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Original Research Article

Risk factors associated with metastatic site failure in patients with high-risk neuroblastoma

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A B S T R A C T

Purpose: This retrospective study sought to identify predictors of metastatic site failure (MSF) at new and/or original (present at diagnosis) sites in high-risk neuroblastoma patients.

Methods and materials: Seventy-six high-risk neuroblastoma patients treated on four institutional prospective trials from 1997 to 2014 with induction chemotherapy, surgery, myeloablative chemotherapy, stem-cell rescue, and were eligible for consolidative primary and metastatic site (MS) radiotherapy were eligible for study inclusion. Computed-tomography and I-123 MIBG scans were used to assess disease response and Curie scores at diagnosis, post-induction, post-transplant, and treatment failure. Outcomes were described using the Kaplan–Meier estimator. Cox proportional hazards frailty (cphfR) and CPH regression (CPHr) were used to identify covariates predictive of MSF at a site identified either at diagnosis or later.

Results: MSF occurred in 42 patients (55%). Consolidative MS RT was applied to 30 MSs in 10 patients. Original-MSF occurred in 146 of 383 (38%) non-irradiated and 18 of 30 (60%) irradiated MSs ($p = 0.018$). Original- MSF occurred in post-induction MIBG-avid MSs in 68 of 81 (84%) non-irradiated and 12 of 14 (85%) radiated MSs ($p = 0.867$). The median overall and progression-free survival rates were 61 months (95% CI 42.6-Not Reached) and 24.1 months (95% CI 16.5-38.7), respectively. Multivariate CPHr identified inability to undergo transplant (HR 32.4 95%CI 9.3-96.8, $p < 0.001$) and/or maintenance chemotherapy (HR 5.2, 95%CI 1.7-16.2, $p = 0.005$), and the presence of lung metastases at diagnosis (HR 4.4 95%CI 1.7-11.1, $p = 0.002$) as predictors of new MSF. The new MSF-free survival rate at 3 years was 25% and 87% in patients with and without high-risk factors.

Conclusions: Incremental improvements in systemic therapy influence the patterns and type of metastatic site failure in neuroblastoma. Persistence of MIBG-avidity following induction chemotherapy and transplant at MSs increased the hazard for MSF.

Introduction

Neuroblastoma is a biologically diverse extracranial solid tumor in children with a spectrum of clinical manifestations and divergent clinical outcomes [1]. Despite improvements in systemic therapy, the primary contributor to impaired event-free survival in High-Risk Neuroblastoma is failure at new and/or originally-diagnosed metastatic bone and soft tissue sites [2]. Metastatic site progression rates as high as

Abbreviations: COG, Children's Oncology Group; CCG, Children's Cancer Group; MIBG, meta-iodobenzylguanidine; ALK, anaplastic lymphomakinase; LDH, lactate dehydrogenase; MYCN, v-myc avian myelocytomatosis viral oncogene neuroblastoma derived homolog, MYCN proto-oncogene; GD2, Disialoganglioside; BuMel, Busulfan-Melphalan; MEC, Melphalan-Etoposide-Carboplatin; IMRT, Intensity Modulated Radiotherapy; SIOPEN, European SIOP Neuroblastoma Group; SIOP, International Society of Pediatric Oncology; MSF, Metastatic Site Failure; CBCT, Cone Beam Computed Tomography; HR, Hazard Ratio; CI, Confidence interval; Met, Metastasis; Maint, Maintenance; MS, Metastatic Sites; cphfR, Cox proportional hazards frailty regression; CPHr, Cox proportional hazards regression; CNS, Central Nervous System; CT, Computed Tomography; MR, Magnetic Resonance Imaging; Cor, Correlation.

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17% during initial protocol therapy have been drastically reduced from historic studies like CCG-3891 [3] with the incorporation of combinations of intensified systemic therapy with or without stem cell support (single or tandem transplant) [4], new biologics (Anti-GD2 antibody) [5,6], targeted therapy (i.e. ALK inhibition)[7], radionuclides (therapeutic MIBG) [8], and metastatic site–directed radiotherapy[2,9–12]. Prior to the incorporation of high-dose myeloablative chemotherapy, total-body irradiation was utilized for conditioning prior to an autologous stem cell rescue to consolidate sites of disease[13]. Clinicians have largely abandoned the use of total-body irradiation given concerns over its late effects [14] despite some suggestion that total-body irradiation reduces the rate of relapse in previously identified sites of metastatic disease[15].

Current trials incorporate various combinations of the above approaches to reduce metastatic site failure (ANBL1531)[16]; however, the risk for metastatic site failure at new metastatic sites likely limits the utility of metastatic site directed radiotherapy. Patients at high risk for failure at new metastatic sites that were previously unidentified at diagnosis are unlikely to benefit from consolidative radiation at old sites and may require treatment intensification. Although predictors of increased hazard for progression such as lung metastases[17], high ferritin and/or LDH levels, MYCN amplification status[18], and Curie scores > 2 [19] have been well described, their effect on metastatic site failure at new or previously identified sites is unknown.

Furthermore, limited data exist to guide the selection of metastatic sites for consolidation with metastatic site radiotherapy. The timing of MIBG avidity, number of total sites, and site-specific risk of late effects have been suggested as criteria for metastatic site selection for consolidative radiotherapy(2); however, these features' relationship to site-specific failure has not been evaluated.

