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Incidence and risk factors for secondary malignancy in patients with neuroblastoma after treatment with ^{131}I-metaiodobenzylguanidine

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Abstract

Several reports of second malignant neoplasm (SMN) in patients with relapsed neuroblastoma after treatment with ^{131}I-MIBG suggest the possibility of increased risk. Incidence of and risk factors for SMN after ^{131}I-MIBG have not been defined.

This is a multi-institutional retrospective review of patients with neuroblastoma treated with ^{131}I-MIBG therapy. A competing risk approach was used to calculate the cumulative incidence of SMN from time of first exposure to ^{131}I-MIBG. A competing risk regression was used to identify potential risk factors for SMN.

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Contributions

K.E.H. conceived the study, designed and implemented the study with K.K.M., collected the data for the study, assisted with statistical analysis and wrote the manuscript. K.T.V. assisted with study design, performed statistical analysis and reviewed the manuscript. S.G.D. and J.N. assisted with study design, assisted with statistical analysis and reviewed the manuscript. S.F., V.B., J.M., B.W., A.M. and G.Y. assisted with data collection for the study and reviewed the manuscript. K.K.M. conceived the study, designed and implemented the study with K.E.H., assisted with data collection for the study, assisted with statistical analysis and reviewed the manuscript.

Conflict of interest statement

None declared.

The analytical cohort included 644 patients treated with ^{131}I-MIBG. The cumulative incidence of SMN was 7.6% (95% confidence interval [CI], 4.4e13.0%) and 14.3% (95% CI, 8.3−23.9%) at 5 and 10 years from first ^{131}I-MIBG, respectively. No increase in SMN risk was found with increased number of ^{131}I-MIBG treatments or higher cumulative activity per kilogram of ^{131}I-MIBG received ($p = 0.72$ and $p = 0.84$, respectively). Thirteen of the 19 reported SMN were haematologic. In a multivariate analysis controlling for variables with $p < 0.1$ (stage, age at first ^{131}I-MIBG, bone disease, disease status at time of first ^{131}I-MIBG), patients with relapsed/progressive disease had significantly lower risk of SMN (subdistribution hazard ratio 0.3, 95% CI, 0.1−0.8, $p = 0.023$) compared to patients with persistent/refractory neuroblastoma.

The cumulative risk of SMN after ^{131}I-MIBG therapy for patients with relapsed or refractory neuroblastoma is similar to the greatest published incidence for high-risk neuroblastoma after myeloablative therapy, with no dose-dependent increase. As the number of patients treated and length of follow-up time increase, it will be important to reassess this risk.

Keywords

Neuroblastoma; Paediatrics; Cancer; MIBG; I-metaiodobenzylguanidine; SMN; Second malignancy; Chemotherapy; Solid tumour; Survivorship

1. Introduction

Neuroblastoma, an embryonal tumour of the peripheral sympathetic nervous system, is the most common extracranial solid malignancy in children, with approximately 700 new cases diagnosed in the United States each year. Nearly half of patients have metastatic disease at presentation, and long-term survival with high-risk disease is less than 50% [1]. Treatment for neuroblastoma depends on extent of disease, age at presentation, and tumour biology. For example, surgical resection is often curative for tumours that are small and localised with favourable biology [2]. Patients with high-risk disease require multimodality therapy, including intensive chemotherapy, myeloablative therapy with autologous stem cell transplantation, local radiation, and treatment for minimal residual disease with immunotherapy and differentiation therapy. Despite these intensive measures that have improved event-free survival (EFS), outcomes remain unsatisfactory for children with high-risk disease [1,3,4].

Metaiodobenzylguanidine (MIBG) is a guanethidine derivative that, when labelled with iodine-123, has high specificity and sensitivity as an imaging tool for detection of primary and metastatic neuroblastoma [5]. Clinical trials of high-dose ^{131}I-MIBG have utilised this agent as a radiopharmaceutical and have shown response rates of 30−40%, with apparent prolongation of survival in patients with relapsed neuroblastoma [6–8]. More recently, pilot studies are ongoing incorporating this radiopharmaceutical into up-front treatment of high-risk patients [9].

