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Individualised 131I-mIBG Therapy in the Management of Refractory and Relapsed Neuroblastoma

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	administrations) was individualised according to the clinical status of the patient and dosimetry data from either a tracer study or previous administrations. Three-dimensional tumour dosimetry was also performed for 8 patients. Results: Mean administered activity: 11089 +/- 7222 MBq, mean whole-body dose for a single administration: 1.79 +/- 0.57 Gy. Tumour absorbed doses varied substantially (3.70 ± 3.37 mGy/MBq). CTCAE grade 3/4 neutropenia was documented following 82% treatments, grade 3/4 thrombocytopenia following 71% treatments. Further acute toxicity was seen in 49% of patients. All acute toxicities resolved with appropriate therapy. 58% patients had complete or partial response following therapy and 29% patients had stable disease. Conclusion: Excellent response rates and acceptable toxicity were seen following individualised 131I-mIBG therapy. Due to the considerable variability in patient age and status, the absorbed doses delivered to tumours and to the whole-body per MBq administered, a highly personalised approach is required, combining patient-specific dosimetry and clinical judgement. This approach is enabled by the high activities that can be tolerated by patients, particularly with stem cell support.

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Individualised ^{131}I-mIBG Therapy in the Management of Refractory and Relapsed Neuroblastoma

Short title: Individualised ^{131}I-mIBG Therapy

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Abstract

Objective: ^{131}I-mIBG therapy is an established treatment modality for relapsed/refractory neuroblastoma, most frequently administered according to fixed or weight-based criteria. We evaluate response and toxicity following a dosimetry based, individualised approach.

Materials and methods: A review of 44 treatments in 25 patients treated with ^{131}I-mIBG therapy. Patients received ^{131}I-mIBG therapy following relapse (n=9), in refractory disease (n=12), or with surgically unresectable disease despite conventional treatment (n=4). Treatment schedule (including administered activity and number of administrations of mIBG) was individualised according to the clinical status of the patient and dosimetry data from either a tracer study or previous administrations. Three-dimensional tumour dosimetry was also performed for 8 patients.

Results: Mean administered activity: 11089 +/- 7222 MBq, mean whole-body dose for a single administration: 1.79 +/- 0.57 Gy. Tumour absorbed doses varied substantially (3.70 ± 3.37 mGy/MBq). CTCAE grade 3/4 neutropenia was documented following 82% treatments, grade 3/4 thrombocytopenia following 71% treatments. Further acute toxicity was seen in 49% of patients. All acute toxicities resolved with appropriate therapy. 58% patients had complete or partial response following therapy and 29% patients had stable disease.

Conclusion: Excellent response rates and acceptable toxicity were seen following individualised ^{131}I-mIBG therapy. Due to the considerable variability in patient age and status, the absorbed doses delivered to tumours and to the whole-body per MBq administered, a highly personalised approach is required, combining patient-specific dosimetry and clinical judgement.

Key words: Neuroblastoma, ^{131}I-mIBG, therapy, refractory, relapse, dosimetry

Introduction

Neuroblastoma is an embryonal tumour of childhood arising from the neural crest. The majority of patients have high-risk disease at presentation, which is associated with a poor outcome despite intensive multimodal therapy. Targeted Molecular Radiotherapy (TMRT) with ^{131}Iodine labelled meta-iodobenzylguanidine (^{131}I-mIBG) has been used for patients with relapsed and refractory disease and as an induction and consolidation therapy for over 20 years [1-7], although reported treatment schedules vary widely and are hard to standardise due to the wide range of presentations, including disease status, patient age and treatment history. An individualised approach to treatment is therefore required to maximise therapeutic potential.