Methods and Materials

Patient population

We retrospectively reviewed the records of 76 consecutively treated patients with high-risk neuroblastoma consecutively treated on prospective clinical trials at St. Jude Children's Research Hospital from 1997 to 2014. This study was approved by the St. Jude Children's Research Hospital Institutional Review Board. High-risk neuroblastoma was defined by the COG and INRG risk stratification system, which combines MYCN amplification, Shimada histology, age, ploidy, and the International Staging System[20,21,36]. Bone marrow involvement was assessed at diagnosis, post-induction, and post-transplant and was classified as either positive, negative, or indeterminate. All patients were treated with induction chemotherapy followed by local disease reassessment and maximal safe surgical resection. Surgical resection was followed by consolidative/myeloablative chemotherapy and autologous stem cell transplant. Radiotherapy to metastatic sites and the patient's primary site was delivered according to institutional protocol (Supplementary Fig. 1).

Induction and consolidation chemotherapy

Induction chemotherapy varied across the study time period and is detailed in Supplementary Fig. 1 [22 23 24 25]. Following induction chemotherapy and resection, patients received consolidative chemotherapy, which generally consisted of 3 regimens and included BuMel (52.6%), MEC (21.1%), or cyclophosphamide/topotecan (25%).

Transplant

Although transplant was planned in all patients, 19 patients (25%) experienced toxicity or early progression and thus, did not undergo autologous stem cell transplant. Transplant consisted of autologous, non-purged peripheral blood stem cells in all patients.

Radiotherapy

Primary-site radiotherapy was utilized on 3 of the 4 trials queried over this time period. In general, the presurgical volume was targeted as the gross tumor volume, with a 1- to 2-cm margin to clinical target volume and a 0.5-cm margin to planning target volume. Metastatic lesion treatment volumes were based on a combination of the post-induction MIBG and anatomic imaging studies as well as imaging at the time of primary site treatment. Similar disease expansions were applied as for the primary site. Before 2002, radiotherapy was delivered anterior to posterior, with partial transmission blocks. Thereafter, a combination of 3D and IMRT techniques were used to create a conformal radiotherapy plan. During the study period, both megavoltage portals and kilovoltage CBCT were used for on-board imaging. Radiotherapy was typically initiated by post-transplant day 42 unless persistent cytopenia or veno-occlusive disease was present. Metastatic sites were systematically consolidated with 23.4 Gy delivered in 1.8 Gy fractions in 3 of the 4 protocols included in the study [23–25] contemporaneously with the primary site. Metastatic sites were generally not treated unless patients had persistent, MIBG-avid disease following induction [24,25] or, following transplant just prior to RT[22]. The exception to this rule was in that of NB97 which did not employ radiotherapy as a component of protocol treatment. In cases where > 5 persistent sites, a post-transplant MIBG study was used to select sites to consolidate. In situations where the number of metastatic sites prior to radiotherapy was extensive, metastatic site radiotherapy can be omitted [23,24]. When MIBG scans were not used, 99 m-technetium bone scans, CT scans, and/or MRI were used to quantify residual disease post induction.

Maintenance therapy

Maintenance therapy varied by trial and study time period. NB97 [22] initially didn't include *cis*-Retinoic Acid until Matthay *et al* was published(3). Thereafter, NB2005 [23] and NB2008 [24] included alternating courses of *cis*-Retinoic acid and Topotecan. NB2012 [25] integrated the use of IL2, GM-CSF, and Anti-GD2 antibody (Hu14.18K322A[26]) with *cis*-Retinoic acid(6). Further details regarding the use of maintenance therapy are shown in Supplementary Fig. 1.

Extent of therapy

Patients were stratified according to the extent of systemic therapy utilized into the following categories; Refractory and/or did not complete treatment, Intent to treat with induction and consolidation chemotherapy followed by transplant with limited maintenance therapy consisting of differentiation therapy alone (NB97), Intent to treat with induction and consolidation chemotherapy followed by transplant with maintenance chemotherapy (NB2005 and NB2008), and intent to treat with induction and consolidation chemotherapy followed by transplant with maintenance chemotherapy with immunotherapy (NB2012).

Outcomes

Overall, 76 patients had an evaluable follow-up period$>$2 years, for a median follow-up period of 8.7 years (range 1.2–20.3). Time to any, new metastatic site (+/- original metastatic site), original metastatic site failure (only), and death were calculated as the event of interest from the date of diagnosis.

Radiologic serial Assessment, response Evaluation, and follow up

At diagnosis, all patients received either a bone scan or MIBG scan in combination with CT or MR imaging. Repeat assessments using MIBG or bone scans were completed following induction chemotherapy,

following transplant, and during therapy and were completed less frequently following treatment completion (generally every 4–6 months). CT or MR imaging was used as a corollary when bony or soft-tissue disease required further evaluation.

Metastatic site features and response characteristics

Metastatic sites were annotated anatomically and chronologically by reviewing serial and progression imaging. Serial imaging time points collected include diagnosis, post-induction chemotherapy, and post-transplant. Metastatic sites were classified according to tissue where the metastasis arose (bone, lymph node, liver, CNS, lung or other soft-tissue). The anatomic site of each metastatic lesion was documented as previously described(2), with small modifications as seen in Fig. 1. Failure at metastatic sites were subcategorized into failure at a site originally identified at diagnosis (original metastatic site failure), failure at a new metastatic site not identified at diagnosis (new metastatic site failure), and distant metastatic site failure (any combination of original and/or new metastatic site failure). The number of metastatic lesions, Curie score, and SIOPEN score were documented for each of the above time points (Fig. 2) Supplementary Figs. 2 and 3) as previously described [19,27].

