The Efficacy of Iodine-131-Metaiodobenzylguanidine Therapy in Relapsed or Refractory Neuroblastoma: A Meta-Analysis

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Research Article

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Abstract

Objective
Neuroblastoma is a common extracranial solid tumor of childhood. Recently, multiple treatments have been practiced including Iodine-131-metaiodobenzylguanidine radiation ($^{131}$I-MIBG) therapy. However, the efficacy varies greatly. The aim of this meta-analysis is to evaluate the efficacy of $^{131}$I-MIBG for relapsed or refractory neuroblastoma and to provide evidence and hints for clinical decision-making.

Methods
Medline, EMBASE database and the Cochrane Library were searched for relevant studies. Eligible studies were clinical trials of refractory assigned to $^{131}$I-MIBG with data on efficacy including tumor response. The overall efficacy was calculated using a random-effects model considering of the heterogeneity.

Results
A total of 26 clinical trials including 883 patients were analyzed. The overall rates of objective response SD, PD and MR was 39% (95% CI: 32%-47%), 31% (95% CI: 24%, 37%), 22% (95% CI: 15%, 30%) and 15% (95% CI: 3%, 31%), respectively. Overall objective response rates of $^{131}$I-MIBG in combination with chemotherapy was 28%±95% CI: 14%, 44%. Median event-free survival (EFS) ranged from 10 to 16 months in the studies included.

Conclusion
$^{131}$I-MIBG treatment is effective on clinical outcomes in relapsed or refractory neuroblastoma, more randomized-controlled clinical trials investigating the efficacy of $^{131}$I-MIBG in combination with chemotherapy should be conducted.

Introduction
Neuroblastoma is a common extracranial solid tumor of childhood, accounting for approximately 8% of total pediatric malignant tumors [1, 2]. It derives from primitive sympathetic nervous system tissue and arises mostly from adrenal medulla or paraspinal ganglia of the neck, chest, abdomen, or pelvis [3]. Statistically, neuroblastoma occurs more common in boys than in girls, however, the potential causes remain long-standing mysteries [4]. Furthermore, over one-third of the patients are diagnosed at the age of < 12 months and the median age at diagnosis is 17 months More than 50% of children present with widely metastatic disease [5].

The type of therapy for neuroblastoma depends on risk group in which a patient identifies [5, 6]. Risk stratification is determined according to a patient's International Neuroblastoma Risk Group (INRG) stage, age, histological condition of tumor, degree of tumor differentiation, and et al [6]. Typically, in low-risk patients may be monitored for spontaneous differentiation or regression of tumor and either chemotherapy or radiation may not be necessary in these patients. Conversely, chemotherapy may be used in patients with intermediate or high risk. Moreover, patients with high risk may receive stem cell transplant, immunotherapy and surgery.

Despite multiple choices of treatment mentioned above, patients with neuroblastoma continue to be at high risk of treatment failure [7–10]. Unfortunately, patients with refractory or relapsed neuroblastoma suffer from poor prognosis, while novel therapy is in need [11]. Currently, there is no consensus on the optimal treatment for neuroblastoma.

Meta-iodobenzylguanidine (MIBG) is an analogue of adrenergic neuron blockers, it shows high affinity to cells of the sympathetic nervous system and by neoplasms arised from them, such as neuroblastoma [9]. Interestingly, iodine-131 labeled MIBG ($^{131}$I-MIBG) was used to treat neuroendocrine tumors including neuroblastoma after the development of MIBG [12, 13]. Since then, findings on the treatment role of $^{131}$I-MIBG have occurred [14, 15]. The first I-131 MIBG therapy for neuroblastoma were reported in 1986 [16]. In the following years, several other groups also conducted phase I or phase II clinical trials on the efficacy of $^{131}$I-MIBG on the treatment of neuroblastoma. However, the objective response (partial or complete response) rate varied widely, from 30–71% [14, 15, 17–24].

As far as we know, a few studies limited to small sample sizes and heterogeneity of treatment outcomes have investigated the efficacy of $^{131}$I-MIBG for the treatment of neuroblastoma. The aim of this study was to conduct a meta-analysis by collating the available
evidence to generate an accurate and sounding assessment of the efficacy of $^{131}$I-MIBG monotherapy and $^{131}$I-MIBG in combination with chemotherapy, and subsequently to provide evidence and hints for clinical implement and decision-making.

