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Revisiting the role of radiotherapy in the treatment of neuroblastoma 4S: 30 years of institutional experience and systematic review

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ABSTRACT

Background and purpose: Neuroblastoma 4S is a rare subtype of metastatic neuroblastoma found in children younger than 12 months, characterized by liver, skin, or bone marrow metastases. While the prognosis for patients is generally favorable, rapid progression of liver metastases can lead to life-threatening organ insufficiency. In such cases, immediate treatment with chemotherapy or radiotherapy is necessary. Given the recent decline in radiotherapy utilization, this study aims to reassess its role, evaluating its effectiveness and toxicity.
Materials and methods: We conducted a systematic review and an institutional retrospective analysis to assess the use of radiotherapy for hepatomegaly in patients with neuroblastoma 4S. The study included data from 164 patients from the literature and 16 patients from our institutional cohort. We extracted and analyzed data on short- and long-term outcomes, as well as reports of radiotherapy-induced toxicity.
Results: Our institutional data showed that 81 % of patients responded to low-dose radiotherapy administered at a median dose of 450 cGy in three fractions, resulting in liver shrinkage and symptom resolution. Based on the systematic review, 1-year survival rate was 80 %, while 5-year survival rate was 75 %. No serious toxicity was observed with the current low-dose radiotherapy; however, one case of induced secondary malignancy was reported.
Conclusion: Radiation therapy is an effective treatment modality for hepatomegaly in patients with neuroblastoma 4S, with a success rate of about 80 %. Despite being administered to infants, a low dose of 450–600 cGy does not result in toxicity related to the kidneys, liver, or posture defects.

1. Introduction

1.1. Background

Neuroblastoma is the most common malignant extra-cranial tumor in children. It originates from neural crest cells in the peripheral sympathetic nervous system, and is often diagnosed at an advanced stage, with the metastatic disease being present in more than half of patients at diagnosis [1]. The metastatic disease is classified as stage 4 in the International Neuroblastoma Staging System (INSS) or stage M in the International Neuroblastoma Risk Group (INRG) staging system. A subtype of metastatic neuroblastoma, stage 4S or MS, is characterized by metastases present only in the liver, skin, or bone marrow in children under 12 months of age (INSS) or 18 months of age (INRG) [2]. Neuroblastoma may be present at birth; however, the average age at diagnosis for neuroblastoma 4S is 2 or 3 months [1].

Despite the advanced stage of the disease, the prognosis for patients with stage 4S is generally good, with a high rate of spontaneous maturation and regression without treatment in about 50 % of cases [3,4]. In some cases, a rapid progression of liver metastases can lead to life-threatening compression of the liver, kidneys, lungs, inferior vena cava, or gastrointestinal tract, requiring immediate treatment with chemotherapy or radiotherapy [5]. Although both chemotherapy and radiotherapy are highly effective treatment options for neuroblastoma

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4S, there has been a tendency to avoid using radiotherapy in recent years [1,6]. This is due to concerns about late side effects such as radiation nephritis, hepatic fibrosis, secondary cancers, or scoliosis [1,6,7]. The last report from Children's Oncology Group Study ANBL0531 recommends that immediate emergent chemotherapy should be considered in children under 2 months with increasing liver size, especially when organ dysfunction appears (e.g., gastrointestinal dysfunction, respiratory compromise, impaired venous return, renal dysfunction, hepatic dysfunction). Radiotherapy is allowed for symptomatic hepatomegaly that is unresponsive to chemotherapy, although without dose specification [8].

The effectiveness of radiotherapy in treating neuroblastoma 4S was initially reported in 1941 when two infants with hepatomegaly were successfully treated with irradiation [9]. Originally, the doses were not standardized, varying from 500 rad to over 4000 rad [10,11]. However, over the years, there has been a gradual unification and reduction of doses, as neuroblastoma is a radiosensitive tumor. The current standard involves liver irradiation in fractions of 150 cGy, providing reasonable control of the disease with a total dose of 450–600 cGy [7,12]. Although radiotherapy may be an effective option for patients with hepatomegaly who do not respond to initial therapy, some pediatric oncology centers avoid its use, citing concerns about its ineffectiveness and potential toxicity [7,13,14].

1.2. Aim of the study

This study aims to summarize current knowledge on the use of radiotherapy in the treatment of hepatomegaly in patients with neuroblastoma 4S, and to find a current role of radiotherapy in multimodality neuroblastoma 4S treatment. To achieve this goal, we review our institutional experience and conduct a systematic review of the use of radiotherapy in the treatment of liver metastases in patients with neuroblastoma 4S. We want to answer two research questions:

RQ1: What are the short- and long-term outcomes of radiotherapy?
RQ2: What is the toxicity connected to radiotherapy?

2. Materials and methods

2.1. Literature review

We conducted a systematic review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [15] to assess the role of radiotherapy in treating liver metastases in children with neuroblastoma 4S. Our inclusion criteria were as follows:

- Original studies investigating the impact of irradiation on hepatomegaly in patients with neuroblastoma 4S.
- Studies allowing for the extraction of individual data concerning the effectiveness or toxicity of irradiation.
- A minimum follow-up period of 6 months.