^{131}I-MIBG therapy is generally well tolerated. The most common acute toxicity is myelosuppression, which can be abrogated with autologous haematopoietic stem cell infusion [10,11]. However, reports of second malignant neoplasm (SMN) in patients treated

with ^{131}I-MIBG suggest that this therapy may be associated with increased risk of secondary malignancy, particularly myelodysplasia and leukaemia [12,13]. It has been postulated that the increased risk for malignancy results from bystander irradiation to the bone marrow that is not high enough to be lethal to stem cells, increasing the risk for leukaemia [12]. The risk of secondary malignancy is not unique to ^{131}I-MIBG, as the reported crude incidence of secondary malignancy in all patients with neuroblastoma is between 0.5% and 6% [14–23]. The cumulative incidence in high-risk patients has been estimated to be as great as 16.5% at 10 years [24], without evidence of plateau. High dose alkylating agents, topoisomerase II inhibitors and platinum-based drugs, have been shown to increase the risk of myelodysplastic syndrome and treatment-related acute myelogenous leukaemia [25–27]. Moreover, children with high-risk neuroblastoma typically receive external beam radiation to the primary tumour bed. Survivors of childhood cancers that were treated with radiation therapy have been shown to have an increased risk of SMN [28,29].

The incidence of and risk factors for SMN after ^{131}I-MIBG are not well understood. The primary aim of this study was to determine the incidence, characteristics, and predisposing factors of secondary malignancy in a large, multi-institutional cohort of patients with neuroblastoma treated with ^{131}I-MIBG. By understanding SMN risk from ^{131}I-MIBG, we hope to guide therapeutic decisions in this vulnerable patient population.

2. Patients and methods

2.1. Study population

We conducted a multi-institutional retrospective review of patients with neuroblastoma treated with ^{131}I-MIBG therapy at four institutions between 1st March 1984 and 1st March 2014. Study participants were identified from neuroblastoma ^{131}I-MIBG databases at participating institutions (University of California San Francisco, Children's Hospital of Philadelphia, University of Michigan, and Cincinnati Children's Hospital). Medical record abstraction was used to augment information missing from databases. To ensure most recent follow-up, we contacted referring institutions as allowed by study consents signed by families upon original ^{131}I-MIBG trial enrolment. Institutional review board approval was obtained from all participating sites to allow transfer of deidentified patient data for study use.

2.2. Variables

Patient data obtained included age and stage at diagnosis, *MYCN* gene amplification status, and known history of other cancer predisposition syndrome. We classified treatment prior to ^{131}I-MIBG by the number of prior chemotherapy regimens, prior radiation treatment, and prior myeloablative therapy with haematopoietic cell transplantation. Data collected regarding ^{131}I-MIBG therapy were number of treatments, age at first ^{131}I-MIBG treatment, time from neuroblastoma diagnosis to first ^{131}I-MIBG treatment, sites of disease at ^{131}I-MIBG therapy, disease status (refractory/persistent or relapsed) at ^{131}I-MIBG therapy, use of stem cells or bone marrow support after ^{131}I-MIBG, cumulative ^{131}I-MIBG dose per kilogram, and cumulative radiation dose to the whole body.

SMN data collected included time from neuroblastoma diagnosis to SMN diagnosis, time from first ^{131}I-MIBG therapy to SMN diagnosis, bone marrow cytogenetics or fluorescence in situ hybridisation for haematopoietic malignancy, molecular analysis for solid tumours, treatment of SMN, length of follow-up, time from SMN diagnosis to death, and cause of death, if applicable.

2.3. Statistical analysis

We used a competing risk approach to calculate the cumulative incidence of SMN from time of first exposure to ^{131}I-MIBG. Death prior to development of SMN was considered a competing risk.

To identify potential risk factors and outcomes of secondary malignancy, we used competing risk regression by the method of Fine and Gray to model the risk of SMN according to a range of potential clinical covariates, including dose per kilogram of ^{131}I-MIBG, age at time of treatment, and total body radiation exposure [30]. Similar to Cox survival models, the Fine−Gray approach provides estimates of the associations of risk factors with time to SMN, subhazard ratios (SHR), that accommodate the competing risk of death. Outcomes and treatment following diagnosis of SMN are also presented descriptively. All statistical analyses were performed using Stata, version 13 (Stata, College Station, TX).

