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Outcome of radiotherapy for metastatic neuroblastoma

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ABSTRACT

Background. Neuroblastoma (NB) is a prevalent solid extracranial tumor that primarily affects children. It is the third most common type of cancer in children, following leukemia and brain tumors.

Aim. The study aimed to discuss the clinical outcomes after adjuvant radiotherapy to the primary site in case of metastatic NB after good response to chemotherapy.

Methods. A retrospective clinical-dosimetric study of 25 patients metastatic NB treated with radiotherapy at Baghdad Radiotherapy and Nuclear Medicine Center, at Baghdad Medical City Complex, Baghdad, Iraq. Data collection begin from December 2023 and March 2024. Data were collected retrospectively with review of records. The following variables were studied: sex, age, date of diagnosis, site of primary tumor, site of metastasis, chemotherapy, surgery, RT, RT sites, doses of RT, fractions of RT, recurrence sites, date of relapse and survival outcome for each patient. Follow-up period include look up to metastasis, site of metastasis, recurrence, site of recurrence and survival rates.

Results. In relation to sex, males (14, 56%) were more than females (11, 44%). The mean age of NB cases was 45.64±17.6 months. In NB, suprarenal masses were the most common site of primary in 21 (84%) of patients. The most common site of metastasis of NB was bone marrow in 12 (48). The multi sites of recurrence was the commonest presentation in 48%. The relapse-free survival (RFS) was 22.38 months. 5 out of 25 patients were alive whereas 20 (80%) of cases were dead. The median follow-up time was 6 years, and the OS of NB in this study after optimal treatment was 2.46 years (95%CI= 1.705-3.21) for survivors. The MS was 4.84 years. The OS was 6 yrs for those diagnosed at 2017, 2 yrs for those diagnosed at 2018, 1.5 yrs for those diagnosed at 2019, 1.75 yrs for those diagnosed at 2020, 3 yrs for those diagnosed at 2021 and 1.5 yrs for those diagnosed at 2022. There was a significant difference among doses (Log Rank (Mantel-Cox)= 11.425, p=0.044).

Conclusions. This study is the first study in Iraq that examines the clinical results of radiotherapy on the primary site in cases of metastatic neuroblastoma following induction chemotherapy. The suprarenal masses of neuroblastoma are the most often occurring main site. The primary sites of metastases for neuroblastoma (NB) are the bone marrow and bones. Timely detection and proactive treatment of NB can improve overall results. Reoccurrence of skeletal issues and the infiltration of bone marrow are frequently observed. There were no significant differences observed in terms of relapse-free survival and overall survival based on factors such as sex, age, location of the main tumor, chemotherapy, radiation treatment, surgery, and radiation therapy dosages.

Keywords: neuroblastoma, radiotherapy, gray, fraction, overall survival, relapse-free survival

INTRODUCTION

In 1864, Rudolf Virchow, a German physician, was the first to provide a description of neuroblastoma (NB). According to his studies, he identified these tumors discovered in the abdomens of children as gliomas. In 1910, James Homer Wright diligently endeavored to chart the source and progression of tumor cells, bestowing the label “blastoma” upon tumors of neuroblasts, denoting an assemblage of young, undifferentiated cells. His thorough investigation revealed that these tumors derived from a nascent, rudimentary type of brain cell [1]. This collection of tumors is classified as a condition that primarily affects children. Neuroblastoma (NB)

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is the most frequently occurring solid tumor outside of the skull, making it the third most prevalent type of cancer in children, after leukemia and brain tumors. Neuroblastoma accounts for 15% of all childhood malignancies. White children exhibited a higher occurrence rate compared to black neonates. The incidence rate in males is greater compared to females, with a male-to-female ratio of 1.3 to 1 [2].

NB is believed to have sporadic occurrences, with 2% of instances being familial [3]. The most prevalent type of tumor in the abdomen are neuroblastomas, accounting for 65% of cases. Among these, 50% originate from the adrenal glands (adrenal neuroblastomas), whereas 1/3 arise from paravertebral ganglia (extra-adrenal neuroblastomas) [4].

The symptoms of NB include stomach pain or discomfort, as well as the presence of a firm and immovable mass in the abdomen. The characteristic nodularity of abdominal neuroblastoma resembles the sensation of palpating a bag of potatoes, distinguishing it from other types of neuroblastomata. Occasionally, the presence of hepatomegaly, splenomegaly, and intestinal obstruction may be observed [5].

Over 50% of cases exhibit metastatic illness. NB is linked to the dissemination through the lymphatic and hematogenous routes. The most frequent locations of hematogenous metastasis include the bone marrow (70.5%), bones (such as the skull, long bones, ribs, and vertebrae), liver, and skin. Infrequently spread to the brain or lungs. 6 reported that 35% of individuals exhibited regional lymph node metastases in the presence of localized malignancies [6]. Hutchinson syndrome, also known as long bone involvement, is characterized by discomfort, limping, and an increased incidence of pathological fractures [7]. The presence of periorbital ecchymoses, swelling, and proptosis, commonly known as raccoon eyes, is caused by the involvement of the sphenoid bone and retrobulbar tissue [7].

The presence of painless proptosis, periorbital edema, and ecchymosis of the upper lid is suggestive of trauma or child abuse. An irritable and fussy infant requires attention. Pancytopenia can occur because of bone marrow infiltration. Extensive liver involvement is frequently observed in newborns with stage Ms/4S metastatic disease and can lead to the development of Pepper syndrome (PS), a disorder characterized by respiratory distress, as described by W. Pepper [7].

Certain newborns in stage (4S) NB succumb to extensive enlargement of the liver, respiratory failure, and severe infection. The presence of non-tender, blue, and movable epidermal and subcutaneous nodules is indicative of metastasis to these locations. This phenomenon is commonly referred to as the "blueberry muffin sign." Once stimulated, these nodules appear noticeably red and then quickly become pale due to the production of vasoconstrictive metabolic substances. These nodules can serve as a diagnostic indicator of neuroblastoma and should be distinguished from metastatic cutaneous leukemic infiltrates [7-10].