Although ^{131}I-mIBG is usually administered either as a fixed activity [8] or according to patient weight [9-11], an alternative approach is to modify the administration according to a prescribed whole-body absorbed dose (WBD), which offers the possibility to deliver large activities and to maximise the absorbed doses delivered to disease sites without unnecessary toxicity [12, 13]. Administrations can be further increased with stem cell support. It has previously been demonstrated that the prescribed WBD can be delivered accurately and closely correlates with haematological toxicity, thereby acting as a surrogate biomarker for red marrow absorbed dose [14].

The aim of this study was to evaluate the response, toxicity and long-term outcome of ^{131}I-mIBG therapy in the treatment of refractory and relapsed neuroblastoma, based on an individualised approach: Administrations were tailored to patients according to

their bio-kinetics in addition to their clinical status at the time of ^{131}I-mIBG therapy including: age, stage, previous therapies, site(s) of disease, and response to previous therapies.

Materials and Methods

Ethical Considerations

^{131}I-mIBG therapy is considered a standard treatment option in patients with relapsed and refractory neuroblastoma. For all patients who received ^{131}I-mIBG therapy, clinical details were scrutinised in an institutional multidisciplinary meeting, and consensus regarding treatment was reached. Informed written consent was obtained before therapy for all patients. Institutional review board approval was obtained for the retrospective collection of clinical data throughout follow up at our institution.

Patients

A review was conducted of 44 ^{131}I-mIBG treatments given between 1994 and 2013 in 25 patients with a histologically proven diagnosis of neuroblastoma. Patients were considered eligible for ^{131}I-mIBG therapy if there was greater tumour uptake than in normal liver, following relapse (n=9), in refractory disease (n=12), or with surgically unresectable disease despite conventional treatment (n=4).

A median of 2 different chemotherapy regimens was given prior to ^{131}I-mIBG therapy (range 1-5). In addition, 8/25 patients had previously received high dose chemotherapy with autologous stem cell rescue and 6 patients had previously received external beam radiotherapy. Patient characteristics are shown in Table 1.

^{131}I-mIBG therapy

Patients were treated in a room specially designed for radioisotope therapy within the children's ward. ^{131}I-mIBG was given intravenously over 2 hours with hydration. Thyroid protection was provided with potassium iodide. Blood pressure and heart rate were monitored during the procedure and for 24 hours after treatment. For the first treatment, 15 patients received a tracer study from which the activity required to deliver a WBD of 2 Gy was calculated. The initial administered activity for the remaining 10 patients was calculated from a simple weight-based formula of 444 MBq/kg followed by an adjustment to the administered activity according to a measured WBD for subsequent therapies.

The methodology for whole-body dosimetry has been described previously [14, 15]. Briefly, lead shielded ceiling mounted counters (a NaI detector for ^{123}I tracer studies and a compensated Geiger counter for ^{131}I-mIBG therapies) were used to acquire whole body counts. The first measurement was acquired immediately after administration and before the first bladder void to obtain the reading corresponding to 100% activity. Subsequent readings were taken consistently after the child's natural void and were not performed overnight, unless the child woke naturally. Between 40 and 60 readings were acquired to define multi-exponential effective decay phases. The cumulated activity was determined from the integral of the curve, extrapolated to infinity. The absorbed dose was calculated according to the MIRD schema [16], using an S-factor modified according to patient weight.

Tumour dosimetry

Image data were obtained to calculate tumour-absorbed doses for 8 of the 25 patients. Between 3 and 8 SPECT acquisitions were made on consecutive days following the treatment, depending on patient availability and remaining activity. Scans were acquired on a Philips Forte (Philips Medical Systems, Milpitas, CA) or a GE Millennium VG gamma camera (GE Healthcare, Waukesha, WI) using high-energy general-purpose collimators and a 128 x 128 matrix were used, with the same camera used for all scans for any given patient. Image processing and reconstruction were performed with Triple Energy Window scatter correction (20% photopeak energy window centred on 364 keV, with a 6% window of the peak on either side), a uniform attenuation correction (Chang) and deadtime corrections determined experimentally for each camera [17]. Reconstructed scans for each patient were sequentially co-registered to allow 3D voxelised dosimetry to be performed with an in-house dosimetry software package (Qrius) [18]. This software is based on patient-specific convolution dosimetry calculations at the voxel level, with ^{131}I absorbed dose voxel kernels generated using the general purpose Monte Carlo code EGSnrc/EGS++ [19].The radiation spectra of ^{131}I used to calculate dose voxel kernels was taken from the MIRD decay Scheme [20].The image-based 3D dosimetry application provides an absorbed dose map of consecutive therapies from which dose volume histograms were derived.