Statistical analysis

Descriptive statistics are reported for all continuous and count data. Continuous data are summarized using the median and range and were tested across groups using the Wilcoxon rank-sum test. Count data are summarized using frequencies and were tested across groups using either the Fisher's exact or chi-squared test. All time-to-event estimates were completed using the Kaplan–Meier method and were tested across stratum using the log-rank test. Univariate and multivariate Cox-proportional hazards analysis was used to described predictors of new metastatic site failure in a per-patient analysis. Backwards stepwise selection was used to select covariates for the final model, with set threshold p-values of inclusion ($p = 0.2$) and retention ($p = 0.1$). In a per site–based analysis of predictors of metastatic site failure, a Cox proportional hazards frailty model was used to consider un-measured random effects and allow for multiple events per individual[28]. The significance level for statistical tests was $p < 0.05$. Excel 2013 was used for all data management. SAS v.9.3 or RStudio v. 1.0.136 were used for analyses.

Results

Patient and treatment characteristics

Patient characteristics are shown in Supplementary Table 2. Most patients were male, with a median age at diagnosis of 2.8 years. Most patients (85.5%) had Stage 4 disease at diagnosis, and 30.3% had MYCN-amplified disease. The most common metastatic sites were lymph node (86.8%), bone marrow (72.3%), and bone (69.7%). Induction regimens varied and are detailed in Supplementary Table 1. Busulfan and melphalan was the most common consolidation regimen (52.6%). Nineteen patients (25%) were unable to undergo transplant. Maintenance therapy was used in 43% of patients (although as proportion of NB97 patients received *cis*-Retinoic acid after Matthay *et al* was published (3).

Metastatic site characteristics and treatment outcome

Metastatic site characteristics and location at diagnosis and treatment failure are shown in Table 1 and Fig. 1. The respective median number of MIBG-avid metastases at diagnosis, post induction, post-transplant, and at treatment failure were 7, 0, 0, and 3 respectively. The median Curie and SIOPEN scores at diagnosis were 8 and 9,

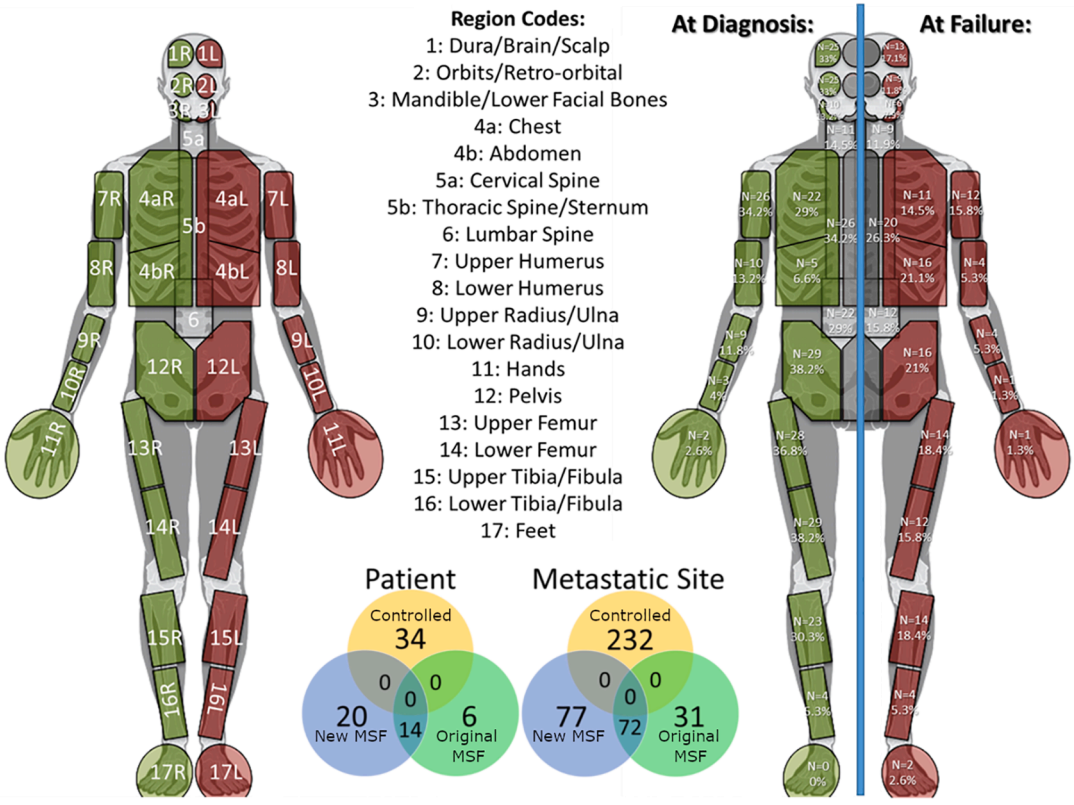

Fig. 1. Metastatic Site Locations and Breakdown of Metastatic Site Failure Location. MSF = Metastatic Site Failure, N = Number. Two patients were excluded from determination of metastatic site failure analysis due to indeterminate failure imaging.