We included articles in all languages, and for publications in languages other than English, German, or Polish, we conducted translations to English.

To identify eligible studies, we comprehensively searched Scopus, Web of Science, and PubMed databases up to June 30, 2023. The search was conducted by two independent researchers (DW and MC) using the following query: ("neuroblastoma" AND ["4S" OR "IVS" OR "IV-S" OR "MS"] AND ["radiotherapy" OR "radiation" OR "irradiation"]). We also reviewed the references in the analyzed papers, and the search yielded 108 articles from PubMed, 147 from Web of Science, and 93 from Scopus.

After removing duplicates, 249 articles were identified for further analysis. These papers underwent a two-stage screening process, initially based on evaluating titles and abstracts. This screening yielded 102 articles that underwent full-text examination, and among these, 70 articles were excluded because they did not meet the predefined inclusion criteria. After the screening process, we included 32 publications in the final analysis. We resolved discrepancies during the screening process through consensus among the reviewing team. A visual representation of the search process is presented in Fig. 1, illustrating the flow of articles selection.

2.2. Institutional experience

We conducted a retrospective analysis using the patient database at the Maria Sklodowska-Curie National Research Institute of Oncology in Warsaw to identify individuals diagnosed with neuroblastoma 4S, who underwent radiotherapy between 1994 and 2023. To gather information on patient outcomes and follow-up, we collaborated with pediatric oncology departments responsible for monitoring patients after treatment.

The treatment paradigm in our department can be divided into two periods: before the year 2000 when patients received irradiation using the Co-60 two-dimensional technique, and later when we shifted to three-dimensional conformal radiation therapy on linear accelerators. Currently, our standard irradiation technique is three-dimensional adaptive conformal radiotherapy with daily cone-beam computer tomography (CBCT). We utilize 2.5 mm CT slices for contouring the clinical target volume (CTV) and organs at risk (OARs). The CTV encompasses the entire liver, while the OARs include the lungs, heart, and kidneys. We do not contour the intestines, pancreas, and stomach, as these organs are typically compressed by an enlarged liver and are not clearly distinguishable on CT scans. Table 1 presents the dose parameters of a sample treatment plan generated in accordance with our current protocol. Additionally, during the treatment, we regularly measure the circumference of the abdomen to assess the response to irradiation. This method provides a simple way to estimate the decrease in liver volume.

The daily CBCT allows us to monitor the tumor's response. In cases where the liver undergoes shrinkage during treatment, we prepare a

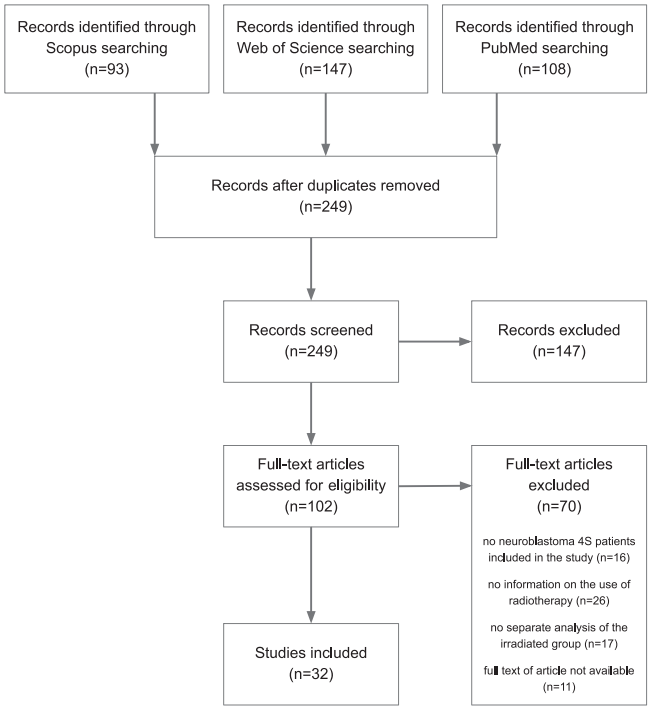

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

Table 1
Dose parameters in patients treated with a modern VMAT plan.

Structure	Parameter	Dose
PTV	D_{min} [cGy]	392.8
	D_{max} [cGy]	474.1
	D_{mean} [cGy]	450.0
Lungs	D_{mean} [cGy]	303.0
Left kidney	D_{mean} [cGy]	443.4
Right kidney	D_{mean} [cGy]	449.2
Heart	D_{mean} [cGy]	362.7
Intestines	D_{max} [cGy]	474.1
	D_{mean} [cGy]	305.6

new adaptive treatment plan to reduce the toxicity of radiotherapy. Our treatment protocol typically involves three fractions of 150 cGy, administered every other day. In situations where the initial response is unsatisfactory, we consider administering one or two additional fractions. Throughout the treatment process, we work closely with our team of anesthesiologists, as the patients are infants in life-threatening condition.

2.3. Treatment outcomes and side effects

We comprehensively analyzed outcomes and side effects by utilizing current literature and our institutional data. In the review of articles, we extracted pertinent information regarding the study population, survival rates, and side effects. Survival analysis was performed based on studies that reported survival after treatment in more than two patients (excluding case reports). To provide a detailed description of potential toxicity, irrespective of their frequency, we incorporated all articles, including case reports. In all cases, we aimed to gather as much individual patient data as possible. Initially, we sought individual data provided in tables, and if unavailable, we searched for it within the text. For survival analysis, we exclusively utilized data from populations for which such information was obtainable.