Toxicity

Acute toxicity was defined as any consequence arising from the point of administration until neutrophil count recovery to >1. Acute and long-term treatment toxicity was assessed in all patients by electronic record and case note review. In

patients where data were available (those whose blood counts were monitored at our institution post ^{131}I-mIBG therapy) haematological toxicity was graded according to Common Terminology for Adverse Events (CTCAE) criteria version 4.0.

Response assessment, follow up and survival analysis

Following ^{131}I-mIBG therapy, response was assessed by a combination of diagnostic ^{131}I-mIBG scanning and cross-sectional imaging (CT or MRI) which was chosen in accordance with the base line imaging modality to enable a direct comparison. Imaging was reviewed by at least 2 radiologists and consensus response was classified according to the International Neuroblastoma Risk Classification (INRC) definition of response.

Overall survival (OS) analysis was performed using the Kaplan Meier method and one year OS and median OS calculated. Any further therapy given to consolidate ^{131}I-mIBG response was also recorded.

Statistical Analysis

Statistical analysis was performed with GraphPad Prism software (version 6.00, La Jolla, CA, USA) using a two-tailed *t* test for paired data (Wilcoxon matched-pairs signed rank test in the case for non-parametric data). A double-sided *P* value of less than 0.05 was considered significant.

Results

Whole body Dosimetry

The administered ^{131}I-mIBG activity and whole body absorbed dose for each patient is shown in Table 2. The mean administered activity was 11089 MBq (range 3539 – 32871 MBq, SD 7222). The mean ^{131}I-mIBG WBD was 1.79 Gy (range 0.93-3.51, SD 0.57). The median interval between treatments was 67 days (range 15-1134 days, IQR 45-94). The use of tracer and weight-based methods to prescribe a therapeutic administration enabled substantially higher activities to be delivered than is standardly the case with fixed activity administrations although as previously reported, both methods slightly overestimated the absorbed whole body dose delivered during therapy [15]. There was no difference between WB dose predicted from a previous therapy and the delivered WBD (P=0.28), thus indicating the predictive power of consecutive therapies.

Tumour dosimetry

A representation (studies no. 2, 20 and 25) of patient tumour dosimetry utilizing the 3D dosimetry tool is given in Figure 1. The generated 3D absorbed dose maps with isodose curves enable dose volume histograms (DVH) to be produced to evaluate the spatial heterogeneity of absorbed dose following therapy.

Tumour absorbed doses were calculated for 8 patients and are summarised in Figure 2. The mean tumour absorbed dose delivered was 43.7± 27.5 Gy, while mean liver and kidney doses were 5.7 ± 1.4 and 2.5 ± 0.4 Gy respectively. Allowing for the uncertainty in the dosimetry the absorbed doses delivered were consistent. Absorbed dose ratios between consecutive therapies are summarised in Table 3.

Toxicity

CTCAE grade 3/4 neutropenia was seen following 18/22 (82%) treatments and grade 3/4 thrombocytopenia following 19/24 (71%) treatments. Autologous stem cell transplant was given following ^{131}I-mIBG therapy in 14/24 patients. In addition to the haematological toxicity, further acute toxicity was documented following 21/43 (49%) treatments. With the exception of 4 treatments, all acute toxicity involved either culture negative fever or documented infection. Of the 4 patients who had non-fever/infection related complications: 2 patients experienced parotitis, 1 patient had a hypertensive episode and 1 patient complained of back pain. All acute toxicities resolved with appropriate therapy. With regards to potentially vulnerable target organs such as the liver, kidneys and thyroid gland, one patient with a transient fever had an associated transaminitis, although there was no long-term target organ toxicity seen in any patient. Only one patient, who did not receive stem cell rescue, experienced prolonged thrombocytopenia.