Tumors located in the paraspinal areas of the thoracic, abdominal, and pelvic regions frequently result in compression of the spinal cord. This occurs when the tumors invade the spinal canal through the neural foramina, leading to symptoms associated with the compression of nerve roots and the spinal cord. Possible symptoms include subacute or acute paraplegia, bladder or bowel problems, and less frequently, radicular discomfort. Cervical neuroblastoma can manifest as Horner's syndrome [8].

The aim of this study is to examine the clinical results following the use of additional radiotherapy to the main location in cases of metastatic NB after a positive response to chemotherapy.

METHODS

Study design

This study is a retrospective clinical-dosimetry analysis of 25 patients with metastatic neuroblastoma (NB) who underwent radiotherapy at the Baghdad Radiotherapy and Nuclear Medicine Center, located in the Baghdad Medical City Complex, Iraq. Data gathering will commence between December 2023 and March 2024.

Ethics

All parents of the patients who participated in this study provided their agreement to participate, in accordance with the Helsinki statement and its subsequent amendments. The study (#No.1674) has been authorized by the Institutional Ethical Board of the Department of Surgery, College of Medicine, University of Baghdad on 26/12/2023.

Data collection

Data were collected retrospectively with review of records. The following variables were studied: sex, age, date of diagnosis, site of primary tumor, site of metastasis, chemotherapy, surgery, RT, RT sites, doses of RT, fractions of RT, recurrence sites, date of relapse and survival outcome for each patient.

Follow-up and survival

Follow-up period include look up to metastasis, site of metastasis, recurrence, site of recurrence and survival rates (overall survival, disease free survival and recurrence rate).

Radiotherapy

RT was then administered to the main locations using CT-based planning to define target quantities. The GTV refers to the volume that is observed during CT scanning after treatment but before surgery. A supplementary CTVm margin of 1.0 to 1.5 cm was established to accommodate microscopic disease, followed by a PTVm margin of 0.5 to 1.0 cm to account for ambiguities in set-up. The minimum beam size will be six centimeters. The equipment includes a LINEAR ACCELERATOR (linac), CT simulator, XIO workstation, and MONACO.

Statistical analysis

The analyses were conducted using SPSS version 25.0 for Windows (SPSS Inc., Chicago, Illinois, USA). The relapse-free survival (LRS), median survival (MS), and overall survival (OS) were computed and graphed using the Kaplan-Meier curves. Patients were excluded from the analysis at the time of their last follow-up if they did not experience any event. Qualitative data refers to information that is expressed in numerical form, such as figures and percentages. The mean and standard deviation for quantitative data is also determined. A P-value less than 0.05 and a 95% confidence interval (95%CI) were deemed to be statistically significant.

RESULTS

Demographic and tumor data

In relation to sex, males (14, 56%) were more than females (11, 44%). The mean age of NB cases was 45.64±17.6 months (median = 48 months). Cases of NB age below 60 months were 17 (68%) whereas those above 60 months were 8 (32%), showed in table 1. In NB, suprarenal masses were the most common site of primary in 21 (84%) of patients. The most common site of metastasis of NB was bone marrow in 12(48%), followed by bone marrow and bone in 5 cases and multiple sites in 5 cases. Orbital metastasis documented in two cases, showed in Table 1.

In this study, all patients received chemotherapy and RT. Although, 80% of cases underwent surgery. Most of patients received RT at tumor bed (24, 96%) while one case received RT on vertebrae. 9 out of 25 (36%) received 36Gy/20Fx RT dose. 8 out of 25 (32%) received 22Gy/12Fx RT dose. 7 out of 25 (36%) received 23Gy/13Fx RT dose. One case received 25.2Gy/14Fx RT dose, showed in Table 1.

At 2017, two(8%) cases were diagnosed. In 2018, 4 (16%) cases were diagnosed and one case of relapsing recorded. In 2019, 12 (48%) cases were diagnosed, two(8%) cases were relapsed and two (8%) cases were died. In 2020, 4 (16%) cases were diagnosed, 10 (40%) cases were relapsed and 9 (36%) cases were died. In 2021, 1 (4%) case was detected, 6 (24%) cases were relapsed and 4 (16%) cases were died. In 2022, 2 (8%) cases were diagnosed, 3 (12%) cases were relapsed and 4 (16%) cases were died. In 2023, 3 (12%) cases were died. In 2024, 3 (12%) cases were died.

TABLE 1. Distribution of demographic data

Variables		No.	%
Sex	Male	14	56
	Female	11	44
Age (months)	<60	17	68
	≥60	8	32
Site of primary tumor	Supra renal mass	21	84
	Para vertebral mass	2	8
	Carotid mass	1	4
	Mediastinal mass	1	4
Site of metastasis	Bone marrow	12	48
	Multiple	5	20
	Orbital	2	8
	Hepatic	1	4
	Bone marrow + Bone	5	20
Chemotherapy	Yes	25	100
	No	0	0
Surgery	Yes	20	80
	No	5	20
Radiotherapy	Yes	25	100
	No	0	0
Radiotherapy site	Tumor bed	24	96
	Vertebrae	1	4
Radiotherapy doses	22Gy/12Fx	8	32
	23Gy/13Fx	7	28
	25.2Gy/14Fx	1	4
	36Gy/20Fx	9	36

Recurrence data

Table 2 showed the distribution of patients in relation to recurrence sites. The multi sites of recurrence was the commonest presentation in 48%. Skeletal relapse was found in 16%. Bone marrow involvement with bone in recurrence in 32% of cases. One case recorded of recurrence in brain.