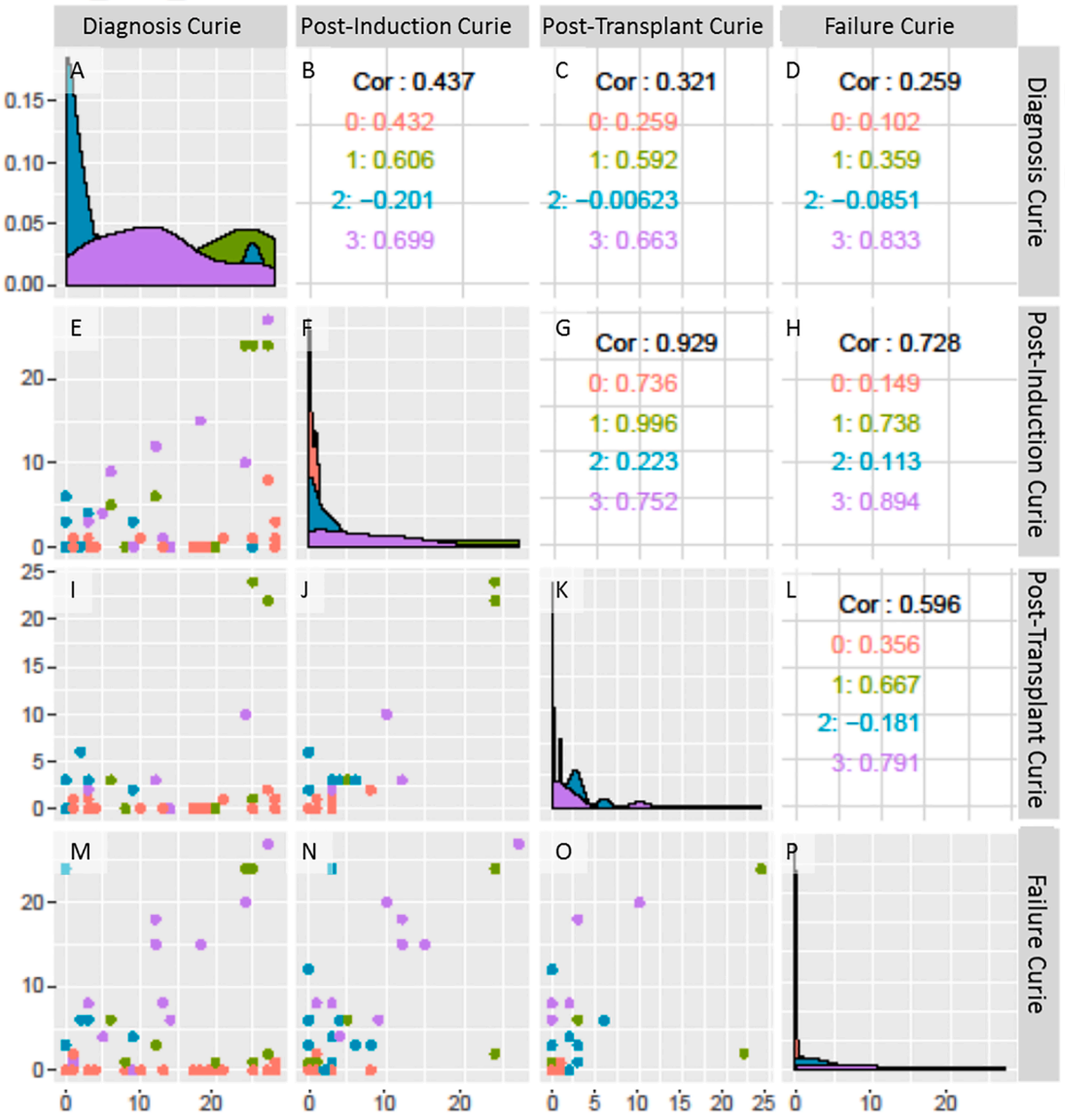

Fig. 2. Relation between Curie score at Diagnosis, Post-Induction, Post-Transplant and at Failure by Failure Type. The distribution of Curie scores at diagnosis, post-induction, post-transplant, and at failure are shown in the diagonal squares. The Curie score at each time-point is plotted against the other time-point in the squares below the central diagonal proportion plots. The correlation between each time point's Curie score is shown on the opposite side of the diagonal. Patients with persistently higher Curie scores following induction chemotherapy and following transplant had a greater proportion of new site failures (purple). Higher Curie scores at failure seemed to correspond to an increased proportion of new site only as well as combined new and original metastatic site failures. Failure type is categorized into; No failure (0, red), original site failure (1, green), original site and new site failure (2, teal), and new site only failure (3, purple).

Table 1
Extent of Disease by Patient.

By Patient		Total N	Timing of Assessment At Diagnosis		Post Induction		Post-Transplant		At Failure	
			N	*%M (range)*	*N*	*%M (range)*	*N*	*%M (range)*	*N*	*%M (range)*
Metastases	#	75	60	7 (0-66)	75	0 (0-54)	52	0 (0-46)	47	3 (0-53)
Curie score	#	75	60	8 (0-28)	75	0 (0-27)	52	0 (0-24)	72	0 (0-27)
SIOPEN score	#	75	60	9 (0-60)	75	0 (0-51)	52	0 (0-43)	72	0 (0-49)
Bone Marrow Status	*Negative*	76	25	32.89	49	64.47	33	43.42	-	-
	Positive	76	51	67.11	8	10.53	2	2.63	-	-
	Indeterminate	76	-	-	11	14.47	-	-	-	-
	NA	76	-	-	8	10.53	41	53.95	-	-

*MIBG scans not available in 16 patients at diagnosis, 1 post-induction, and 24 post-transplant. N= Number, NA = Not available, M = Median, # = Number, INRG = International Neuroblastoma Risk Group.