In our institutional evaluation, we assessed the response of tumor in both the short and long term. Early response was determined by monitoring reductions in liver volume as well as the resolution of symptoms associated with organ failure. For long-term response evaluation, we assessed the remission of the disease. Additionally, we meticulously analyzed medical documentation and radiological scan reports to identify and evaluate late toxicity.

All statistical analyses were performed using the R Statistical Software (version 4.2.1; R Foundation for Statistical Computing, Vienna, Austria). Kaplan-Meier survival analysis was employed to estimate overall survival (OS). The follow-up period was defined as the duration between the completion of radiotherapy and the occurrence of death or the last follow-up.

3. Results

3.1. Patient characteristics

A total of 164 patients with neuroblastoma 4S described in the literature were included in the analysis based on 32 published papers spanning the period from 1941 to 2022, as presented in Table 2. The median age at diagnosis was 2 months, although some authors partially reported this information. Among the patients, 52 out of 164 (32 %) received radiotherapy alone as a treatment for liver metastases, while in 112 patients (68 %), additional chemotherapy was administered in conjunction with radiotherapy.

Our institutional cohort consisted of 16 patients with neuroblastoma 4S treated in our radiotherapy department between 1994 and 2023 for liver metastases, as presented in Table 3. The median age at diagnosis in this group was 2 months, ranging from 6 days to 9 months. The cohort comprised seven females and nine males, and the primary tumor site was the adrenal glands in eight patients and the paraspinal location in four. The primary site could not be determined in four cases. Three patients also had metastases in the skin and five in the bone marrow. The most used fractionation scheme involved delivering a total dose of 450 cGy in three fractions of 150 cGy. However, one patient received a total dose of 750 cGy in five fractions, two patients received a total dose of 600 cGy in four fractions, one patient received a total dose of 400 cGy in four fractions, one patient received 300 cGy in two fractions, and one patient received a total dose of 150 cGy in a single fraction.

3.2. Short-term outcomes

Among the patients in our cohort, 81 % (13 out of 16) exhibited a positive response to radiation therapy, leading to liver shrinkage either during the treatment or shortly after that. Patients who responded to radiotherapy survived for at least 6 months following treatment, and no instances of tumor progression in the liver were recorded during the follow-up period. Three patients who did not respond died shortly after therapy due to disease progression and subsequent cardiopulmonary insufficiency.

Articles included in the systematic review did not provide precise information on the rate of decrease in liver volume during radiotherapy. However, we estimated the 3-month, 6-month, and 12-month survival rates, which are strongly associated with the response to the initial treatment. Fig. 2 presents a Kaplan-Meier curve illustrating the survival of irradiated children reported in the literature. The survival rate at 3 months was 87 %, 81 % at 6 months, and 80 % at 1 year.

We also estimated the efficacy of radiotherapy as a first-line treatment modality. In our institution, seven of nine (78 %) patients responded with a reduction in liver size and symptoms after radiotherapy alone, without prior chemotherapy. We also identified patients described in the literature who received radiotherapy as a first-line treatment, and among them, 40 of 59 (68 %) responded to the treatment.

3.3. Long-term outcomes

Among patients who survived after the initial treatment, the risk of disease progression or relapse was the most important factor affecting survival. In our cohort, three out of 13 patients (23 %) who responded to the initial liver irradiation with chemotherapy experienced disease progression during the first year after the treatment. Two of them were still alive at the end of the observation period; however, one died 7 months after radiation therapy. Previous literature only reported progression as a cause of death without information on the cured cases. Among patients who survived at least 3 months from the initial treatment, progression was described as the cause of death in seven out of 144 patients (5 %). In the systematic review, the 5-year survival rate was reported as 75 %, with a median follow-up of 3 years.

3.4. Toxicity

In our cohort, no early or late toxicity clearly related to radiotherapy was observed. However, one patient developed right kidney insufficiency due to renal vein thrombosis, although this toxicity occurred after surgery during the progression of the disease. Additionally, two patients with massive liver metastases, treated with chemotherapy and radiotherapy, developed liver insufficiency with esophageal varices. Among the analyzed papers, late toxicity associated with radiotherapy was reported in 13 studies [5,11,16–26].

Cases of liver or renal insufficiency after liver irradiation in patients with neuroblastoma 4S were described by Evans et al. [16], Stokes et al. [18], and Blatt et al. [11], who published their results in the 1970 s and 1980 s and used much higher doses than the current standards. For instance, they correspondingly used median doses of 2000 rad, 2493 rad, and 3300 rad in affected patients. Additionally, without providing information on the radiation dose, Hsu et al. [5] reported one patient

Table 2
Studies included in the systematic review.