**Materials And Methods**

**Statement**

This meta-analysis was entirely based on previous published studies which had declared ethical approvals, and no original clinical raw data of the published results were collected or utilized, thereby ethical approval was not conducted for this study. This review was conducted on the basis of the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) [25].

**Literature search and selection criteria**

We conducted a comprehensive literature search of online databases of the Medline (via PubMed), Embase database and the Cochrane Library (until December, 2019) from inception to May 31, 2021. Our search strategy was (("Iodine Radioisotopes"[Mesh] OR ("iodine radioisotopes"[MeSH Terms] OR ("iodine"[All Fields] AND "radioisotopes"[All Fields]) OR "iodine radioisotopes"[All Fields] OR "chemotherapy"[All Fields]) AND "neuroblastoma"[All Fields]). Additionally, we manually searched the reference lists of all accepted papers to ensure that no studies were missed. All articles were published in English. Studies that met the following criteria were enrolled for this meta-analysis: (1) clinical trials designed to evaluate the efficacy of $^{131}$I-MIBG or $^{131}$I-MIBG in combination with chemotherapy in relapsed or refractory neuroblastoma; (2) data available for the extraction or calculation tumor treatment response rates. Once studies recruited participants over the same period or from the same study centers, only the study with the largest sample size or yielding the most pertinent outcomes was included to avoid duplications. All the potentially relevant papers were reviewed independently by two investigators (HH and QX) and disagreement were resolved by discussion and a third reviewer (CY) was involved in case that no consensus was achieved.

**Data extraction and quality assessments**

Two independent reviewers screened the titles and abstracts of articles to judge whether they meet the inclusion criteria. Thereafter a full-text reading of the literature was performed for the final inclusion. Details on patients’ characteristics, $^{131}$I-MIBG dose and schedule, tumor response rates were also extracted independently by two investigators. The main clinical endpoints were tumor response rate, including complete response (CR), partial response (PR), progressive disease (PD), stable disease (SD), minor response (MR). Objective response was defined as patients either undergo a partial or complete response. Event-free survival in each study was also extracted. We used the Newcastle-Ottawa Quality Assessment Scale to assess the methodological quality of enrolled studies [26]. The Newcastle-Ottawa Quality Assessment Scale contains 3 categories (quality selection, comparability and outcome) across which cohort studies are assessed for quality.

**Statistical analysis**

All statistical analyses were conducted using R 3.6.1 software package. The efficacy of $^{131}$I-MIBG treatment in neuroblastoma was assessed depending on the indicators mentioned above. A Cochran Q test was used to assess heterogeneity between studies and $I^2$ statistic was used to investigate the magnitude of the heterogeneity. Pooled rates of objective response, SD, PD, and MR and their respective 95% confidence intervals (CIs) were calculated with a random-effects model or a fixed-effects model. If $I^2$ value was >50%, a random-effects model was used, otherwise we used a fixed-effects model [27]. a sensitivity analysis was conducted in order to check the stability of pooled outcomes. Furthermore, an Egger's test was performed to assess the potential publication bias. A two-tailed P value <0.05 was regarded as statistically significant. was deemed statistically significant.

**Results**

**Identification of relevant studies**

A total of 917 articles were identified from the databases searched. A total of 26 articles were identified for analysis. Figure 1 shows the details of the literature search and study selection process. The enrolled 26 studies containing a total of 883 patients with diagnosed neuroblastoma, provided relevant outcomes that met the inclusion criteria in this meta-analysis. The majority of these studies did not
have a control group. These clinical trials were studies conducted in UK, USA, Italy, Thailand, Japan and Netherlands. All studies included showed low levels of bias. More details of the studies included was shown in Table 1.