Table 2
Predictors of New Metastasis Failure (by patient) and Metastatic Site Failure (by site)

Multivariate Predictors of New Metastatic Site Failure (by patient)		N	HR	95% CI		p-Value
Type of Metastasis	*Lung Metastasis at Diagnosis vs. None*	76	4.394	1.733	11.14	0.0018
Extent of Systemic Therapy	*No Transplant* vs. Transplant+Maint*	76	29.99	9.29	96.82	<0.0001
	Transplant, No Maint vs. Transplant+Maint	76	5.193	1.66	16.24	0.0046
Univariate Predictors of Metastatic Site Failure (by site)		**N**	**HR**	**95% CI**		**p-Value**
Met Location	*Extremity vs. Cranio-Cervical*	309	1.08	0.55	2.13	0.82
	Thorax vs. Cranio-Cervical	309	1.08	0.55	2.13	0.82
	Abdomen vs. Cranio-Cervical	309	0.41	0.14	1.21	0.11
	Spine vs. Cranio-Cervical	309	1.16	0.65	2.10	0.6
Met Directed Radiotherapy	*Yes vs. No*	309	1.18	0.39	3.6	0.78
MIBG Avidity	*Post-Induction vs. Diagnosis Only*	268	4.9	1.1	20.9	0.03
	Post-Transplant vs. Diagnosis Only	268	7.3	1.8	30.2	0.006

N = Number, HR = Hazard Ratio, CI = Confidence interval, Met = Metastasis, MIBG = Metaiodobenzylguanidine, Maint = Maintenance, *Transplant not pursued in 19 patients due to progression or toxicity.

respectively. Bone marrow remained positive in 10.5% of patients following induction chemotherapy and 2.6% following transplant.

The rates of distant metastatic site (original and/or new) failure, original metastatic site failure, new metastatic site treatment failure, and survival are shown in Fig. 3 and Supplementary Table 3. The median time to any distant metastatic site treatment failure was 32.6 months (95% CI 22.7–79.6) (Fig. 3). New-MSF occurred in 20 patients at a median time of 9.8 months (95% CI 5–14.9) (Supplementary Table 3, and Fig. 1). Original-MSF occurred in 8 patients, with a median time to treatment failure of 12.6 months (95% CI 0.3–70.4). Combined original- and new-MSF occurred in 14 patients, with a median time to treatment failure of 16.2 months (95% CI 8–32). Forty-two patients experienced distant-site treatment failure (n = 180 sites) (Fig. 1). New MSF occurred in 34 of 42 patients (81%, n = 149 sites). Fourteen of 34 patients with new MSF (41%) also had a component of original-MSF in 26 of 72 sites (28%). Six of 42 patients (14.3%) failed at 31 previously identified metastatic sites. Original-MSF occurred in 146 of 383 (38%) and 18 of 30 (60%) non-irradiated and irradiated, MSs respectively (p = 0.018). Original-MSF occurred in post-induction MIBG-avid lesions in 68 of 81 (84%) non-irradiated metastatic sites and in 12 of 14 (85%) irradiated metastatic sites (p = 0.867).

Metastatic-site failure was reduced sharply with each subsequent improvement in systemic therapy (addition of differentiation and immunotherapy) (Supplementary Fig. 4). The proportions of original-only, combined new- and original-, and new-only MSF in patients treated with limited maintenance (differentiation therapy alone) shifted from 9.5 → 10.5%, 57.1 → 0%, and 28.6 → 5.3% with the addition of maintenance differentiation and chemotherapy, differentiation therapy,

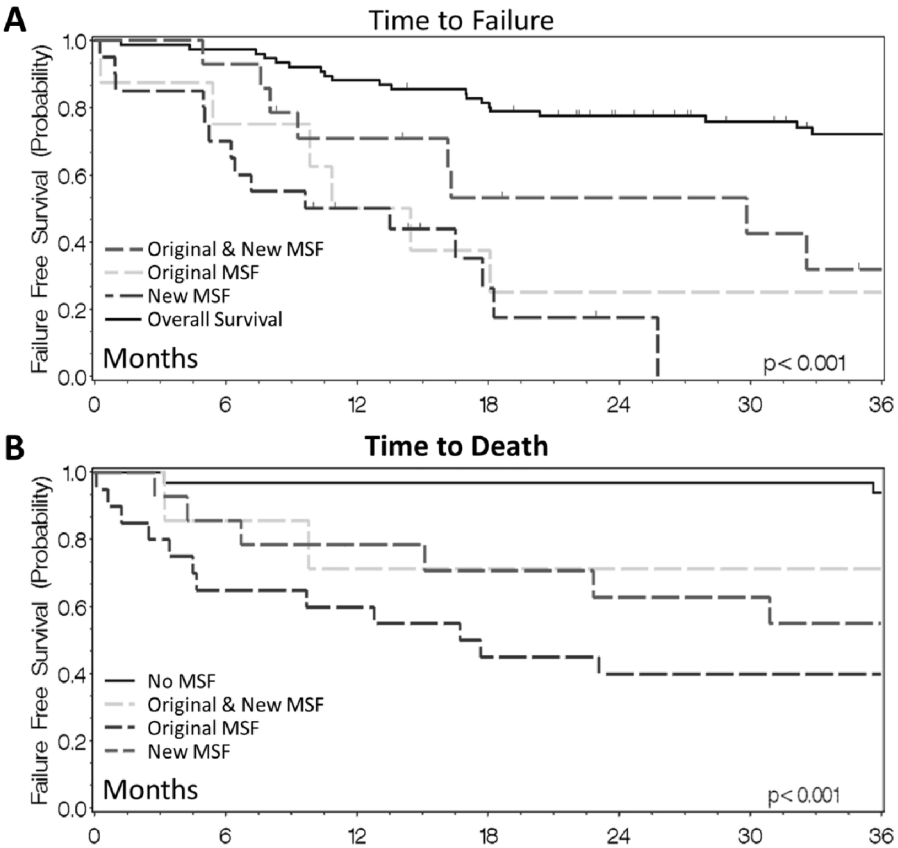

Fig. 3. Overall Survival and Time to Failure according to failure type; original-MSF, combined original- and new-MSF, and new- only MSF. Patients with new- only MSF experienced failure earlier than those with either combined or original-MS only failure.