Study	Number of patients treated with radiotherapy	Number of patients with additional chemotherapy	Age of patients (median)	Radiation dose	Treatment effects	Side effects	Cause of death
Wyatt and Farber (1941)[9]	2	0	2 months	1570 rad in 3 weeks	2 of 2 patients (100 %) survived for 2 years or longer	Not reported	All patients survived
Wittenborg (1950) [24]	6	0	4 months	Not specified	6 of 6 patients (100 %) survived for 3 years or longer	Not observed	All patients survived
D'Angio et al. (1971)[39]	11	9	4 months	Not specified	9 of 11 patients (82 %) survived for two years or longer	Not reported	• Pneumonia at the time of leucopenia after chemotherapy – 2 patients (after 2 and 5 months)
Bond (1976) [10]	2	1	2 months	500 rad in 10 fractions	1 of 2 patients (50 %) survived for 4 years or longer	Not reported	• Recurrent in liver and abdomen, which did not respond to treatment – 1 patient (after 2 years)
Grosfeld et al. (1978) [40]	7	2	5 months	600 – 2100 rad (median 1200 rad)	6 of 7 patients (86 %) survived for 3 years or longer	Not reported	• Respiratory insufficiency or septicemia – 2 patients (time not reported)
Evans et al. (1980) [16]	5	1	3 months	200 rad in 1 fraction – 2000 rad in 2 weeks	2 of 5 patients (40 %) survived for two years or longer	Not reported	• Respiratory failure – 1 patient (after 1 day) • Hemoperitoneum – 1 patient (after 7 weeks) • Radiation nephropathy – 1 patient (after 5 months)
Peschel et al. (1981) [17]	3	0	4 months	1225 rad in 13 days 1400 rad in 18 days 1240 rad in 15 days	3 of 3 patients (100 %) survived for two years or longer	There was no evidence of acute radiation nephritis, hepatitis, or enteritis. Two patients had slightly decreased GFR after 2 years.	All patients survived
Stokes et al. (1984) [18]	10	6	3 months	1525 – 3538 rad (median 2493 rad)	9 of 10 patients (90 %) survived for six years or longer	Four patients have experienced mild asymptomatic scoliosis or kyphoscoliosis at 3 to 12 years after therapy (all of them received orthovoltage irradiation). One patient developed hepatic dysfunction with secondary portal hypertension. One patient was at the 10th percentile of height.	• Widespread progressive disease – 1 patient (after 33 months)
Mancini et al. (1984) [41]	6	5	2 months	150 cGy 400 cGy 450 cGy 500 cGy 1200 cGy in two patients	5 of 6 patients (83 %) survived for 6 months or longer	Not reported	• DIC – 1 patient (after 20 days)
Jereb et al. (1984) [42]	4	3	3 months	400 rad in 7 days 1000 rad in 2 weeks 1300 rad in 2 weeks 1800 rad in 2 weeks	3 of 4 patients (75 %) survived for 16 months or longer	Not reported	• Pneumonia after vomiting and aspiration while receiving chemotherapy – 1 patient (after 5 months)
Blatt et al. (1987) [11]	7	2	2 months	200 – 4156 rad (median 600 rad)	5 of 7 patients (71 %) survived for six months or longer	One patient developed chondromas in multiple ribs and hypoplasia of the muscles and bones of the right pelvis and chest. One patient developed radiation nephritis and hepatic fibrosis.	• Nephritis – 1 patient (after 5 months) • Progressive hepatomegaly, bone involvement – 1 patient (after 7 months)
Wilson et al. (1991) [29]	5	4	2 months	400 – 1500 cGy	4 of 5 patients (80 %) survived for 3.5 years or longer	Not reported	• Late disease progression – 1 patient (time not reported)

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Table 2 (*continued*)