3. Results

3.1. Patient characteristics

From November 1984 to March 2014, 644 patients with neuroblastoma were treated with ^{131}I-MIBG (Table 1) at the four participating institutions. Median age at initial neuroblastoma diagnosis was 4.4 years (range, 0.5−37.8). The majority of patients (565/644, 87.7%) had stage 4 disease at diagnosis. Median follow-up time after first ^{131}I-MIBG for surviving patients was 3.6 years (range, 0.5−20 years). Nineteen of the 644 patients were diagnosed with second malignancies after ^{131}I-MIBG therapy. The cumulative incidence of SMN was 7.6% at 5 years (95% confidence interval [CI], 4.4−13.0%) and 14.3% at 10 years (95% CI, 8.4−23.9%) (Fig. 1).

3.2. Characteristics of second malignancies

The characteristics of the 19 patients diagnosed with second malignancies are shown in Table 2. Thirteen patients were diagnosed with haematologic malignancies, including acute myelogenous leukaemia (n = 7) and acute lymphoblastic leukaemia (n = 2) (Table 3). The remaining 4 patients had myelodysplastic syndrome. Six patients were diagnosed with solid tumours, including osteosarcoma, papillary thyroid carcinoma, peritoneal mesothelioma and an inflammatory myofibroblastic tumour. One patient developed two distinct second malignancies, an undifferentiated sarcoma of the cranium and an inflammatory myofibroblastic pseudotumour of the lung (without an identifiable ALK aberration). Two patients developed benign bone tumours after ^{131}I-MIBG, but were not included in SMN analyses. Median time from first ^{131}I-MIBG therapy to SMN diagnosis was 32 months (range, 5.3−108.4 months) and from diagnosis of neuroblastoma was 68.5 months (range, 45.1−131.2 months). Seven of the SMN were associated with aberrations in chromosome 5

or 7, typical of myelodysplastic syndrome (MDS)/acute myelogenous leukaemia (AML) after alkylator therapy or radiation.

Twelve patients (63.0%) died of SMN or complications of SMN treatment. The remaining three died of progressive neuroblastoma. Of the 4 patients with SMN still alive at the time of data collection, median follow-up time was 34.2 months (range, 9.6−75.6).

3.3. Predictors of SMN

Few statistically significant differences in presentation were noted between patients who developed a SMN and those who did not (Table 4). There were no differences in age at diagnosis of neuroblastoma. There was no statistically significant increase in SMN risk in patients who received autologous stem cell transplant or radiotherapy prior to ^{131}I-MIBG therapy with those who did not. Increased number of chemotherapy regimens prior to ^{131}I-MIBG treatment was not associated with an increased risk of SMN. Increased cumulative ^{131}I-MIBG dose per kilogram and one versus multiple ^{131}I-MIBG treatments were not associated with an increased risk of SMN.

Presence of bone disease at time of first ^{131}I-MIBG therapy was associated with a decreased risk of SMN (SHR 0.36, p = 0.049, 95% CI, 0.13−0.99). No association between presence of bone marrow disease or soft tissue disease at time of first ^{131}I-MIBG therapy was found (p = 0.236 and p = 0.118, respectively). Four variables had p < 0.1 (stage, age at first ^{131}I-MIBG, bone disease, disease status at time of first ^{131}I-MIBG) on univariate analysis. When controlling for these variables in a multivariate analysis, only disease status remained statistically significant, with relapsed/progressive disease associated with decreased risk of SMN (SHR 0.3, 95% CI, 0.1−0.8, p = 0.023) compared to persistent/refractory.

4. Discussion

This retrospective study examined the risk of second malignancy in 644 neuroblastoma patients treated with ^{131}I-MIBG therapy and found a cumulative 10-year incidence of 14.3%. Nineteen patients in our cohort were diagnosed with second malignancies, with the most common being MDS and AML. No dose-dependent increases in risk was found in patients who received more treatments or higher doses per kilogram of ^{131}I-MIBG. The only risk factor in multivariate analysis for SMN was having primary refractory rather than relapsed disease.