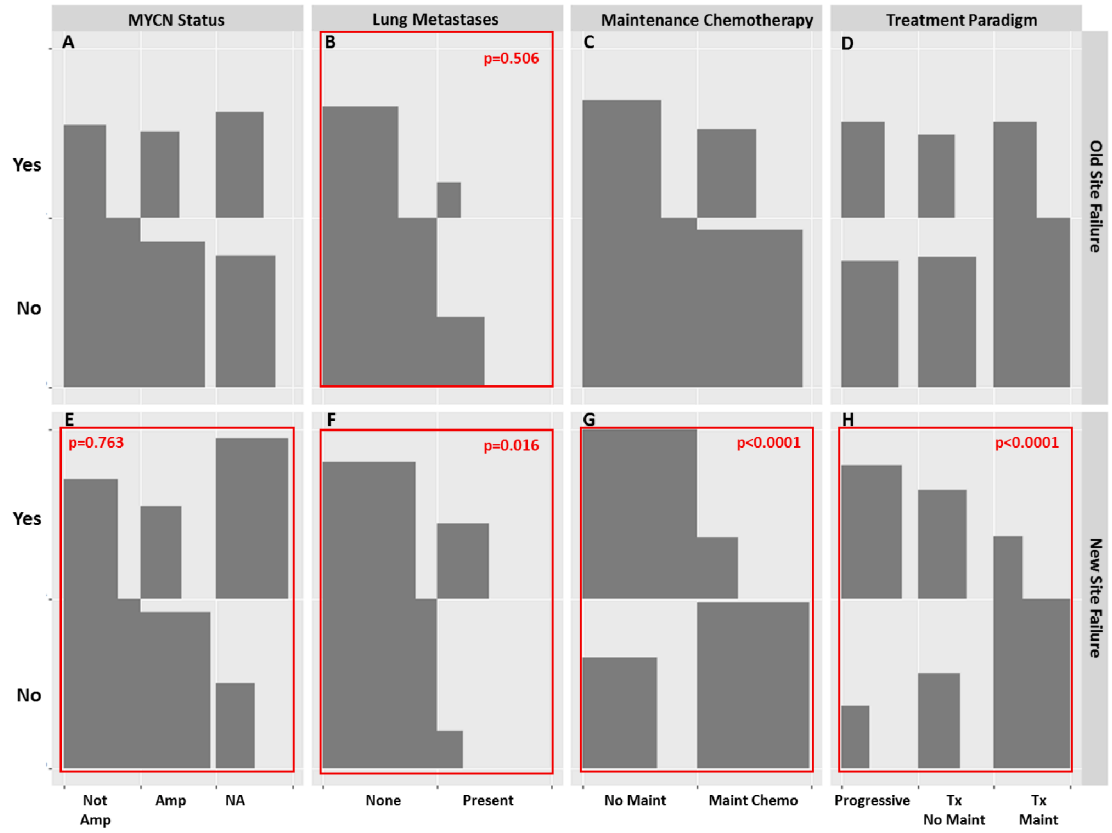

Fig. 4. Factors Predictive of New vs. Original Metastatic Site Failure. The dark grey represents the proportion of patients with each feature. A dark grey box occupying the entire light grey region bounded by the white line indicates 100% of cases with that feature.

and immunotherapy ($p \leq 0.0001$). Patients receiving delayed surgery as specified by the corresponding protocol had rates of metastatic-site failure comparable to those of patients receiving earlier surgical resection despite less intensive systemic therapy [22 29] (Supplementary Fig. 5B, 5F, and 5H, Supplementary Table 4).

Curie and SIOPEN score kinetics

Curie and SIOPEN scores at diagnosis, post induction, post-transplant, and at treatment failure were tested to determine correlation for each combination of time points (Supplementary Figs. 2 and 3). The distributions of Curie and SIOPEN scores at diagnosis were bimodal, but those at subsequent time points were unimodal with a leftward skew. The response in Curie and SIOPEN scores following induction was correlated with the post-transplant response ($r = 0.94$ and $r = 0.93$, respectively) (Supplementary Fig. 2J and 2G, Supplementary Fig. 3J and 3G). Curie and SIOPEN post-induction scores were moderately correlated to the Curie and SIOPEN scores at treatment failure ($r = 0.68$ and $r = 0.70$, respectively) (Supplementary Fig. 2N and 2H, Supplementary Fig. 3N and 3H). The relationship between the Curie score at diagnosis, post induction, post-transplant, and at treatment failure stratified by failure type are shown in Fig. 2. Curie scores at diagnosis ($r = 0.833$, Fig. 2D), post induction ($r = 0.894$, Fig. 2H), and post-transplant ($r = 0.791$, Fig. 2L) were most correlated with the propensity for new metastatic-site failure. We observed no significant relationship between Curie score at diagnosis, post- induction, post-transplant, or at failure with the type of failure (original site, original and new site or new site). Earlier protocols which excluded maintenance chemotherapy (NB97) or immunotherapy (NB2005 and NB2008) had higher Curie scores at failure (Supplementary Fig. 6).