Study	Number of patients treated with radiotherapy	Number of patients with additional chemotherapy	Age of patients (median)	Radiation dose	Treatment effects	Side effects	Cause of death
Suita et al. (1995) [30]	3	3	1 month	Not specified	2 of 3 patients (67 %) survived for 4 years or longer	Not reported	• Progressive disease – 1 patient (after 1.5 years)
Hsu et al. (1996) [5]	10	3	Not reported	300 – 1000 cGy in years 1967 – 1994 Not specified in years 1944-1966	4 of 10 patients (40 %) survived for two years or longer	Not reported	• Hemoperitoneum – 2 patients (after 1 day and 8 weeks) • Intraventricular hemorrhage, liver failure – 1 patient (after 3.5 months) • IVC compression – 1 patient (after 3 weeks) • Sepsis, DIC – 1 patient (after 3 weeks) • Radiation nephropathy, pulmonary edema – 1 patient (after 5 months)
Katzenstein et al. (1998) [28]	7	7	Not reported	550 – 600 cGy	5 of 7 patients (71 %) survived for three years or longer	Not reported	• Hepatomegaly/ respiratory failure – 1 patient (after 1 month) • Relapse, sepsis – 1 patient (after 13 months)
McGahren et al. (1998) [25]	1	1	17 days	600 cGy in 4 fractions	1 of 1 patient (100 %) survived for 2 years	Not observed	All patients survived
Nickerson et al. (2000) [7]	23	22	Not reported	18 patients received 450 cGy in 3 fractions 1 patient received 600 cGy 1 patient received 240 cGy 3 patients not specified	17 of 23 patients (74 %) survived for five years or longer	Not reported	• Progression, respiratory failure – 1 patient (after 6 weeks) • Liver failure – 1 patient (after 19 weeks) • Aspiration into tracheotomy – 1 patient (after 14 weeks) • Progression – 2 patients (after 2 days and 3 weeks) • Progression, hemorrhage – 1 patient (after 6 weeks)
Halperin (2000) [26]	2	2	2 weeks	300 cGy in 2 fractions 750 cGy in 5 fractions	1 of 2 patients (50 %) survived for 3 years or longer	Not observed	• Progression – 1 patient (after 2 months)
Schleiermacher et al. (2003) [1]	17	15	Not reported	450 cGy in 3 fractions	13 of 17 patients (76 %) survived for three years or longer	Not reported	• Relapse – 1 patient (after 8 months) • Progressive disease – 3 patients (time not reported)
Levitt et al. (2004) [19]	4	1	Not reported	308 – 600 cGy (median 450 cGy)	4 of 4 patients (100 %) survived for 3 years or longer	One patient developed induced right hypochondrial hypoplasia	All patients survived
Kerdudo et al. (2004) [43]	2	2	3 months	450 cGy in 3 fractions	2 of 2 patients (100 %) survived for 6 years or longer	Not reported	All patients survived
Boztug et al. (2006) [20]	1	1	1 month	450 cGy in 3 fractions	1 of 1 patient (100 %) survived for 3 years	One patient had a calcified mass at the site of the primary tumor	All patients survived
Kushner et al. (2006) [44]	2	1	0 months	400 – 450 cGy	2 of 2 patients (100 %) survived for 4 years or longer	Not reported	All patients survived
Pagès et al. (2009) [45]	2	2	5 months	Not specified	2 of 2 patients (100 %) survived for 10 ten years or longer	One patient developed adrenal failure after a partial bilateral adrenalectomy.	All patients survived
French et al. (2012) [21]	8	8	Not reported	500 cGy in 5 fractions – 1500	8 of 8 patients (100 %)	Five patients developed liver imaging changes (one	All patients survived

(*continued on next page*)

Table 2 (*continued*)

Study	Number of patients treated with radiotherapy	Number of patients with additional chemotherapy	Age of patients (median)	Radiation dose	Treatment effects	Side effects	Cause of death
				cGy in 15 fractions (median 500 cGy in 5 fractions)	survived for 5 years or longer	clinically significant liver cirrhosis (uBili 21, ALT 43, AST 40), three coarsened liver parenchyma on ultrasound, one focal nodular hyperplasia)	
Yang et al. (2012) [22]	1	1	2 months	Not specified	1 of 1 patient (100 %) survived for 15 years	After 15 years, the patient developed clear cell sarcoma of the gastrointestinal tract.	All patients survived
Steele et al. (2013) [46]	1	1	1 day	800 cGy in 5 fractions	1 of 1 patient (100 %) survived for 1 year	Liver cirrhosis and portal hypertension on day 40 of life – need a liver transplant.	All patients survived
Muftakhova et al. (2015) [34]	4	4	2 months	450–600 cGy in 3–4 fractions	3 of 4 patients (75 %) survived for 1 year or longer	Not reported	• No response to treatment – 1 patient (after 1 month)
Doré et al. (2015) [23]	1	0	12 days	600 cGy in 4 fractions	1 of 1 patient (100 %) survived for 1 year	Not observed	All patients survived
Langenberg-Ververgaert et al. (2019) [33]	1	1	36 weeks	450 cGy in 2 fractions	1 of 1 patient (100 %) survived for 1 year	At 20 months of age, the patient developed a recurrence in the right adrenal region.	All patients survived
Tas et al. (2020) [12]	6	5	4 months	Not specified	5 of 6 patients (83 %) survived for 13 years or longer	Not reported	• Progressive disease – 1 patient (after 22 months)
Montalto et al. (2022) [47]	1	0	18 days	Not specified	1 of 1 patient (100 %) survived for 21 years	Not reported	All patients survived

treated in 1954 at the age of 18 weeks who died because of radiation nephropathy and pulmonary edema 5 months after treatment. Peschel et al. [17] analyzed the glomerular filtration rate (GFR) after treatment and found two patients with slightly decreased GFR 2 years after treatment. However, it is crucial to consider that they also used a higher dose of 1240 or 1400 rad in those patients. Authors using current standard lower total doses of 450–600 cGy did not report severe kidney or liver toxicity. French et al. [21] analyzed eight patients after liver irradiation and found that five developed liver imaging changes, such as coarsened liver parenchyma on ultrasound or focal nodular hyperplasia. However, only one patient showed clinically significant liver fibrosis or cirrhosis with slightly increased bilirubin, AST, and ALT.

The second group of potential toxicities includes scoliosis and secondary neoplasms. Stokes et al. [18] described four patients with mild asymptomatic scoliosis or kyphoscoliosis and one patient with a height in the 10th percentile. It is essential to note that they used orthovoltage irradiation with a high median dose of 2493 rad. Blatt et al. [11] described hypoplasia of the muscles and bones of the right pelvis and chest after a total dose of 4156 rad. Using the current low dose, only Levitt et al. [19] reported right hypoplasia after irradiation. Two authors described secondary tumors. Blatt et al. [11] described chondromas in multiple ribs, which occurred after a high dose of 4156 rad. As a more contemporary finding, Yang et al. [22] presented a case of a patient treated with 450 cGy, who developed clear cell sarcoma of the gastrointestinal tract after 15 years.