Increased SMN risk for high-risk neuroblastoma patients has been well described in the literature. Appelbaum et al. found in a SEER analysis the cumulative incidence of SMN at 30 years for high-risk patients (n = 933) to be 10.5%, with an estimate of only <5% at 10 years, lower than our incidence in relapsed/refractory neuroblastoma patients [31]. Another study of long-term survivors found the crude incidence of SMN to be 6% in high-risk patients [22]. It is likely that in these prior studies, the intensity of treatment and risk stratification may have differed, partially accounting for the difference in incidence. Additionally, all of our population reported here consisted of heavily pretreated patients with multiple regimens, which may have further contributed to the SMN risk. In a study looking specifically at SMN after autologous stem cell transplant for high-risk neuroblastoma, the 5-

and 10-year cumulative incidence rates of 7.2% and 16.5%, respectively, were similar to our observations [24]. Six of the 10 patients with SMN developed haematologic malignancies, similar to our population. Unfortunately, some patients in these study populations may have received ^{131}I-MIBG therapy, making its contribution to the results difficult to tease out. However, it is striking that in our heavily pretreated relapsed/refractory population, this cohort treated with ^{131}I-MIBG, and this cohort does not appear to have a higher cumulative risk of SMN than the high-risk post-transplant population overall.

When controlling for patient variables with an association with second malignancy (defined as $p < 0.1$), refractory disease status after completing induction chemotherapy was significantly associated with SMN, even when controlling for longer survival in this patient population. This finding warrants further exploration. It is possible that refractory/persistent disease status is a surrogate for an underlying genetic predisposition to SMN or that these patients received more aggressive treatment regimens, which increased their risk of SMN. Unlike known increases in SMN risk from treatments such as total body radiation and alkylating agents, the number of ^{131}I-MIBG treatments and cumulative dose per kilogram were not associated with increasing risk of SMN in our patient population [24,32]. It is unexpected that bone disease was associated with a decreased risk of SMN, and this may reflect different biological characteristics.

Our study has many strengths. This is one of the largest sample sizes in a study of this kind, with highly annotated combined data from four large neuroblastoma referral centres in the United States with treatments dating back to 1984. Over 85% of living patients have updated follow-up within the last year, with the longest follow-up after ^{131}I-MIBG therapy being 20 years.

There were a few limitations to this study. Despite being the largest study of its kind, the small number SMN cases (only 19 overall) limited our ability to identify variables with only a modest effect on risk of SMN. Second, although the study encompassed three decades, the number of patients surviving more than 15 years was very small, and the risk of SMN may continue to increase. Furthermore, the inclusion of patients from ^{131}I-MIBG institutions who were often referred from other centres made it impossible to quantify the doses of cytotoxic chemotherapy received, nor to be certain that all medical records obtained detailed family history of cancer. This study was also limited by missing whole body dosimetry information on 62.7% of patients. It is reassuring that available surrogates for this information such as ^{131}I-MIBG dose per kilogram and number of ^{131}I-MIBG treatments did not show an association with ^{131}I-MIBG therapy and risk of SMN [33].

5. Conclusion

The risk of SMN after ^{131}I-MIBG therapy for patients with relapsed or refractory neuroblastoma is similar to the greatest published incidence in high-risk neuroblastoma. We found no dose-dependent increase in SMN risk in patients who received more ^{131}I-MIBG treatments or had larger cumulative doses of ^{131}I-MIBG. In the context of the current study, we were not able to detect an increased risk of SMN above and beyond the known risk associated with other therapies used in the treatment of patients with high-risk

neuroblastoma. As the number of patients treated with ^{131}I-MIBG earlier after diagnosis and length of follow-up time from ^{131}I-MIBG therapy increase, it will be important to reassess this risk.