TABLE 2. The distribution of patients in relation to recurrence sites

Site of recurrence	No.	%
Bone	4	16
Brain	1	4
Bone marrow and bone	8	32
Multiple	12	48

Kaplan-Meier analysis of relapse-free survival (RFS) shown in Figure 1. The RFS was 22.38 months (95% CI = 17.118-27.632).

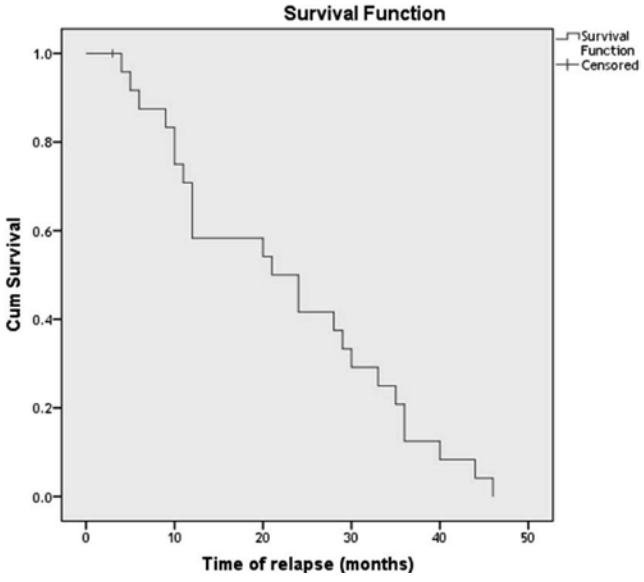

FIGURE 1. Kaplan-Meier curve of relapse-free survival (RFS)

Kaplan-Meier analysis of RFS according to sex shown in Figure 2A. The RFS was 24.27 months (95%CI = 16.563-31.983) for female whereas it was 20.77 months (95%CI = 13.415-28.124) for male, with no significant difference (Log Rank – Mantel-Cox)= 0.19, p=0.663).

Kaplan-Meier curve of RFS according to age (months) shown in Figure 2B. The RFS was 22 months (95%CI = 15.144-28.856) for those aged <60 months whereas it was 23.29 months (95%CI = 15.662-28.124) for those aged ≥60 months with no significant difference (Log Rank – Mantel-Cox) = 0.27, p = 0.605).

Kaplan-Meier curve of RFS according to the site of primary tumor shown in Figure 2C. The RFS was 19.6 months (95%CI = 14.142-25.058) for supra renal masses whereas it was 40 months (95%CI = 32.16-47.84) for paravertebral masses with no significant difference (Log Rank – Mantel-Cox) = 2.6, p = 0.456).

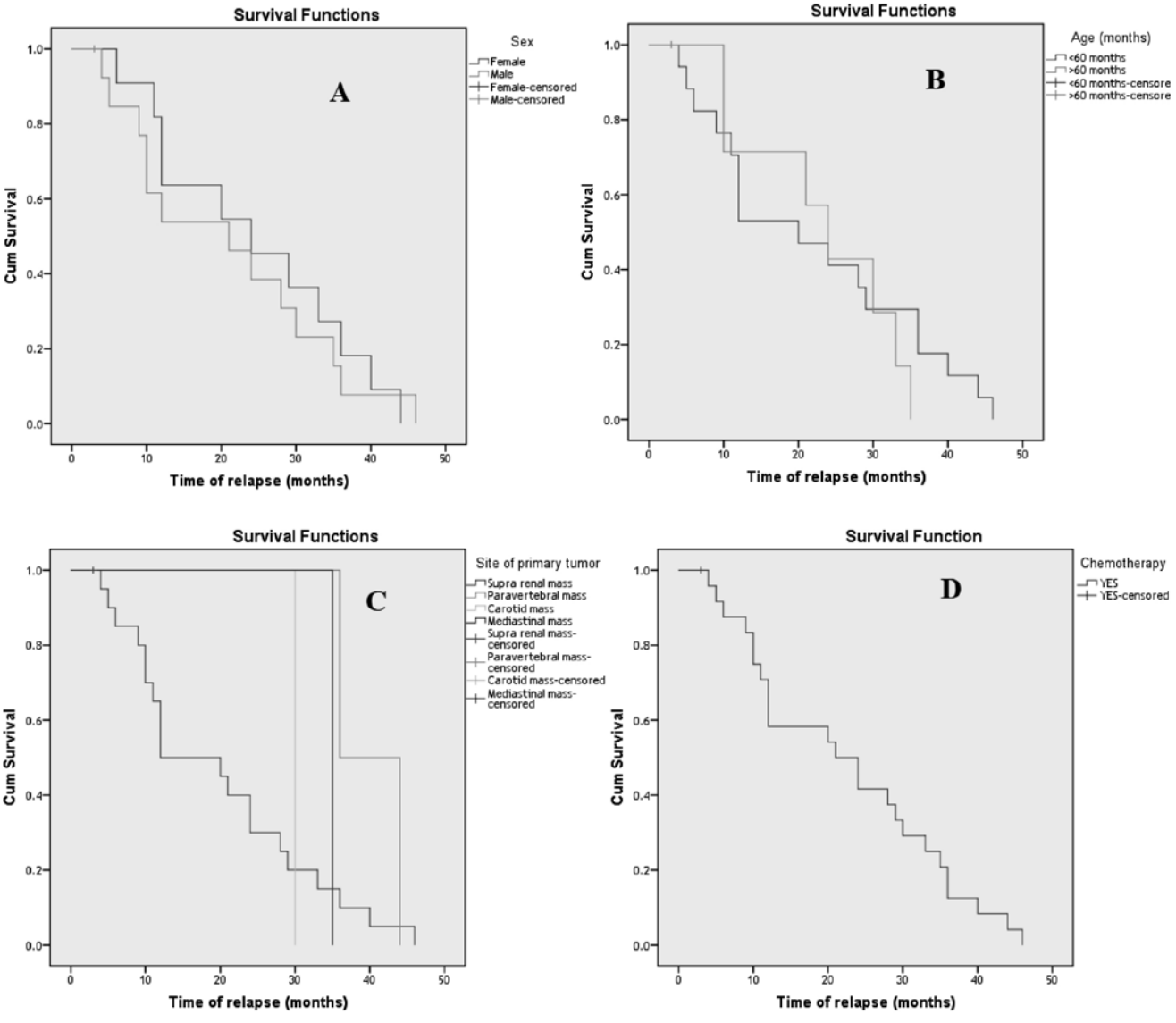

FIGURE 2. Kaplan-Meier curves of relapse-free survival (RFS) for (A) sex, (B) age, (C) site of primary tumor, (D) chemotherapy

