reduction					
≤ 50%	9 (8)	11.1 ± 10.5	.001	12.5 ± 11.7	.001
> 50%	103 (92)	39.4 ± 5.7		48.7 ± 6.1	
Volume reduction					
≤ 65%	15 (13)	6.7 ± 6.4	< .001†	10.3 ± 9.7	.001
> 65%	97 (87)	42.2 ± 6.0		50.8 ± 6.2	
Stage 4					
Overall	189	39.4 ± 4.6	N/A	54.0 ± 4.9	N/A
Maximum diameter reduction					
≤ 30%	54 (29)	50.2 ± 9.1	.029	68.6 ± 8.8	PH assumption violated
> 30%	135 (71)	35.0 ± 5.2		48.3 ± 5.6	
Volume reduction					
≤ 50%	31 (19)	44.0 ± 13.4	.905*	54.4 ± 13.0	.638*
> 50%	158 (81)	38.6 ± 4.8		53.7 ± 5.2	
Volume reduction					
≤ 65%	48 (25)	27.7 ± 8.9	.539*	47.4 ± 10.4	.762*
> 65%	141 (75)	43.5 ± 5.3		55.7 ± 5.5	

Abbreviations: EFS, event-free survival; N/A, not applicable; OS, overall survival; PH, proportional hazards.
*Apparent violation of the PH assumption tested but not statistically significant; log-rank test *P* values remain valid.
†$P < .001$ using time-dependent covariate adjusted Cox model.

There are several limitations of this work. Response was evaluated in patients for whom paired imaging studies were available. Although missing data may have led to exclusion of some potential subjects, the characteristics of patients comprising this cohort are consistent with those of published high-risk cohorts with respect to age, stage, *MYCN* status, and histology.[15,27,28] Key components of high-risk neuroblastoma therapy were included in regimens delivered at participating centers; however, treatment protocols were not identical across sites. The timing of induction cycles varied by institution (Appendix Table A1, online only), and although most centers delivered high-dose chemotherapy with autologous stem cell rescue as part of standard high-risk therapy, not all patients underwent autologous stem cell rescue. Similarly, not all patients received GD2-directed immunotherapy. Additional prospective studies with central radiology review focused on uniformly treated patients should be pursued, as should studies with extended follow-up times. Only patients with high-risk disease were included in this study; evaluation of response measures in patients with non–high-risk neuroblastoma should be considered, particularly as response by imaging may be less dramatic in more differentiated tumors. Finally, this study focused on assessment of primary tumor response to frontline therapy. An effort to address response in the relapse setting is in progress.

In summary, extent of reduction in primary tumor size did not accurately predict outcome in children with high-risk neuroblastoma, whether assessed by change in tumor volume or by reduction in single longest diameter. However, primary tumor response must be considered in overall response evaluation, as primary site progression must be captured. In practical terms, a single measurement is easier to perform than is measurement of three dimensions followed by calculation of volume. In light of our findings, it is recommended that primary tumor response be measured in the upcoming, revised INRC in accordance with RECIST criteria, using the single longest tumor dimension. This approach will be studied prospectively in forthcoming cooperative group trials.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

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AUTHOR'S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Appendix

Table A1. Common Induction Regimens

Regimen Name	Reference
Rapid COJEC	Pearson et al[27]
GPOH NB97	Simon T, et al: Pediatr Blood Cancer 56:578-583, 2011
GPOH NB2004	Simon T, et al: Pediatr Blood Cancer 56:578-83, 2011
Modified NB87	Coze C, et al: J Clin Oncol 15:3433-3440, 1997
COG A3973	Kreissman SG, et al: Lancet Oncol 14:999-1008, 2013
COG ANBL00P1	Seif AE, et al: Bone Marrow Transplant 48:947-952, 2013
CHOP/DFCI Tandem Trial	George RE, et al: J Clin Oncol 24:2891-2896, 2006
COG ANBL02P1/ANBL0532	Park JR, et al: J Clin Oncol 29:4351-4357, 2011
Texas PEPI Trial	NCT00578864