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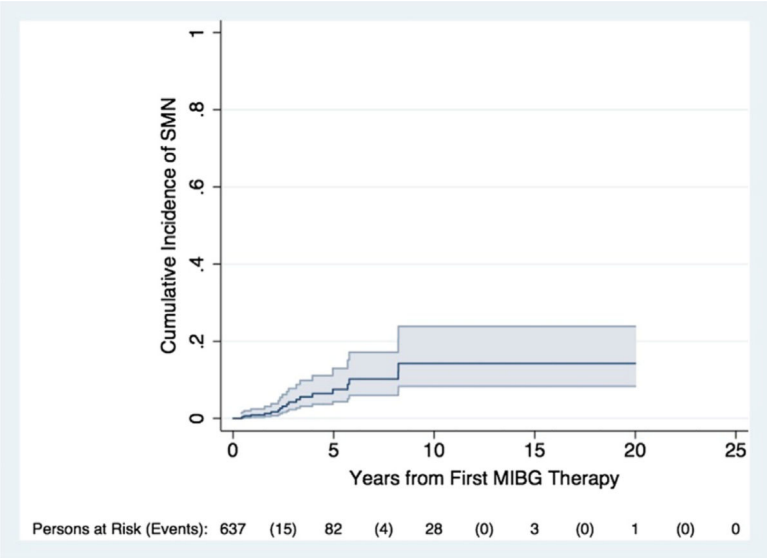

Fig. 1.

Cumulative incidence of SMN in patients treated with ^{131}I-MIBG therapy. SMN, second malignant neoplasm; MIBG, metaiodobenzylguanidine.

Table 1

Clinical and biologic characteristics of patients treated with ^{131}I-MIBG with and without second malignant.

Categorical variables	**Alive patients with no SMN (n = 152)**		**Dead patients with no SMN (n = 473)**		**Patients with SMN (n = 19)**	
	N	**%**	**N**	**%**	**N**	**%**
Male	96/152	63.2	280/473	59.2	10/19	52.6
Other than stage 4 at diagnosis	10/152	6.6	64/473	13.5	5/19	26.3
MYCN amplified	25/116	21.6	140/360	38.9	3/12	25.0
ASCT prior to MIBG	55/151	36.4	309/470	65.7	12/19	63.2
External beam radiation prior to MIBG	59/145	40.7	328/440	74.6	16/19	84.2
Bone marrow disease at initial MIBG therapy	88/142	62.0	252/438	57.5	8/18	44.4
Bone disease at initial MIBG therapy	142/152	93.4	417/472	88.5	14/19	73.7
Soft tissue disease at initial MIBG therapy rowheadDisease status at first MIBG therapy	95/138	68.8	299/459	65.1	16/19	84.2
Refractory/persistent	101/145	70.0	105/385	27.3	10/16	62.5
Relapsed/progressive rowheadNumber of MIBG treatments	45/145	31.0	280/385	72.7	6/16	37.5
1	95/152	62.5	279/473	59.0	12/19	63.2
2	50/152	32.9	153/473	32.3	6/19	31.6
3	5/152	3.3	31/473	6.6	0/19	0.0
≥4	2/152	1.3	10/473	2.1	1/19	5.3
Use of stem cell/bone marrow support after MIBG therapy	98/126	77.8	234/390	60.0	8/18	44.4
Death from progressive neuroblastoma	–	–	443/463	95.7	3/19	15.8
Continuous variables	N	Median (range)	N	Median (range)	N	Median (range)
Median age at diagnosis in years (range)	151	4.4 (0.5–37.8)	473	4.3 (0.2–50.8)	19	5.8 (0.5–18.3)
Median months from ASCT to MIBG (range)	53	11.5 (2.1–162.7)	292	23.7 (1.3–224.7)	19	23.6 (9.9–56.0)
Number of prior chemotherapy regimens (range)	151	2.0 (1–9)	469	3.0 (1–13)	18	3.0 (1–5)
Median age in years at 1st MIBG therapy (range)	152	6.1 (1.4–38.5)	473	6.8 (1.3–51.2)	19	8.1 (3.6–19.7)
Median months from diagnosis to 1st MIBG therapy (range)	151	11.0 (3.4–192.9)	473	26.4 (4.0–229.6)	19	30.2 (6.5–87.1)
Median cumulative MIBG dose in mCi/kg (range)	151	18.0 (8.0–96.0)	472	18.2 (2.0–90.0)	19	18.0 (9.6–50.5)
Median cumulative whole body radiation dose(range)	64	271.0 (78.1–860.0)	164	254.3 (79.0–681.6)	12	267.9 (96.8–699.0)
Median months from first MIBG to last follow-up or death (range)	150	40.8 (0.1–240)	468	9.7 (0.5–143.8)	19	39.7 (5.6–174.2)

Neoplasm (N = 644).