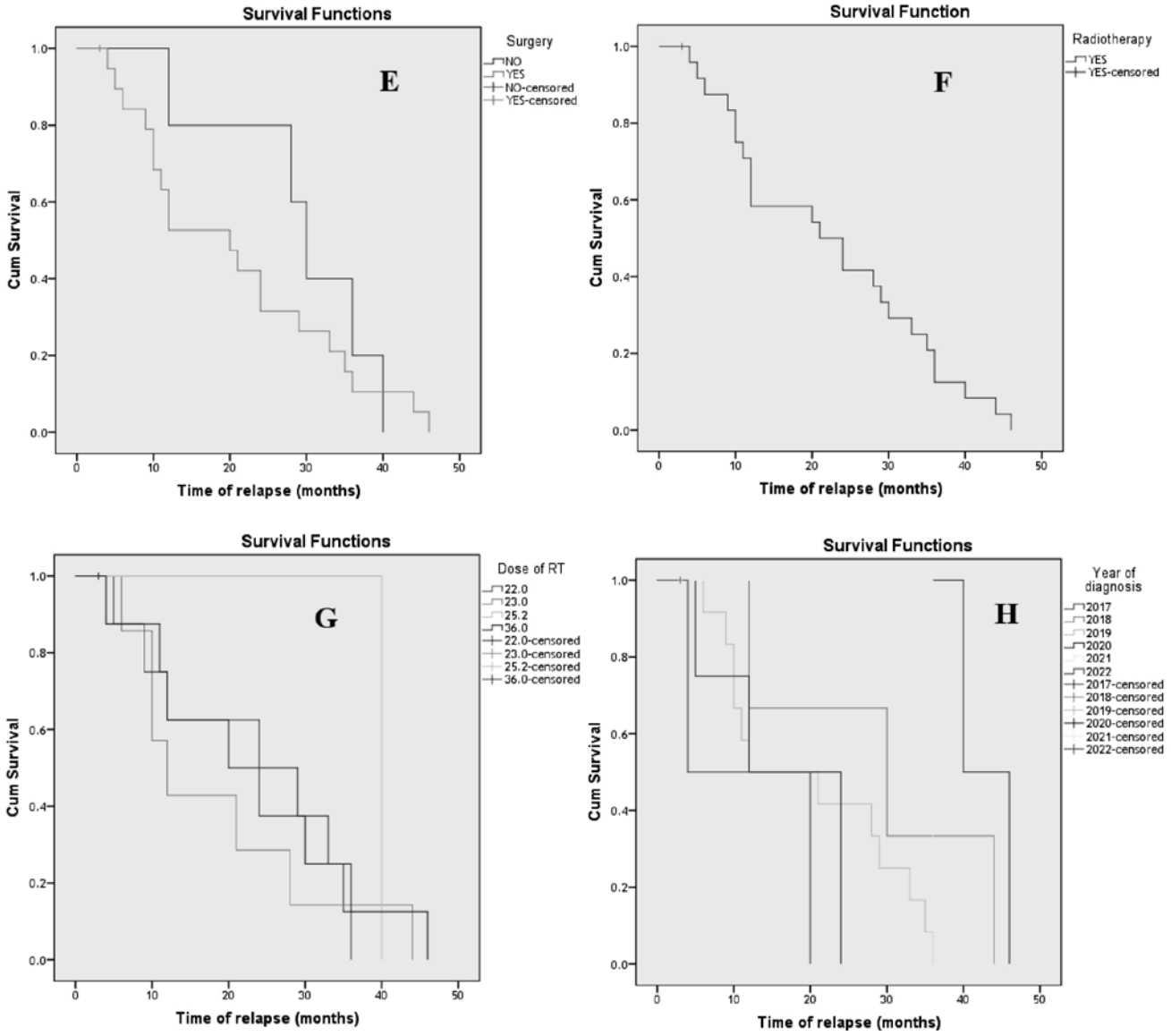

FIGURE 2. Kaplan-Meier curves of relapse-free survival (RFS) for (E) surgery, (F) radiotherapy, (G) doses of RT and (H) year of diagnosis

Furthermore, the RFS for carotid lesion and mediastinal mass were 30 months and 35 months, respectively.

Kaplan-Meier curve of RFS according to chemotherapy and RT shown in Figure 2D,F. The RFS was 22.375 months (95%CI = 17.118-27.632) for those received chemotherapy and/ or RT.

Kaplan-Meier curve of RFS for those underwent surgery was shown in Figure 2E. The RFS was 29.2 months (95%CI = 19.792-38.608) for those underwent surgery while it was 20.579 months (95%CI = 14.568-26.59) for those without surgery with no significant difference [Log Rank (Mantel-Cox) = 0.647, p=0.421].

Kaplan-Meier curve of RFS according to RT doses used in this study was shown in Figure 2G. The RFS was 22.5 months (95%CI = 14.209-30.791) for those received 22Gy, 18.71 months (95%CI = 8.732-28.697) for those received 23Gy, and 23.25 months (95%CI = 13.21-33.29) for those received 36Gy. There was no significant difference among doses [Log Rank (Mantel-Cox) = 1.457, p = 0.692].