**Efficacy of $^{131}$I-MIBG treatment**

The numbers of articles included in the analysis of rates of objective response, SD, PD and MR were 17, 14, 13 and 8, respectively. The objective response rates ranged from 30.0% to 71.0%. The overall objective response was 39% (95% CI: 32%-47%) as calculated utilized the random-effects model (Figure 2). The pooled rates of SD, PD and MR were 31% (95% CI: 24%, 37%), 22% (95% CI: 15%, 30%) and 15% (95% CI: 3%, 31%), respectively. 9 studies investigating the efficacy of $^{131}$I-MIBG in combination with chemotherapy were included, the pooled objective response rate was 28% (95% CI: 14%, 44%). Detailed results of the analyses were presented in Figures 3-6. 3 studies reported median event-free survival (EFS) which ranged from 10 to 16 months.

**Heterogeneity and publication bias**

The results of the heterogeneity tests in rates of objective response, SD, PD, MR and $^{131}$I-MIBG in combination with chemotherapy groups were as follows respectively: $I^2 = 72.0\%, p < 0.01; I^2 = 57.0\%, p < 0.01; I^2 = 73.0\%, p < 0.01; I^2 = 91.0\%, p < 0.01$ and $I^2 = 77.0\%, p < 0.01$ (see Figures 2-6). Egger's tests for publication bias yielded p values of 0.614, 0.240, 0.834, 0.243 and 0.210 for rates of objective response, SD, PD, MR and $^{131}$I-MIBG in combination with chemotherapy groups, respectively.

**Sensitivity Analysis**

We performed the sensitivity analysis to assess the impacts of each single study on the pooled outcomes. For the analysis of MR, the sensitivity analysis revealed that result from Garaventa's study may have impacts on the outcomes, suggesting that the study was probably to be the main source of heterogeneity. Nevertheless, after excluding single study one after another, the pooled rates of objective response, SD, and PD demonstrated the robustness of the results.

**Discussion**

Neuroblastoma is the most common extracranial solid tumor in children, and is regarded as the most common malignant tumor in infants so far [28]. Treatment outcomes vary significantly among patients with neuroblastoma, as patients with low risk of neuroblastoma fare well with little or no treatment, whereas high-risk children was diagnosed with metastatic disease or have an event-free survival (EFS) of approximately 50% despite multimodality therapeutic schedule that give rise to significant long-term side-effects [29–31]. Iodine-131-metaiodobenzylguanidine ($^{131}$I-MIBG) has been used to treat neuroblastoma with a rapid development in recent decades. The efficacy of $^{131}$I-MIBG therapy remains the most concerned issues. However, the efficacy varied greatly in different investigations. The objective response rates ranged from 30.0–71.0% in studies included in this meta-analysis. The overall objective response was 45% (95% CI: 36%-54%). Besides, the pooled rates of SD, PD and MR were 31% (95% CI: 24%, 39%), 19% (95% CI: 12%, 26%) and 16% (95% CI: 2%, 36%), respectively. Event-free survival (EFS) and toxicity were not evaluated because no sufficient information was provided by the studies included so as to be enrolled for pooled analysis.

In this meta-analysis, we did a detailed literature search in PubMed, Embase and the Cochrane Library databases to enhance the probability of retrieving all relevant studies as we can. Data extraction was conducted by two independent investigators using a well-designed form. Moreover, the heterogeneity in the studies included was assessed. The results of the meta-analysis showed that there were significant heterogeneities in all indicators. The potential reasons may be attributed to differences in inclusion criteria of the study participants, study design, drug compliance, median lines of prior therapy in each study, batch of drug and other relevant factors. Sensitivity analysis revealed that the results of objective response, SD, and PD demonstrated the robustness of the outcomes in this meta-analysis. Furthermore, Egger's tests for publication indicated that no potential publication bias was observed in the studies included. Despite the existences of heterogeneity, the results of this analysis may provide hints and assistance for a profile of clinical trials detecting the efficacy of $^{131}$I-MIBG therapy with larger sample sizes and longer follow-ups.

Our study has provided a comprehensive evaluation of $^{131}$I-MIBG as a treatment modality of refractory neuroblastoma. Currently, the best available evidence on the efficacy is derived from several single-arm phase II clinical trials. Our meta-analysis of these trials has demonstrated that though the overall objective response rate is less than 50% (45%, 95% CI: 36%-54%), the efficacy needs to be improved. More randomized controlled trials to furtherly evaluate the efficacy of $^{131}$I-MIBG in the setting of relapsed or refractory neuroblastoma is strongly recommended.
Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Availability of data and materials
The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

Competing interests
The authors declare that they have no competing interests.