^{131}I-MIBG, iodine-131 metaiodobenzylguanidine; MYCN, V-Myc avian myelocytomatosis viral oncogene neuroblastoma derived homolog; ASCT, autologous stem cell transplant; mCi, millicurie; SMN, second malignant neoplasm.

Table 2

Characteristics of 19 patients with second malignancies after ^{131}I-MIBG therapy.

ID	Sex	Stage at NB diagnosis	Age at NB diagnosis (years)	ASCT prior to MIBG	EBRT prior to MIBG	# Chemo regimens	MIBG protocol	Total cumulative MIBG (mCi/kg)
Haematologic malignancies								
1	M	4	3.5	Y	N	3	MIBG only	10.5
2	F	4	18.3	Y	Y	2	MIBG with vincristine and irinotecan	15
3	M	4	5.1	Y	Y	5	MIBG + vorinostat, MIBG irinotecan	36
4	F	4S	0.5	N	Y	4	MIBG only	36
5	F	4	16.8	Y	Y	2	MIBG only	12.44
6	F	4	3.6	N	Y	2	MIBG only	17.7
7	M	4	1.4	N	Y	5	MIBG only	18
8	M	3	11.7	Y	Y	3	MIBG only	36
9	M	4	3.2	Y	Y	2	No carrier added MIBG, MIBG only	36
10	M	4	7.3	Y	Y	3	MIBG only	36
11	M	3	8.6	N	Y	5	MIBG only	18.8
12	M	4	13.6	N	Y	1	MIBG only	14.4
13	F	3	4.3	Y	Y	2	MIBG only	18
Solid malignancies								
14a	M	4	5.8	Y	Y, TBI	Unknown	MIBG only	19
14b	M	4	5.8	Y	Y, TBI	Unknown	MIBG only	19
15	F	4	0.7	N	N	2	MIBG + CEM ASCT	14.7
16	M	3	13.4	Y	Y	4	MIBG only	9.6
17	F	4	12.7	N	Y	2	MIBG only	50.5
18	F	4	2.8	Y	Y	3	MIBG only	36
19	F	4	1.0	Y	Y	4	MIBG only	18

MIBG, metaiodobenzylguanidine; NB, neuroblastoma; ASCT, autologous stem cell transplant; EBRT, external beam radiation therapy; chemo, chemotherapy; mCi, millicurie; kg, kilogram; TBI, total body irradiation; CEM, carboplatin, etoposide and melphalan.

Table 3

SMN characteristics of 19 patients with second malignancies after ^{131}I-MIBG therapy.

ID	SMN diagnosis	SMN biology	SMN treatment	Time from NB diagnosis to SMN (months)	Time from MIBG to SMN (months)	Follow-up time from SMN dx (months)	Cause of death
Haematologic malignancies							
1	ALL, pre-B	46 XY	TPOG-ALL protocol	45.1	22.6	13.9	MDR sepsis 2/2 treatment for all recurrence
2	MDS/AML	Monosomy 7	Umbilical cord blood transplant, 5-azacitidine (for relapse)	44.6	27.0	8.0	NB/AML
3	MDS/AML	Monosomy 2	None	64.0	32.0	3.0	AML
4	AML	Monosomy 7; additional material in long arms of chromosomes 2 and 4	MTX, Ara-C, HC	97.8	10.7	4.0	AML
5	AML	Deletion in chromosome 20; t(9; 11)	Hydroxyurea/allopurinol, Ara-C/ VP-16, Mylotarg, cyclosporine, Ara-C, fludarabine, clofarabine	65.8	33.1	6.6	AML
6	T cell ALL	Unknown	None	52.8	40.0	0.4	ALL
7	AML	Unknown	None	71.5	5.5	0.0	AML/ARDS
8	AML	Monosomy 5q-	5-azacytidine	98.6	68.4	9.5	AML
9	MDS	Trisomy 1q and 7q- t(1; 7) along with subclone containing trisomy 8	Matched sibHSCT conditioned w/ busulfan and fludarabine	70.6	47.4	18.4+	–
10	MDS	Monosomy 7	5-azacytidine	95.9	37.7	4.4	MDS
11	MDS	Trisomy 11 and der(12p) and monosomy 13.	Unknown	43.1	6.6	4.6	MDS/NB
12	MDS, AML	Monosomy 5,7q-, Y-	Allogenic HSCT from brother with melphalan, cytoxan, cyclosporin A	25.3	18.8	4.6	ARDS 2/2 HSCT/ GVHD
13	MDS	Monosomy 7	None	63.0	28.0	4.0	MDS, NB
Solid malignancies							
14a	Undifferentiated sarcoma, cranium	Not done	Resection, doxorubicin and isofosfamide, EBRT	128.9	108.4	65.8+	–
14b	Inflammatory myofibroblastic pseudotumour, lung	ALK1 negative by IHC	Resection	119.1	98.6	75.6+	–
15	Osteosarcoma, R humerus	Stage 2A	Doxorubicin, cisplatin, high dose MTX	68	57.1	53.3	NB