4. Discussion

4.1. Effectiveness

Our systematic review provides compelling evidence for the high effectiveness of radiotherapy as a crucial component of a multimodal treatment approach in patients with neuroblastoma 4S. The overall 1-year survival rate in the analyzed studies was remarkable, with an average of 80 %. Our institution also demonstrated consistent results, with a 1-year survival rate of 81 %. Considering that this patient population often includes critically ill individuals who have not responded favorably to initial-line chemotherapy, their prognosis at the beginning of irradiation is worse than average [14]. Within our literature subanalysis, focusing on using radiotherapy as a standalone treatment modality, we found that hepatomegaly resolved in 68 % of cases. The authors reported effectiveness from 20 % to 100 % [1,17–19,24]. Encouragingly, the results observed in our institution were slightly more favorable, with radiotherapy alone achieving hepatomegaly resolution in 78 % of cases.

The efficacy of chemotherapy alone in patients with abdominal compartment syndrome also displays considerable variability in the literature, ranging from 40 % to 100 % [6,13,27]. These discrepancies could be attributed to differences in the treatment inclusion criteria employed by various treatment centers. It is important to note that neuroblastoma 4S can resolve spontaneously without any treatment in approximately 50 % of cases [1]. The first recommendations regarding the criteria for the implementation of therapy were published by Hsu et al. in 1996 [5]; nevertheless, it is still a topic of research today [8,12]. Consequently, the overtreatment of patients with more favorable prognoses may lead to overestimating the treatment outcomes reported in certain studies.

In current clinical practice, chemotherapy is generally recommended as the first-line treatment for symptomatic hepatomegaly in neuroblastoma 4S [1,6,8]. However, beyond its effectiveness in treating hepatomegaly, chemotherapy also offers systemic effects on the primary tumor and potential metastases in the skin and bone marrow [8]. Furthermore,

Table 3
Description of institutional patients.

Case number	Year	Sex	Age at radiotherapy	Primary site	Distant disease	Radiotherapy	Response to radiotherapy	Chemotherapy	Progression	Survival after radiotherapy	Toxicity	Cause of death
1	1994	M	20 weeks	left adrenal gland	liver	Co-60, 450 cGy (3 fractions)	liver shrinkage	–	–	29 years of observation	unknown	–
2	1995	F	19 weeks	unknown	liver	Co-60, 450 cGy (3 fractions)	liver shrinkage	–	–	28 years of observation	unknown	–
3	1995	M	20 weeks	both adrenal glands	skin, liver, marrow	Co-60, 450 cGy (3 fractions)	liver shrinkage	VCR + CTX before radiotherapy, without effect	Progression – time not specified	7 months	unknown	progression
4	1996	M	5 weeks	not found	skin, liver	Co-60, 400 cGy (4 fractions)	liver shrinkage	–	–	28 years of observation	unknown	–
5	1997	F	8 weeks	left adrenal gland	liver	Co-60, 450 cGy (3 fractions)	no treatment effect	–	–	7 days	–	cardiorespiratory failure
6	1997	M	8 weeks	not found	liver, marrow	Co-60, 450 cGy (3 fractions)	liver shrinkage	–	–	12 years of observation	–	–
7	2000	M	7 weeks	not found	liver	4 MV, 150 cGy (1 fraction)	no treatment effect	chemotherapy – not specified	–	0 days	–	cardiorespiratory failure
8	2001	M	14 weeks	right adrenal gland	liver	4 MV, 450 cGy (3 fractions)	slight liver shrinkage	–	lost from observation			
9	2003	F	14 weeks	paraspinal in chest	skin, liver	4 MV, 600 cGy (4 fractions)	liver shrinkage	–	–	20 years of observation	unknown	–
10	2006	M	1 week	left adrenal gland	liver	6 MV, 450 cGy (3 fractions)	liver shrinkage	–	–	16 years of observation	–	–
11	2006	M	1 week	right adrenal gland	liver	4 MV, 450 cGy (3 fractions)	no treatment effect	CTX + ADH after radiotherapy	–	2 months	–	cardiorespiratory failure
12	2011	F	39 weeks	left adrenal gland	liver	6 MV, 600 cGy (4 fractions)	liver shrinkage	COJEC chemotherapy, without effect	Progression after 1 year	12 years of observation	–	–
13	2011	F	7 weeks	paraspinal Th	liver, marrow	6 MV, 450 cGy (3 fractions)	liver shrinkage	CTX without effect before radiotherapy	–	10 years of observation	–	–
14	2019	M	4 weeks	left adrenal gland	liver, marrow	6 MV, 750 cGy (5 fractions)	liver shrinkage	CTX + VCR before radiotherapy VP/Carbo after radiotherapy	–	4 years of observation	Liver insufficiency, ascites, esophageal varices	septic shock
15	2021	F	0 weeks	paraspinal Th4-Th10	liver, marrow	6 MV, 300 cGy (2 fractions)	liver shrinkage	CTX + VCR before radiotherapy VP/Carbo after radiotherapy	–	2 years of observation	Liver insufficiency, liver fibrosis, veno-occlusive disease, splenomegaly, hypersplenism, esophageal varices	–
16	2022	F	13 weeks	paraspinal Th10-L2	liver	6 MV, 450 cGy (3 fractions)	liver shrinkage	COJEC chemotherapy, before radiotherapy	Progression after 1 year	1 year of observation	Right kidney insufficiency – renal vein thrombosis after surgery	–

VCR – vincristine.
CTX – cyclophosphamide.
ADH – N-cadherin blocking peptide ADH-1.
VP – etoposide.
Carbo – carboplatin COJEC – vincristine, carboplatin, and etoposid.