Response

Data were available on response in 24/25 patients (Table 4). Two patients achieved CR after ^{131}I-mIBG therapy. The first patient remained in CR for 11 months before relapse (at time of writing is alive with disease 16 months post ^{131}I-mIBG therapy). The second patient relapsed 6 months after ^{131}I-mIBG therapy and subsequently died of disease.

Two patients with PR following ^{131}I-mIBG therapy subsequently achieved CR after further consolidation therapy. One patient who had previously received multiple lines of chemotherapy, surgery and high dose therapy for metastatic neuroblastoma had a localised recurrence that was surgically unresectable. She received 5 cycles of

^{131}I-mIBG therapy with a continued PR after each cycle, then further treatment with surgical resection, radiotherapy and cis-retinoic acid treatment. She remains alive and disease free after 6 years of follow up. The second patient had a surgically unresectable localised disease despite multiple previous lines of chemotherapy. PR following ^{131}I-mIBG therapy enabled surgical resection. This was consolidated with radiotherapy and she remains alive and disease free 12 years from diagnosis. The median overall survival was 18.6 months (95% CI 10.4-26.9) with one year overall survival of 65% (95% CI 48-88%). The median follow up was 44 months (Fig. 3). Six patients were alive with disease at last follow up (median follow up from ^{131}I-mIBG therapy 12 months, range 4-32 months), while 16 patients are known to have died from disease. The median time from the last ^{131}I-mIBG therapy to death was 12 months (range 2-82 months).

Discussion

Cumulative evidence from institutional reports and some early phase trials has established ^{131}I-mIBG therapy as a standard treatment option in patients with relapsed and refractory neuroblastoma [2, 8, 9, 13]. There has also been limited use of ^{131}I-mIBG as part of first line treatment [4, 7]. However, to date there are currently no published randomised controlled trials of ^{131}I-mIBG therapy for neuroblastoma at any stage of treatment [21]. In order to maximise the therapeutic potential of ^{131}I-mIBG therapy, well designed clinical trials incorporating dosimetry are needed. A whole body absorbed dose approach for ^{131}I-mIBG therapy as followed here enables safe delivery of substantially higher activities than are standardly given with fixed

administrations and can be used to deliver reproducible therapy results on a patient-specific basis [14, 22].

Patients with stage III or stage IV neuroblastoma present with tumours of varying sizes and uptake distributions. There is a wide inter-patient variation in the absorbed doses delivered to tumours, although these are consistent between consecutive therapies. The heterogeneity of the absorbed dose distribution will affect the outcome of subsequent therapies and may help to explain the variation in responses. In light of this, a 3D dosimetry approach with DVHs could help with the development of more effective treatment protocols. The data in this study were acquired without the benefit of SPECT/CT imaging for attenuation correction. Current hybrid scanners will enable improved image quantification for more accurate dosimetry.

It is difficult to make direct comparisons of trials of ^{131}I-mIBG therapy in neuroblastoma as the study groups are very heterogeneous and treatment protocols, including administration and concomitant therapy, are highly variable. ^{131}I-mIBG therapy is often administered with a fixed or weight-based activity and with these techniques, response rates (PR and CR) vary between 30 and 56% [1, 8, 23]. Within this context our response rate of 58%, with 88% of patients having stable disease or better following ^{131}I-mIBG therapy is of note. Our data also support a previous study showing that a dosimetry based approach to augment mIBG intensity may improve response rates [13]. It is also noteworthy that in our series in two cases a CR was obtained following either surgery or radiotherapy consolidation after mIBG therapy and that in several cases the duration of response was long.