ID	SMN diagnosis	SMN biology	SMN treatment	Time from NB diagnosis to SMN (months)	Time from MIBG to SMN (months)	Follow-up time from SMN dx (months)	Cause of death
16	Papillary thyroid carcinoma	Not done	Resection	131.2	69.3	33.0+	–
17	Peritoneal mesothelioma, pelvis	Translocation 13p11.2	Unknown	37.7	19.4	49.2	NB
18	Inflammatory myofibroblastic tumour	ALK1+ by IHC	Unknown	69.0	5.3	5.3	NB
19	Papillary thyroid carcinoma	Not done	Total thyroidectomy and i131 therapy	87.4	59.4	9.6+	–

SMN, second malignant neoplasm; MIBG, metaiodobenzylguanidine; NB, neuroblastoma; ALL, acute lymphoblastic leukaemia; TPOG, Turkish paediatric oncology group; MDR, multidrug resistant, MDS, myelodysplastic syndrome; AML, acute myelogenous leukaemia; MTX, methotrexate; Ara-C, cytosine arabinoside; HC, hydrocortisone; VP-16, Etoposide; ARDS, acute respiratory distress syndrome; HSCT, haematopoietic stem cell transplant; GVHD, graft versus host disease; EBRT, external beam radiation therapy; IHC, immunohistochemistry.

Table 4

Competing risk regression results comparing patients with and without SMN.

	Subhazard ratio	95% confidence interval	P value
Male	0.70	0.29−1.73	0.444
Other than stage 4 at diagnosis	0.43	0.15−1.17	0.099
MYCN amplified	0.59	0.16−2.17	0.158
Age at diagnosis in years	1.03	0.99−1.07	0.108
ASCT prior to MIBG	1.14	0.45−2.89	0.777
Months from ASCT to MIBG	1.01	0.99−1.02	0.505
Number of prior chemotherapy regimens	0.91	0.75−1.11	0.347
History of external beam radiation prior to MIBG	2.42	0.71−8.29	0.160
Age in years at 1st MIBG therapy	1.03	0.99−1.07	0.057
Months from diagnosis to 1st MIBG therapy	1.00	0.99−1.01	0.558
Bone marrow disease at initial MIBG therapy	0.60	0.24−1.51	0.236
Bone disease at initial MIBG therapy	0.36	0.13−0.99	0.049*
Soft tissue disease at initial MIBG therapy	2.67	0.78−9.13	0.118
Relapsed/progressive disease at first MIBG therapy (versus refractory/persistent)	0.40	0.15−1.06	0.065
One MIBG Tx (versus >1)	0.84	0.33−2.14	0.718
Cumulative MIBG dose in mCi/kg	0.99	0.96−1.03	0.842
Cumulative whole body radiation dose in cGy	1.00	0.99−1.01	0.409
Use of stem cell/bone marrow support after MIBG therapy	0.49	0.19−1.24	0.132

SMN, second malignant neoplasm; ^{131}I-MIBG, iodine-131 metaiodobenzylguanidine; MYCN, V-Myc avian myelocytomatosis viral oncogene neuroblastoma derived homolog; ASCT, autologous stem cell transplant; mCi, millicurie.