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Author Contributions
HH conceived and designed this study. HH and QX were responsible for the collection, extraction, and analysis of the data. HH and CY was responsible for writing the paper. CY performed the quality evaluation and completed data analysis. HH and CY polished the English language. All authors and participants reviewed the paper and reached an agreement to approve the final manuscript.

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**Tables**

**Table 1** Characteristics and efficacy results of the studies included in the meta-analysis
| Year | Name of First Author | Country | Trial design | Schedule | Response criteria | Patients Enrolled | Tumor response |
|------|----------------------|---------|--------------|----------|------------------|------------------|---------------|
| 1991 | Hutchinson[32]       | NS²     | Single-arm Phase I | Doses ranged from 50-220 mCi, with cumulative doses of 50-654 mCi in one to three doses | NS | 14 | 4 | - | - | 2 |
| 1991 | Klingebiel[33]       | Germany | NS | NS NS NS | 47 | 9 | - | - | - |
| 1991 | Matthy[34]           | NS      | Single-arm Phase I | 100-400 mCi/m²/course | NS | 11 | 2 | 2 | 7 | 0 |
| 1991 | Troncone[35]         | Italy   | Single-arm Phase I | single doses (2.6-9.5 GBq) | NS | 11² | 2 | 4 | 2 | 1 |
| 1992 | Lashford[24]         | UK      | Single-arm Phase I | NS | ENSG Criteria[24] | 25 | 8 | 9 | 7 | - |
| 1994 | Hoefnagel[14]        | Netherlands | Single-arm Phase I | First 200mCi, If necessary, more cycles with100mCi at 4 weeks intervals | NS | 31 | 22 | 8 | - | - |
| 1995 | de Kraker[15]        | Netherlands | Single-arm Phase II | First 200mCi, If necessary, more cycles with100mCi at 4-6 weeks intervals | INRC[36] | 33 | 19 | 11 | 3 | - |
| 1999 | Garaventa[17]        | Italy   | Single-arm Phase II | 67.5-148mCi 1-5 courses | INRC | 43 | 13 | - | 5 | 25 |
| 2005 | Howard[18]           | USA     | Single-arm Phase II | 3-19mCi/kg 2 to 4 courses | INRC | 28 | 11 | 8 | 8 | 1 |
| 2007 | Matthy[19]           | USA     | Single-arm Phase II | 12 or 18mCi/kg | INRC | 164 | 59 | 55 | 44 | 5 |
| 2008 | de Kraker[23]        | Netherlands | Single-arm Phase II | 200 mCi for the first infusion and 100-150 mCi for the second and all subsequent infusions. | INRC | 41² | 27 | 5 | 4 | 4 |
| 2009 | Matthy[20]           | USA     | Single-arm Phase I | Day 0 and day 14, 12-21mCi/kg | RECIST[37] | 20 | 10 | 3 | 7 | 8 |
| 2011 | Johnson[21]          | USA     | Single-arm | 18mCi/kg | INRC | 117 | 35 | 52 | 30 | - |
| Year | Name         | Country | Study Type | Treatment Description                                      | Criteria         | Response Rate | Progression Rate | Total | Duration | Notes |
|------|--------------|---------|------------|------------------------------------------------------------|-----------------|--------------|-----------------|-------|----------|-------|
| 2011 | Mastrangelo[38] | Italy   | Pilot study | 
|      |              |         | Phase II 131I-MIBG combined with chemotherapy              | INRC            | 13           | 6              | -    | -        | 1     |
| 2011 | Polishchuk[22] | USA     | Single-arm Phase II | 17.8 millicuries (mCi)/kg | INRC            | 39           | 18             | 17   | 2        | 2     |
| 2012 | DuBois[39]   | USA     | Single-arm Phase I | 131I-MIBG combined with chemotherapy | NANT Response Criteria[39] | 24           | 6              | -    | -        | -     |
| 2013 | Kushner[40]  | USA     | NS        | 131I-MIBG combined with chemotherapy                       | INRC            | 3            | 1              | 2    | 0        | 0     |
| 2015 | DuBois[41]   | USA     | Single-arm Phase I, II | 131I-MIBG combined with chemotherapy | NANT Response Criteria | 32           | 9              | -    | -        | -     |
| 2015 | DuBois[42]   | USA     | Single-arm Phase I | 131I-MIBG combined with chemotherapy                       | NANT Response Criteria | 27           | 7              | -    | -        | -     |
| 2015 | Kraal[43]    | Netherlands | Single-arm Phase II | 131I-MIBG combined with chemotherapy                       | INRC            | 16           | 9              | -    | -        | -     |
| 2015 | Yanik[44]    | USA     | Single-arm Phase II | 131I-MIBG combined with chemotherapy                       | INRC            | 49           | 7              | 26   | 6        | 10    |
| 2016 | George[45]   | UK      | NS        | 131I-MIBG monotherapy                                      | INRC            | 25           | 15             | 8    | -        | -     |
| 2016 | Modak[46]    | USA     | Single-arm Phase II | 131I-MIBG combined with chemotherapy                       | INRC            | 19           | 0              | -    | 7        | -     |
| 2019 | Genolla[47]  | Spain   | NS        | 131I-MIBG combined with chemotherapy                       | INRC, RECIST    | 10           | 7              | 2    | 1        | 0     |
| 2020 | Anongpornjossakul[48] | Thailand | NS    | mean dose of 136 mCi per treatment                        | RECIST 1.1[49]  | 22           | 7              | 3    | 12       | 0     |
| 2020 | Kayano[50]   | Japan   | NS        | single dose of 444 to 666 MBq/kg                         | RECIST 1.1      | 19⁴         | 5              | 10   | 3        | 0     |