Administrations based on fixed activities must inevitably be limited according to the most vulnerable of patients. This can lead to under-treatment of the majority. As found in this study an individualised approach, based on patient pharmacokinetics,

will often result in the administration of higher activities. The capacity to include stem cell support and concomitant chemotherapy necessitates a multidisciplinary approach and specialised care as detailed in the EANM guidelines [24].

As this report is a retrospective collation of data from patients who received individualised ^{131}I-mIBG therapy schedules based on their clinical features and dosimetry there are a number of inherent limitations. Our patient group was heterogeneous in many ways; they had different disease stages and tumour burdens, had received various different previous chemotherapy regimens, and ^{131}I-mIBG therapy was used under several different clinical scenarios. However, although the heterogeneity in our patient group makes drawing direct comparisons with other series difficult, this is a true reflection of the diverse nature of the clinical situations where ^{131}I-mIBG therapy is applied in standard clinical practice.

Neuroblastoma has an extremely variable clinical picture with regards to site(s) of presentation, tumour biology and disease aggressiveness. In infants with metastatic disease their disease may spontaneously regress. However, metastatic disease in older patients is associated with rapid progression and a poor prognosis. Other patients may have surgically unresectable localised disease compressing vital structures but with differentiated histology and little propensity to metastasise. In such a heterogeneous group of patients an adaptive approach that incorporates adjustment of dose and schedule, according to clinical judgement, based on a patient's individual needs and dosimetry may maximise the potential benefit to the patient.

A limitation of our study is that there is a significant amount of missing data specifically on haematological toxicity. This is because patients are referred for ^{131}I-mIBG therapy from a wide geographical area and blood counts following therapy are monitored at the patients' local institution. This is a common situation with this

relatively rare and highly specialised treatment and indicates the need for a Europe-wide initiative to ensure data collection. Nevertheless our reported haematological toxicity is as expected following ^{131}I-mIBG therapy and previous work from our institution has demonstrated the clear correlation between the absorbed whole body dose and haematological toxicity [14]. Data on non-haematological toxicity is more complete due to a 'shared care' system whereby the treating centre is notified by local hospitals of any admission or problems requiring intervention. Further non-haematological toxicities seen in our patients were all resolved with appropriate treatment and no long-term effects were seen.

In summary, excellent response rates have been seen in our institution following individualised ^{131}I-mIBG therapy whilst keeping toxicity within acceptable limits. Our data supports the use of patient-specific dosimetry in future clinical trials to maximise the efficacy of ^{131}I-mIBG therapy.

Conclusion

^{131}I-mIBG therapy is a safe and effective treatment for relapsed or refractory neuroblastoma. A highly personalised approach, combining clinical judgment with patient-specific dosimetry can be used to safely maximise therapeutic efficacy. Further multi-centre clinical trials are essential to optimise the treatment and to determine its place within the patient pathway.

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Figure 1: Representation of 3D tumour dosimetry
Figure 2: Tumour absorbed doses
Figure 3: Kaplan Meier plot of overall survival