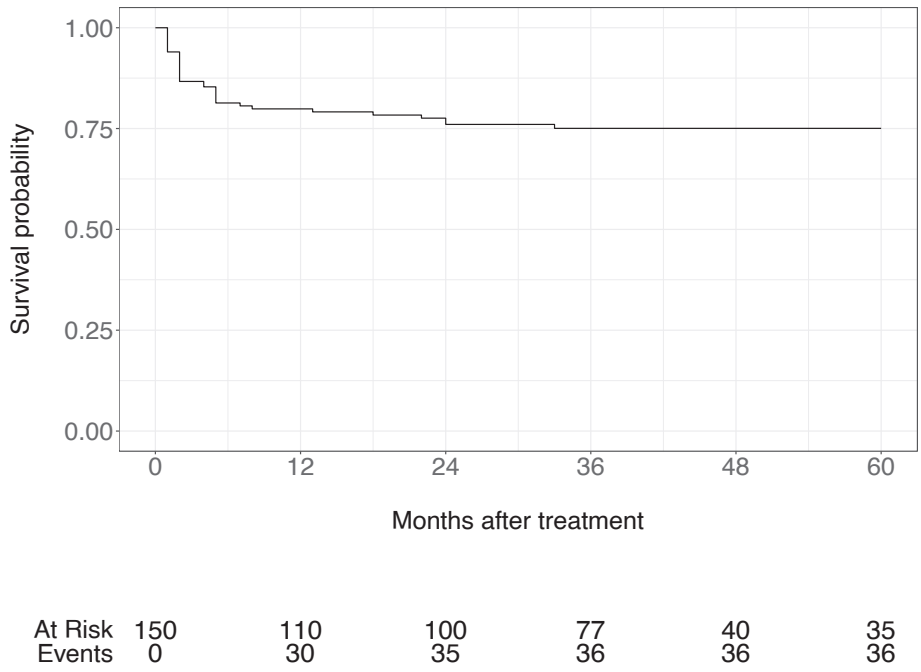

Fig. 2. Overall survival of patients presented in the systematic review.

chemotherapy can be promptly administered in life-threatening cases of abdominal compartment syndrome without prior preparation or treatment planning required for radiotherapy. However, non-responsiveness to chemotherapy is significantly associated with mortality [14], necessitating preparedness for second-line treatment options. In such cases, radiotherapy appears to be a promising treatment option. However, other potential approaches include second-line chemotherapy or the surgical creation of a ventral hernia [25].

While the initial risk of death in patients with neuroblastoma 4S is primarily linked to worsening hepatomegaly and subsequent organ failure, a successful initial treatment shifts the leading causes of mortality toward disease relapse or progression. For instance, our institutional analysis revealed that three patients (23 %) experienced disease relapse after successful initial treatment, and two of them survived. Within the systematic review, 5 % of patients died due to disease progression or relapse despite their initial response to treatment. The quality of data provided by the authors of the included papers in the systematic review did not allow for sub-analyses of patients treated solely with radiotherapy. However, it is noteworthy that the most significant risk of disease progression occurs within the first year after the initial treatment, which aligns with the findings from our institutional analysis [1,11,18,26,28–30].

4.2. Safety

Toxicity is a concern regarding the use of radiotherapy in patients with neuroblastoma 4S [7]. Notably, these patients are typically under 12 or 18 months of age, with those under 2 months having the worst prognosis and most often requiring treatment for life-threatening hepatomegaly [8,14]. This is generally the age at which radiotherapy is rarely used in all diagnoses due to the potential for severe late adverse effects [31]. In neuroblastoma 4S, early reports documented a high incidence of early and late side effects. Kidney and liver toxicity as well as scoliosis and second cancers were the major concerns. For instance, the early literature describes three cases of fatal nephropathy [5,11,16] and one of liver dysfunction [18]. Multiple cases of scoliosis [18,19] and one case of radiation-induced chondromas [11] were also reported. It is important to note that these complications were associated with different methods than those used today. In those early years, orthovoltage irradiation with AP-PA field orientation was the primary treatment [32]. Furthermore, the total doses used in patients with documented late side effects were much higher than those used today, ranging from 2000 rad to over 4000 rad.