Kaplan-Meier curve of RFS according to early year of diagnosis was shown in Figure 2H. The RFS was 43 months for those diagnosed at 2017, 28.67 months for those diagnosed at 2018, 20 months for those diagnosed at 2019, 16.25 months for those diagnosed at 2020, 36 months for those diagnosed at 2021 and 12 months for those diagnosed at 2022. There was a significant difference among doses [Log Rank (Mantel-Cox) = 12.572, p = 0.028].

Survival data

Table 3 shown the distribution of patients in relation to survival outcome. 5 out of 25 patients were still alive, whereas 20 (80%) of cases were dead.

The median follow-up time was 6 years, and the OS of NB in this study after optimal treatment was

TABLE 3. The distribution of patients in relation to survival outcome

Outcome	No.	%
Alive	5	20
Dead	20	80

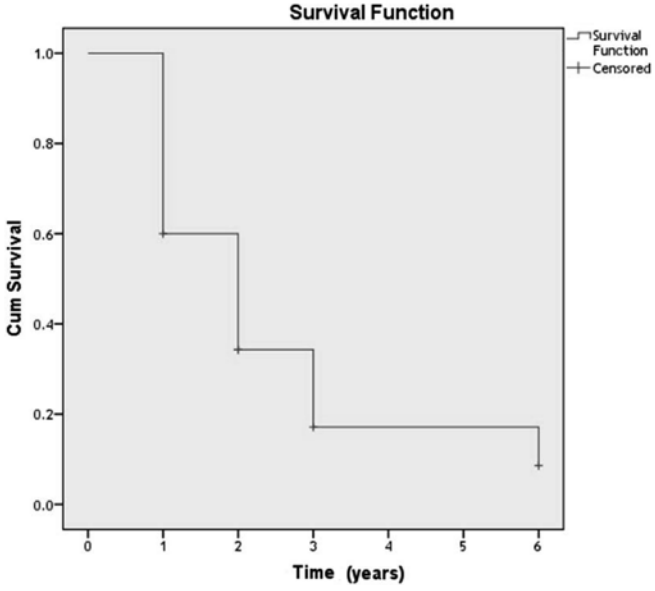

FIGURE 3. Kaplan-Meier curve of overall survival (OS)

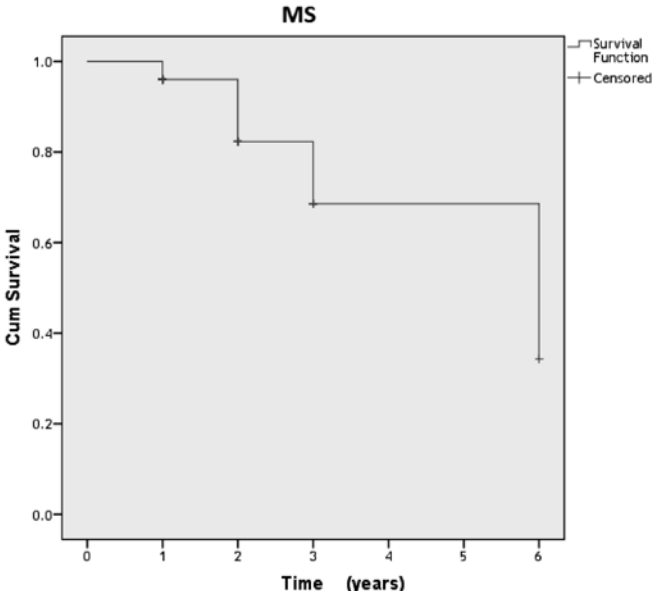

FIGURE 4. Kaplan-Meier curve of median survival (MS)

2.46 years (95%CI = 1.705-3.21) for survivors, as shown in (Figure 3).

Kaplan-Meier analysis of median survival (MS) shown in Figure 4. The MS was 4.84 years (95% CI = 3.713-5.967).

Kaplan-Meier analysis of OS according to sex shown in Figure 5A. The OS was 2.09 yrs (95%CI = 1.236-2.945) for female whereas it was 2 yrs (95%CI = 1.259-2.741) for male, with no significant difference [Log Rank (Mantel-Cox) = 0.011, p = 0.918].

Kaplan-Meier curve of OS according to age (months) shown in Figure 5B. The OS was 2.12 yrs (95%CI = 1.368-2.867) for those aged <60 months whereas it was 1.875 yrs (95%CI = 1.188-2.562) for those aged ≥60 months with no significant difference [Log Rank (Mantel-Cox) = 0.015, p = 0.903].

Kaplan-Meier curve of OS according to the site of metastasis shown in Figure 5C. The OS was 1.75 yrs (95%CI = 1.26-2.24) for those with bone marrow secondaries. OS was 2.6 yrs (95%CI = 0.782-4.418) for those with multiple secondaries. OS was 1 yr for those with orbital secondaries. OS was 2 yrs for those with hepatic secondaries. OS was 2.6 yrs (95%CI = 0.891-4.309) for those with bone marrow and bone involvement with no significant difference between rates of survival [Log Rank (Mantel-Cox) = 4.013, p=0.404].

Kaplan–Meier curve of OS according to year of diagnosis was shown in Figure 5 D. The OS was 6 yrs for those diagnosed at 2017, 2 yrs for those diagnosed at 2018, 1.5 yrs for those diagnosed at 2019, 1.75 yrs for those diagnosed at 2020, 3 yrs for those diagnosed at 2021 and 1.5 yrs for those diagnosed at 2022 with a significant difference among doses [Log Rank (Mantel-Cox)= 11.425, p=0.044].

Kaplan-Meier curve of OS according to chemotherapy and RT shown in Figure 5E,G. The OS was 2.04 yrs (95%CI = 1.492-2.588) for those received chemotherapy and/ or RT.