Figure 1

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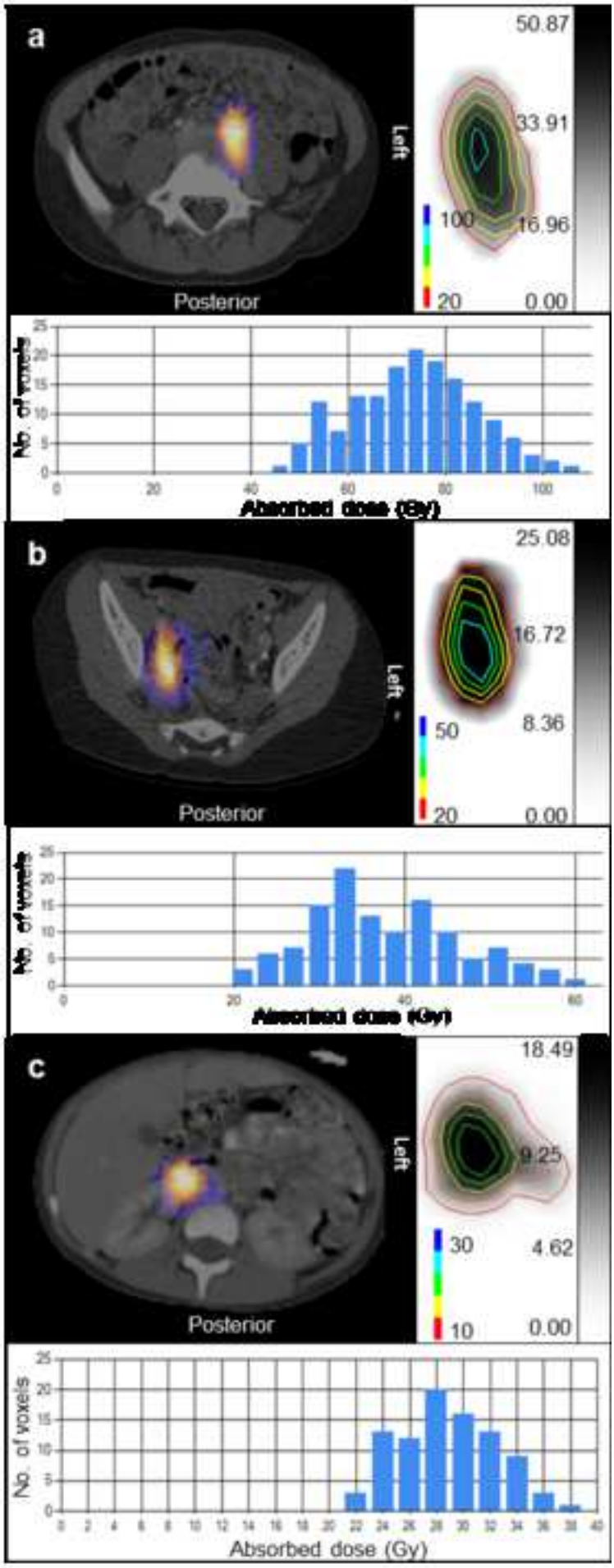