Predictors of new metastatic site failure

Univariate analyses identified increasing LDH level at diagnosis (HR 1.01 95% CI 1.0–1.05, $p < 0.0001$), lung metastases at diagnosis (HR 2.203 95% CI 0.995–4.876, $p = 0.05$), limited maintenance therapy (HR 10 95% CI 3.5–28.6, $p < 0.0001$), BuMel consolidation (HR 6.8 95% CI 1.9–24.4, $p < 0.0001$), and indeterminate findings on post-induction bone marrow examination (HR 5.862, 95% CI 2.5–153, $p < 0.0001$) as predictors of new metastatic-site failure. Similar findings were noted evaluating the proportion of original- and new-MSFs, irrespective of time and censoring (Fig. 4). MYCN amplification did not affect the proportion of original- vs. new-MSFs ($p = 0.763$, Fig. 4A and 4E). The presence of lung metastases at diagnosis increased the proportion of new site failures ($p = 0.016$, Fig. 4B and 4F) but did not affect the proportion of cases with original-MSF ($p = 0.5$). Similarly, the use of maintenance chemotherapy ($p < 0.0001$, Fig. 4C and 4G) and transplant ($p < 0.0001$, Fig. 4D and 4H) reduced the proportion of patients with new site failure. After adjusting for additional covariates and eliminating interactions, the presence of lung metastases at diagnosis (HR 4.4, 95% CI 1.7–11.1, $p = 0.002$), lack of transplant (HR 30 95% CI 9.3–997, $p < 0.0001$), and limited use or omission of maintenance chemotherapy (HR 5.2 95%CI 1.7–16.2, $p = 0.0046$) all increased the hazard for new metastatic site failure.

Site-based predictors of metastatic site failure

Metastatic site–specific characteristics, including location, utilization of radiotherapy, and MIBG-avidity timing during treatment, were evaluated for their contribution to site-specific metastatic site failure (Table 2). Neither metastasis location nor use of radiotherapy affected the hazard for metastatic site failure in the multivariate model, although sample size was likely limiting in the case of radiotherapy utilization

(Supplementary Fig. 4I and 4G). Having metastatic sites that remained MIBG avid following induction therapy (HR 4.9 95% CI 1.1–20.9, p = 0.03) and post-transplant (HR 7.3 95% CI 1.8–30.2, p = 0.006) increased the hazard for metastatic-site failure (Table 2).

Discussion

Metastatic site failure is the predominating mode of treatment failure in neuroblastoma and incomplete response at sites identified at diagnosis remains a significant barrier to cure. Some have proposed consolidative radiotherapy to metastatic sites to improve event free survival in high-risk neuroblastoma, although risk for progression in new sites not only negates the potential therapeutic benefit of metastatic site–directed radiotherapy but also adds to potential morbidity of treatment without improving the therapeutic ratio(2). We identify imaging-, clinical-, and treatment-related factors predictive of distinctive modes of metastatic-site failure and offer recommendations for the management of metastatic disease.

Previous studies have described adverse prognostic factors in neuroblastoma, but none have specifically explored the relationship of these prognostic factors to their corresponding patterns of failure. Classic prognostic factors include MYCN amplification[30], chromosome 11q status[31,32], DNA ploidy[33], stage[34], age[21,35], histologic category(35), LDH(36), Ferritin, and grade of tumor differentiation[21,37]. Although many of those factors were either borderline significant or significant on univariate analysis for predictors of new metastatic site failure (Supplementary Table 5), many lost significance after the inclusion of the extent of systemic therapy in the multivariate model. This study highlights the substantial advancements that have been made by incorporating novel therapies and intensification of systemic therapy. Unfortunately, incomplete information for marrow status and some pathologic features (MYCN, Shimada) may have limited the power of these analyses. Conversely, some have noted that the prognostic significance of some features, such as MYCN, is more prominent at progression than at diagnosis[38]. Finally, the interaction of treatment paradigms and cytotoxic chemotherapy regimens with guiding protocols limit our inference into what systemic therapy combinations are the most and least advantageous during each phase of treatment (induction, consolidation, maintenance, etc.).

New criteria for differentiating progressive from refractory disease has been defined by the INRG and subsequently adopted in ANBL1531 [16]. Although we did not include an increase in the Curie score > 1.2 or a $> 20\%$ increase in the longest diameter of a target soft tissue or bony lesion, we could systematically dissect which factors were selectively predictive of progressive or refractory disease by focusing on the presence or absence of new sites not previously identified at diagnosis. By limiting our analysis to focus on predictors of progression, we could determine which patients were unlikely to benefit from consolidative radiotherapy and may be better candidates for intensified systemic therapy.

We and others previously reported on the prognostic significance of pleural effusion and pulmonary metastases in high-risk neuroblastoma [17,39,40]. In prior reports, lung metastases co-occurred with MYCN amplification, adrenal primary, and elevated LDH levels but were not independently associated with poor prognosis. In our analysis, pulmonary disease was independently associated with the risk of new metastatic site failure but not failure at original MSs (Table 2). Management of pulmonary metastases in pediatric solid tumors typically involves metastasectomy or whole-lung radiotherapy, but this approach is not typically recommended in high-risk neuroblastoma[41]. Our finding that patients with pulmonary disease typically succumb to new sites of disease (extra-pulmonary metastatic failure) confirms that consolidative metastatic site–directed therapy in the form of surgical metastasectomy or radiotherapy is unlikely to be beneficial.