Kaplan-Meier curve of RFS for those underwent surgery was shown in Figure 5F. The OS was 3 yrs (95%CI = 1.360-4.640) for those underwent surgery while it was 1.8 yrs (95%CI = 1.276-2.324) for those without surgery with no significant difference [Log Rank (Mantel-Cox) = 2.834, p=0.092].

Kaplan-Meier curve of OS according to RT doses used in this study was shown in Figure 5H. The OS was 1.75 yrs (95%CI = 1.26-2.24) for those received 22Gy, 1.71 yrs (95%CI = 1.154-2.274) for those received 23Gy, and 2.11 yrs (95%CI = 1.006-3.216) for those received 36Gy. There was no significant difference among doses [Log Rank (Mantel-Cox) = 4.313, p = 0.23].

Kaplan-Meier curve of OS according to the site of primary tumor shown in Figure 5I. The OS was 2 yrs (95%CI = 1.366-2.634) for suprarenal masses whereas it was 2.5 yrs (95%CI = 1.52-3.48) for paravertebral masses with no significant difference [Log Rank (Mantel-Cox) = 2.356, p=0.502]. Furthermore, the OS for carotid lesion and mediastinal mass were 3 yrs and 1 yrs, respectively.

Outcome data

All patients underwent surgery and received chemotherapy. Complete response was found in 23

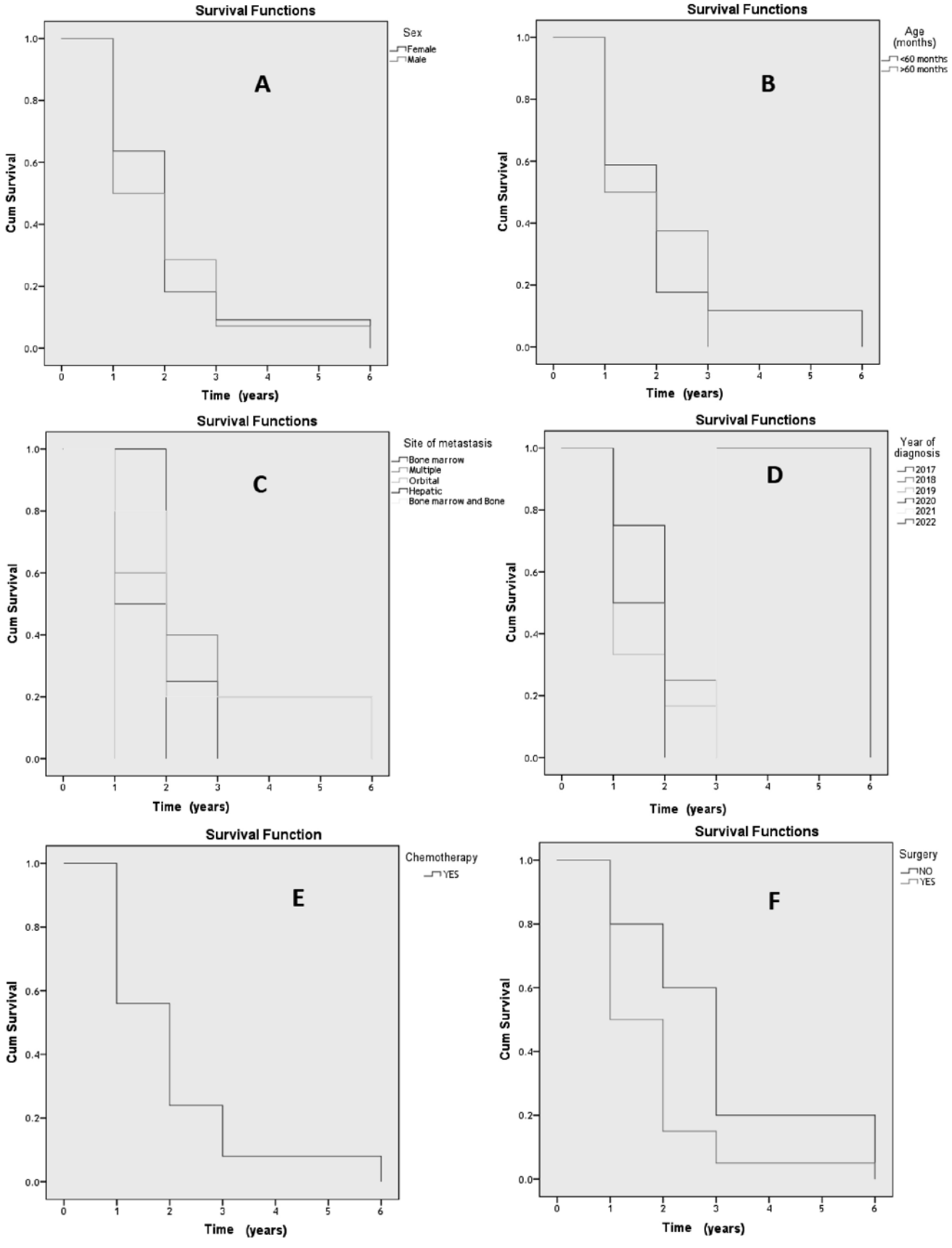

FIGURE 5. Kaplan-Meier curves of relapse-free survival (RFS) for (A) sex, (B) age, (C) site of metastasis, (D) year of diagnosis, (E) chemotherapy, (F) surgery

(92%) of cases whereas partial response was 8%. The recurrence rate post radiotherapy was reported in 24 (96%) patients and only one case still had stable disese. Recurrence at primary site was recorded in 4 (16%) while distance metastasis was reported in 20 (80%) (Figure 6).