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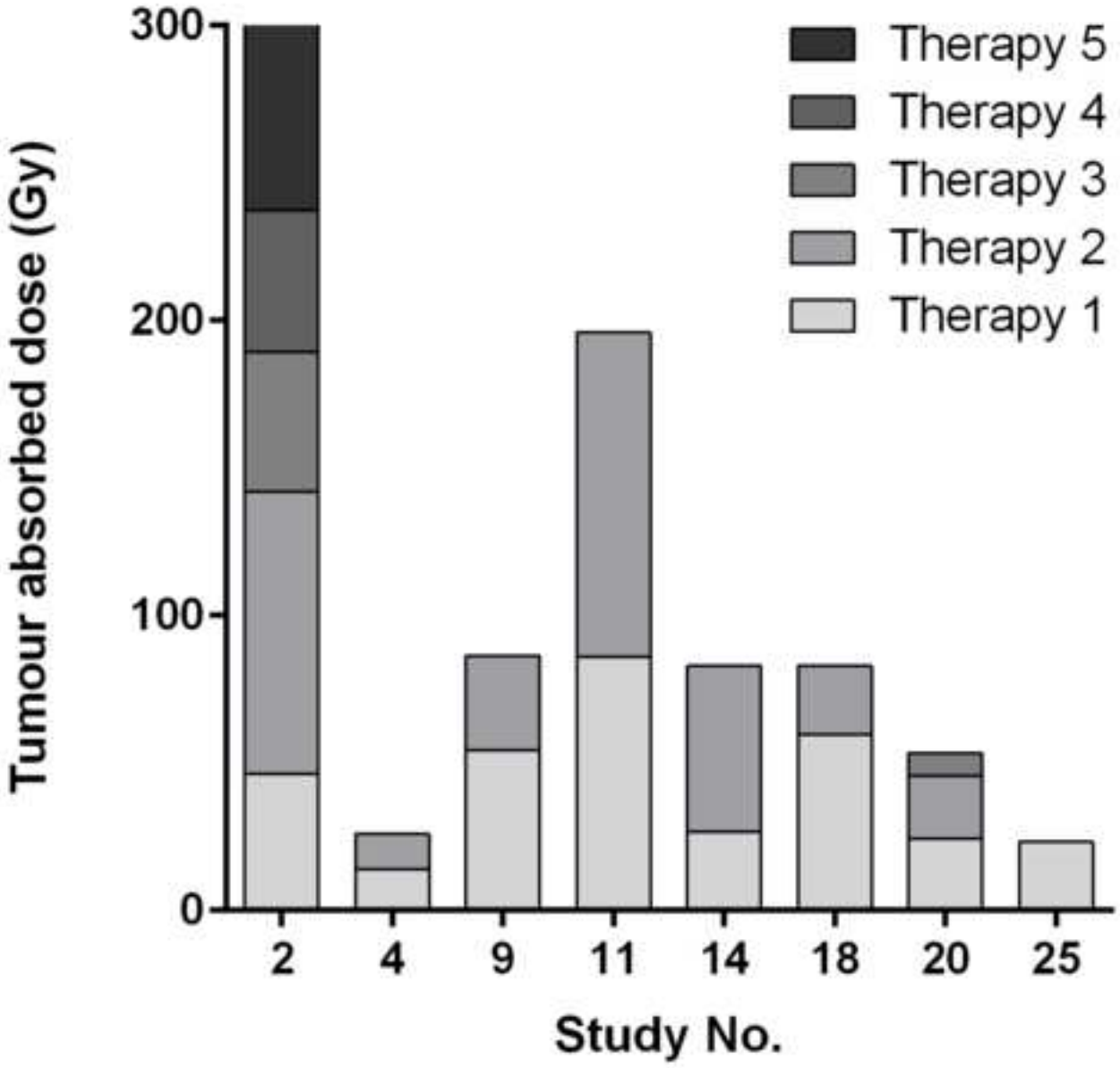

Figure 3

Fig. 3. Kaplan-Meier plot of overall survival (OS).