a: 2 patients were not evaluable. b: 1 patient was not evaluable. NS: Not specified. RECIST, Response Evaluation Criteria in Solid Tumors.

INRC, the International Neuroblastoma Response Criteria. NANT, the New Approaches to Neuroblastoma Therapy. ENSG, European Neuroblastoma Study Group

**Figures**
Figure 1

Flow diagram of study selection process
### Figure 2

Forest plot of overall objective response rates in studies included.
### Figure 3

Forest plot of overall stable disease rates in studies included.
Figure 4

Forest plot of overall progressive disease rates in studies included.
Figure 5

Forest plot of overall minor response rates in studies included.
### Figure 6

Forest plot of overall objective response rates of 131I-MIBG in combination with chemotherapy in studies included.

| Study          | Events | Total | Proportion | 95%-CI  | Weight (fixed) | Weight (random) |
|----------------|--------|-------|------------|---------|----------------|-----------------|
| Mastrangelo2011 | 6      | 13    | 0.46       | [0.19; 0.75] | 6.8%           | 10.5%           |
| DuBois2012     | 6      | 24    | 0.25       | [0.10; 0.47] | 12.4%          | 12.3%           |
| Kushner2013    | 1      | 3     | 0.33       | [0.01; 0.91] | 1.8%           | 5.5%            |
| DuBois2015     | 9      | 32    | 0.28       | [0.14; 0.47] | 16.5%          | 12.9%           |
| DuBois2015     | 7      | 27    | 0.26       | [0.11; 0.46] | 13.9%          | 12.6%           |
| Kraai2015      | 9      | 16    | 0.56       | [0.30; 0.80] | 8.4%           | 11.2%           |
| Yanik2015      | 7      | 49    | 0.14       | [0.06; 0.27] | 25.1%          | 13.7%           |
| Modak2016      | 0      | 19    | 0.00       | [0.00; 0.18] | 9.9%           | 11.7%           |
| Genolla2016    | 7      | 10    | 0.70       | [0.35; 0.95] | 5.3%           | 9.7%            |

**Fixed effect model**
- Total: 193
- Proportion: 0.24 [0.17; 0.31] (100.0%)

**Random effects model**
- Proportion: 0.28 [0.14; 0.44] (100.0%)

Heterogeneity: $I^2 = 77\%$, $Q^2 = 0.0399$, $p < 0.01$