In current practice, a total dose of 450–600 cGy is considered the standard of care, allowing for effective treatment while minimizing toxicity and completing the treatment within 2 weeks, which is crucial given the life-threatening nature of hepatomegaly [23,33,34]. Our institutional experience supports the effectiveness of such doses without significant early or late toxicity, and this is consistent with findings from previous literature, which reported no severe toxicity following low doses of radiotherapy. There is no information on potential kidney toxicity, although liver disorders have been described [21], which cannot be directly attributed to radiotherapy. This is because extensive liver involvement by metastatic lesions and chemotherapy also carries damage risk. French et al. [21] found no differences in the incidence of hepatic abnormalities in patients treated with radiotherapy compared to those treated with chemotherapy alone. In addition, two large cohorts of neuroblastoma 4S patients with liver involvement showed that approximately 33 % of patients treated with chemotherapy alone had post-treatment liver fibrosis or milder liver disorders [19,35].

Additionally, after low-dose radiotherapy, one case of postural defects has been reported, although this occurred in a patient who also underwent surgery during the course of the disease [19]. Generally, it is well-established that the primary risk factors for scoliosis after neuroblastoma treatment are radiotherapy and surgical procedures. While isolating their individual effects is challenging, studies have indicated that doses lower than 1750 cGy only marginally increase the risk of scoliosis [36]. Additionally, cases of scoliosis have been documented following surgery alone, without additional irradiation [37]. Yang et al. [22] presented a case report of clear cell sarcoma of the gastrointestinal tract that manifested 15 years after treatment, possibly as a secondary tumor. Children are particularly at risk of developing radiation-induced secondary cancers due to the longer life expectancy after treatment [38]. These reports collectively indicate that radiation therapy at a dose of 450–600 cGy is not associated with a high incidence of side effects. However, it is essential to acknowledge that, like any use of ionizing radiation, there is a potential risk of inducing secondary cancers.

4.3. Limitations

The analyzed papers in this study varied in reporting approaches and lacked uniformity in patient data presentation. For instance, some studies focused explicitly on radiotherapy and provided comprehensive case summaries in tabular form. In contrast, others examined radiotherapy in conjunction with chemotherapy and surgery, providing detailed descriptions for select cases of interest. Consequently, it was not always possible to determine whether chemotherapy was administered concurrently with radiotherapy, or if a particular modality was employed due to treatment failure with previous interventions. Despite our efforts to extract as much individual patient data as possible, sometimes the information was not readily available in datasets containing individual patients. In such cases, we had to reconstruct this data from textual descriptions. Although we aimed to utilize only high-quality information for survival analysis, we incorporated data from numerous papers spanning different years, and thus, the quality of the data may vary. Furthermore, the included papers exhibited variations in the duration of follow-up. Some studies only assessed treatment outcomes up to 6 months, while others evaluated late toxicity even after more than 20 years. It is noteworthy that in the 1970 s and 1980 s, higher radiation doses were occasionally utilized. While it is plausible to assume that higher doses may be associated with increased toxicity, it is also possible that higher doses could be more effective. However, our data do not allow us to establish the comparative efficacy of different radiation doses.

4.4. Future directions

In future research, we propose the inclusion of radiotherapy in trial protocols investigating treatment options for patients with neuroblastoma 4S. While some centers currently utilize radiotherapy as a second-line treatment option, others attempt to avoid its use even in critically ill patients who do not respond to chemotherapy. Therefore, it is essential to establish the precise role of radiotherapy in the treatment of neuroblastoma 4S, including indications and timing of its inclusion, to standardize guidelines and provide patients with optimal treatment.

Additionally, experts need to develop standardized operating procedures for pediatric radiotherapy centers conducting hepatic irradiation for patients with neuroblastoma 4S, although due to the relatively low number of cases, it is challenging for each center to gain sufficient experience and independently establish these procedures. This becomes particularly crucial given that abdominal compartment syndrome is a medical emergency that necessitates the prompt implementation of radiotherapy once the pediatric oncologist identifies the patient. Therefore, collaborative efforts in creating standardized protocols will ensure the safe and effective delivery of radiotherapy in these urgent situations. Those protocols should also encompass potential measurements, such as abdominal circumference, enabling the estimation of treatment response and the potential requirement for higher irradiation doses.

5. Conclusions

Radiotherapy is a valuable therapeutic tool in managing symptomatic hepatomegaly in neuroblastoma 4S, offering high efficacy and acceptable toxicity profiles. With appropriate patient selection and adherence to the current standard dose of 450–600 cGy, radiotherapy should be considered an integral part of the treatment strategy for patients not responding to standard approaches. Furthermore, continued research and collaboration among pediatric oncology centers as well as radiotherapy departments are essential for optimizing the use of radiotherapy and improving the outcomes for this vulnerable patient population.

CRediT authorship contribution statement

Dominik Wawrzuta: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. **Marzanna Chojnacka:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Writing – original draft, Writing – review & editing. **Bożenna Dembowska-Bagińska:** Conceptualization, Resources, Validation, Writing – original draft, Writing – review & editing. **Anna Raciborska:** Conceptualization, Resources, Validation, Writing – original draft, Writing – review & editing. **Łukasz Hutnik:** Conceptualization, Resources, Validation, Writing – original draft, Writing – review & editing. **Mariusz Cieślak:** Conceptualization, Resources, Validation, Writing – original draft, Writing – review & editing. **Katarzyna Pędziwiatr:** Conceptualization, Resources, Supervision, Validation, Writing – original draft, Writing – review & editing.

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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