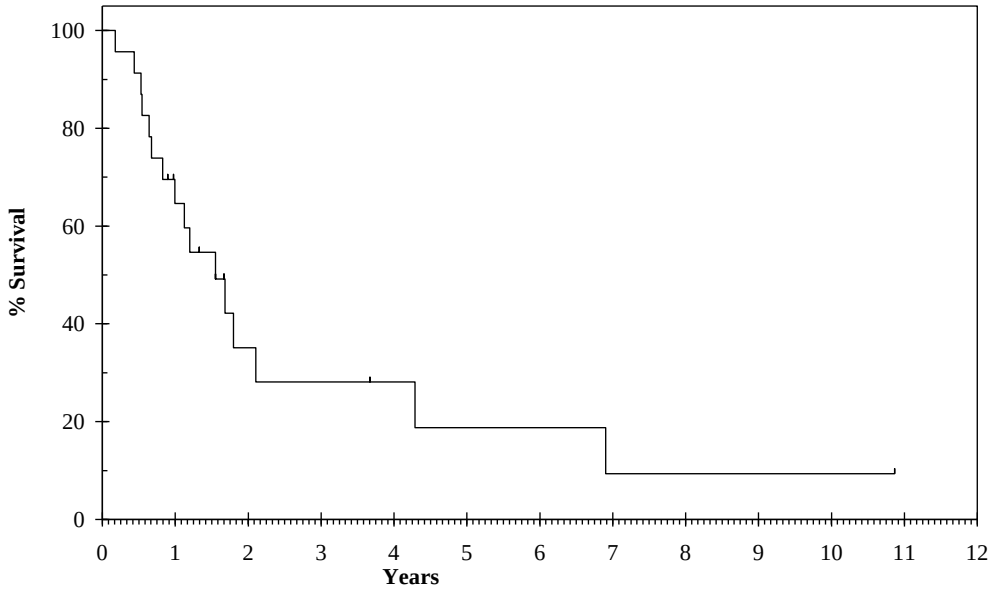

Table 1

Table 1 Patient Characteristics

Characteristic	Value
Sex (%)	
Male	15/25 (60%)
Female	10/25 (40%)
Median age at diagnosis (range)	53 months (5-229)
Median age at 1st ^{131}I-mIBG therapy (range)	72 months (17-241)
Stage at diagnosis* (%)	
2	3/25 (12%)
3	4/25 (16%)
4	18/25 (72%)

*Stage according to International Neuroblastoma Staging System

Table 2 Administered activities (AA) and whole body absorbed dose (WBD)

Study no.	AA (MBq)	Weight (MBq/kg)	WBD (Gy)
1a	6611	398	1.70
1b	6605	398	1.61
2a	10524	357.9	1.00
2b	15673	517.2	1.37
2c	19811	649.5	1.62
2d	19723	644.5	2.2
2e	13988	466.3	1.13
3a	29378	391.2	1.78
3b	32710	352.5	1.12
4	9834	480	1.66
5	3539	281	1.14
6	20823	458	1.64
7	5559	505	1.94
8a	8243	292.3	1.41
8b	9961	348.3	1.67
9a	6893	393.8	1.59
9b	9363	535	2.22
10a	4775	477.5	1.98
10b	4900	490	1.92
11a	8797	472.95	3.36
11b	8652	465.7	3.51
12a	6889	551.4	2.11
12b	4892	391.4	1.55
13a	6400	345.9	1.75
13b	6417	329.1	1.82
14a	21066	322.6	1.00
14b	32871	483.4	2.12
15	13457	497	2.46
16a	5321	273.8	0.93
16b	15733	815.2	2.11
17a	6941	341.9	1.83
17b	6572	315.5	1.71
18	11652	433	2.28
19	9358	307	1.45
20a	7766	413.1	1.35
20b	11227	578.7	1.83
20c	9270	501	1.47
21a	6701	446.7	1.76
21b	6397	412.7	1.62
22	6144	361	1.11
23	14538	434	1.62
24a	7636	406.2	3.25
24b	5271	289.1	2.26
25	9060	458	1.96

Table 3 Absorbed Tumour dose ratios for consecutive therapies (T)

Study no.	T2 / T1			T3 / T2		
	AA ratio*	Tumour uptake ratio	Tumour dose ratio	AA ratio*	Tumour uptake ratio	Tumour dose ratio
2	1.5	1.0	1.5 ± 0.9	1.3	0.5	0.6 ± 0.4
4	1.1	0.8	0.9 ± 0.4	-	-	-
9	1.4	0.4	0.6 ± 0.2	-	-	-
11	1.0	1.3	1.3 ± 0.2	-	-	-
14	1.6	1.3	2.1 ± 0.9	-	-	-
18	1.4	0.3	0.4 ± 0.2	-	-	-
20	1.4	0.6	0.9 ± 0.3	0.8	0.4	0.4 ± 0.1

*AA – Administered activity

Table 4

Table 4 INRC Response

INRC Response	Number (%)
Complete Remission (CR)	2 (8.3)
Partial Response (PR)	12 (50)
Stable Disease (SD)	7 (29.2)
Progressive Disease (PD)	2 (8.3)
Mixed Response (MR)	1 (4.2)

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