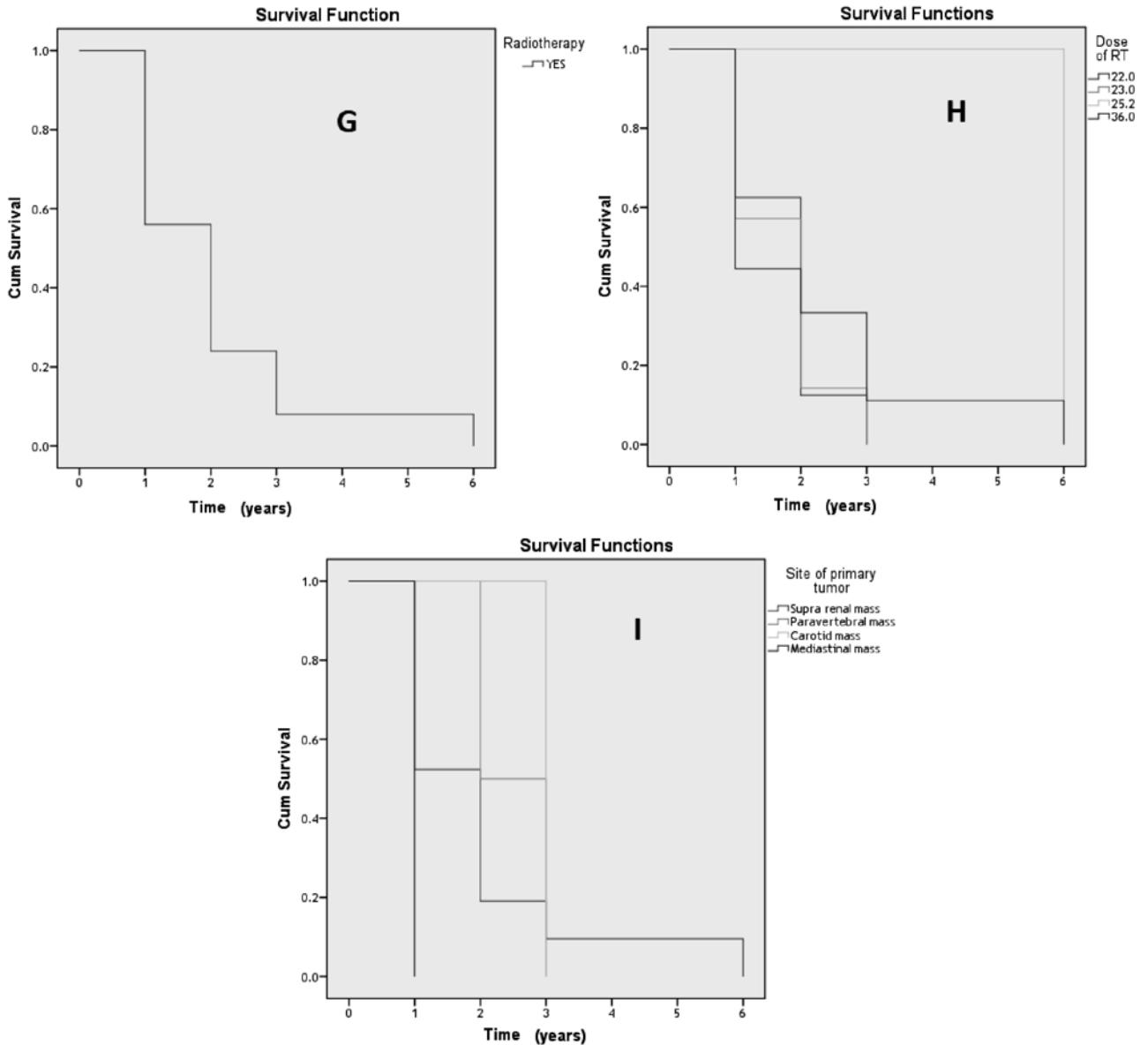

FIGURE 5. Kaplan-Meier curves of relapse-free survival (RFS) for (G) radiotherapy, (H) doses of RT and (I) site of primary tumor

DISCUSSION

In this study, males (14, 56%) were more than females (11, 44%). The mean age of NB cases was 45.64 ± 17.6 months (median = 48 months). In the study, suprarenal masses were shown to be the primary site in 21 out of 25 patients, making it the most prevalent location. The bone marrow was the most frequent site of metastasis in 12 instances (48%). Although, 80% of cases underwent surgery. These finding are similar to previous studies of Jazmati et al. [11], Wei et al. [12], Lucas et al. [13] and Albrecht et al. [14].

Nevertheless, Jazmati and colleagues [11] conducted a study that the age at the midpoint of the distribution was 46 months. The irradiation metastatic sites were found in the skull (n = 7), extremity (n = 10), spine (n = 5), or ribs (n = 2). Casey et al. [15] examined 159 cases of neuroblastoma, the age at which half of the population was older and half was younger at the time of RT was 4 years.

In 2015, Kandula et al. [16] conducted a study on 37 instances of neuroblastoma, with a median age of 3.7 years. Every patient received chemotherapy. The median radiation therapy dose delivered to the main location was 21.6 Gy.

In the present study, the multi-sites of recurrence was the commonest presentation in 48%. The RFS was 22.38 months. There was a significant difference among doses (p=0.028), so early diagnosis of NB could be effect the relapse-free survival. Similar to pervious study of Jazmati et al. [11] and Kandula et al. [16].