Perhaps more than any other pediatric solid tumor, high-risk neuroblastoma has seen the benefit of novel systemic therapy in that carefully selected combinations of cytotoxic chemotherapy, differentiating agents(13), immunotherapy(5), cell-directed therapy[42–44], surgery[45,46], and radiotherapy[2,10,15] are all prescribed to treat patients with metastatic disease. Metastatic site–directed radiotherapy is routinely recommended, but its utility is poorly supported by the literature, and data guiding the application to specific sites are limited(2). Current COG guidelines recommend the application of radiotherapy to metastatic sites that are MIBG avid following induction chemotherapy, but no data has previously reported the metastatic site–specific risk of recurrence according to changes in MIBG-avidity during therapy. We demonstrated an increasing hazard for metastatic site–specific failure with persistent MIBG avidity following the sequential stages of systemic therapy (Table 2). Location and type of metastasis (bone vs. soft tissue) were not related to the propensity for failure, like prior reports(2). Although location was hypothesized to be a risk factor for poor metastatic-site control due to the reticence on the part of the treating radiation oncologist to deliver radiotherapy to cranial sites due to morbidity concerns, we observed no significant difference in the proportional failure rate according to metastatic site or in the rate of application of radiotherapy according to metastatic-site location (Table 2, Supplementary Fig. 4).

Whereas prior series documented a trend towards reduced metastatic-site failure with the application of radiotherapy, we were unable to demonstrate such a benefit (Table 2) (2,10). Instead, we noticed a trend associated with metastatic site control, specifically reduced new site failure and increasing extent of systemic therapy (addition of maintenance chemotherapy, differentiation therapy, and immunotherapy. While the lack of a demonstrated benefit of consolidative metastatic site RT is likely due to an imbalance in the proportion of metastatic sites which were irradiated, this may also be due to insufficient dose and/or the selection of treatment-resistant disease. Therapeutic doses of 36 Gy had been previously recommended to treat gross residual disease following primary site resection; however, 21.6 Gy has been recommended to treat persistently avid metastatic sites. Recent data from Liu et al, has suggested that 21.6 Gy may be enough for residual soft tissue disease at the primary site [47]. It remains unclear if higher doses would further improve original metastatic site control as this had not been systematically explored in any prospective therapeutic studies. Historic data from a time when radiotherapy was used as consolidation prior to transplant suggest that even lower doses of radiotherapy may be sufficient to reduce the risk for treatment failure at metastatic sites identified at diagnosis, although this study did not take into account the persistence of MIBG avidity nor the extent of concurrent systemic therapies on the risk for site-specific recurrence [15]. Patients in our series were treated with 20–30.6 Gy to metastatic sites, with varying fractionation schemes. Because only 10 patients were treated (n = 30 sites), our analysis was underpowered for analyzing either the impact of radiotherapy on site-specific local control or the impact of radiotherapy dose. Current Children's Oncology Group studies, such as ANBL1531 [16], continue to use 21.6 Gy because of concerns for toxicity with concurrent therapeutic MIBG(16). Future analyses of metastatic-site control will likely be confounded by the interaction of these two means of delivering radiotherapy.

The timing of surgery and extent of systemic therapy were evaluated for their impact on the incidence and type of metastatic-site failure. The extent of systemic therapy was the most impactful covariate in our analysis of predictors for new-site failure. Those patients undergoing consolidation, transplant, and maintenance therapy with immunotherapy experienced the greatest reduction in both new-site and combined original- and new- MSF (Supplementary Figs. 4, 4, Table 2). The risk for original-MSF persisted even in patients who received maintenance chemotherapy with immunotherapy. Although we previously identified a significant improvement in survival and event-free survival among patients who had resection of the primary site at diagnosis(29), the implications of early resection on event-free survival and propensity for metastatic-site failure is unclear (29). We previously postulated that

early resection may reduce the number of tumor cells and, thus, reduces the risk of developing resistant-clones and treatment failure(29 [48]). Although this prior analysis suggested benefit, more recent concepts that better define resectability, such as the presence or absence of image-defined risk factors, may modify the effect of early resection substantially[49]. The present analysis (completed on a more recent population) refutes the notion that delayed resection may lead to an increased predisposition for metastatic-site failure (Supplementary Fig. 5H, Supplementary Table 4). Although reasons such as volume of disease, presence of image-defined risk factors, or risk for perioperative complications may determine the timing of primary site surgery, the risk for impaired event-free survival due to metastatic site failure should not be considered a reason(48,49).

In summary, persistence of MIBG avidity increased the hazard for metastatic site failure. Increasing intensity of systemic therapy reduced the rate of distant failure, and specifically, new metastatic site failure. Both Curie and SIOPEN scores following systemic therapy were useful for selecting patients with increased risk for failure at increasing numbers of metastatic sites. Limited utilization of consolidative metastatic site radiotherapy precluded the attempt to estimate its impact on original metastatic site failure according to MIBG avidity at each time point. Patient characteristics like the presence of lung metastases at diagnosis and the inability to undergo transplant or maintenance therapy were associated with high rates of new metastatic site failure and these should be considered high risk features. Patients with high risk features are poor candidates for consolidative metastatic site RT.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctro.2022.02.009.

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