In the study of Jazmati et al. [11], the median follow-up time was 56.5 months. The LRFS rate was 83.3 and the MFS was (77.8). Kandula et al. [16] found that the median RFS was 35.1 months. Five cases (38%) were alive with no disease, three (23%)

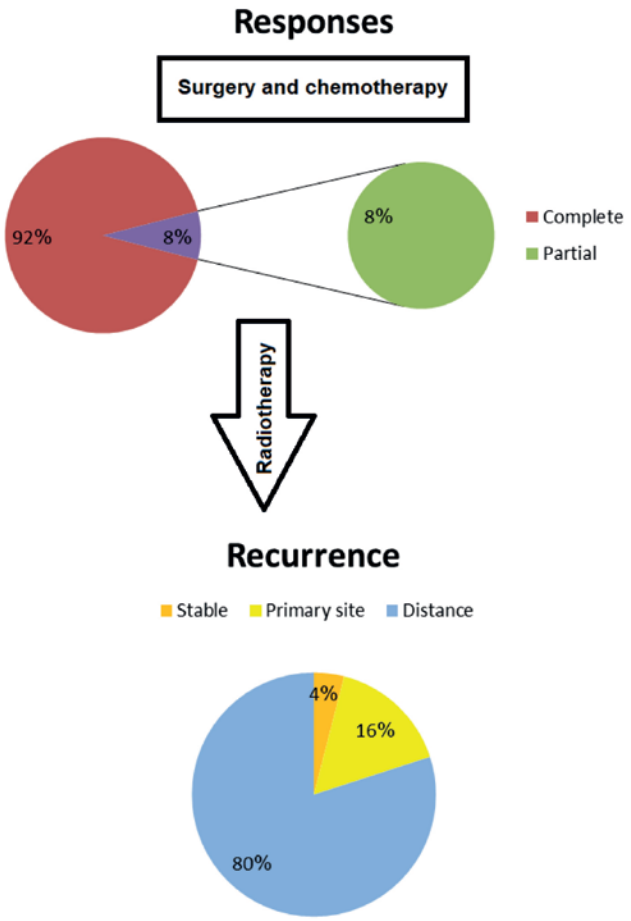

FIGURE 6. Responses and outcome after management of NB

were alive with disease, and five (38%) died. Recurrence occurred in three cases (23%).

Polishchuck et al. [17] reported most of the lesions were treated with a dosage of 21.6 Gy/12 Fx, and Kandula et al. [16] discovered comparable data.

The impact of RT on neuroblastoma (NB) survival was investigated by both the Texas Children's Hospital and the Memorial Sloan Kettering Cancer Center (MSKCC). The TCH study [18], revealed a local control rate of 74% at 5 years for irradiation metastatic lesions, while the MSKCC study reported a rate of 81% [15].

Casey and colleagues [15] reported that local failure occurred in 43 (18%) of cases. The 5-year LC rate was 81.0%.

The integration of myeloablative therapy, immunotherapy, and differentiation therapy utilizing 13-cis-retinoic acid has resulted in enhanced survival rates for individuals with high-risk neuroblastoma. Nevertheless, more than 50% of children will still experience systemic relapse [19].

The COG protocol ANBL0532 advises the use of irradiation on areas of metastatic illness that remain present after the administration of induction chemotherapy. At our center, we have administered four doses of radiation therapy to treat both persistent areas of disease and earlier areas of quantifiable or bulky disease that have shown complete response, particularly in emergent cases. The justification for the latter strategy is based on past evidence indicating that most failures occur at areas that were previously affected, even in cases where there was a complete response to induction therapy [17,20,21].

Comparable to the findings of this investigation, the control rate in patients where there is visible illness at the main site after first chemotherapy and surgical removal is lower [22,23]. According to current procedures, it is recommended to administer a dose of 36 Gy following surgery to the primary site for all instances when there is a significant amount of remaining illness after removal [24].

In Bradfield et al.'s study [25], all primary sites of metastatic illness were subjected to irradiation following stem cell transplantation, irrespective of the response to induction therapy. All patients had radiotherapy (RT) and there were no instances of local treatment failure at the irradiated locations. According to Polishchuk et al. [17], bone relapse tends to happen at the same locations where the disease was first diagnosed, and relapses are less frequent in areas that have been treated with radiation.

In this study, the complete response was found in 23 (92%) of cases post-surgery and chemotherapy. The recurrence rate post RT was reported in 24 (96%) patients. Recurrence at primary site was recorded in 4 (16%) while distance metastasis was documented in 20 (80%). Furthermore, five out of 25 patients were alive whereas 20(80%) of cases were dead. Jazmati et al. [11] found that the overall survival rates were 72.2% and 49.4%, respectively. During the analysis, a total of 11 individuals had died.

The Kandula et al. [16] investigation found that the median duration without relapse was 61 months. The 5-year overall survival rate was 67%. The 5-year overall survival (OS) rate for cases treated with RT to a metastatic location was 73%, whereas the rate for cases treated without RT was 63%. Similarly, the 5-year recurrence-free survival (RFS) rate for cases treated with RT was 46%, compared to 55% for cases treated without RT.

The median follow-up time was 6 years in this study and the OS of NB after optimal treatment was 2.46 years for survivors. While the median follow-up period among surviving patients was 7.4 years in Casey et al. [15] study.

In the present study, OS was 2.04 yrs for those received chemotherapy and/ or RT. It was 3 yrs for those underwent surgery while it was 1.8 yrs for those without surgery with no significant difference ($p=0.092$). Jazmati et al. [11] found that the dose of RT was not statistically evident to correlate with LRFS, MFS, or OS ($p = 0.3$), which supported this study's findings.

Casey et al. [15] observed that the response to induction chemotherapy had a predictive value for local control (LC). They found that the 5-year LC rate was 92% in areas that cleared with chemotherapy, compared to 67% in sites where the illness persisted (P <0.0001).

Jazmati et al. [11] determined that radiation therapy (RT) is possible and well-tolerated for children with high-risk NB metastases. They found no significant acute or late toxic effects and no instances of subsequent cancers.

According to Yu et al., the inclusion of immunotherapy using ch14.18 (a monoclonal antibody that targets the tumor-associated disialoganglioside GD2) along with isotretinoin (standard therapy) and RT resulted in significantly better event-free survival and overall survival results in high-risk NB patients [26]. The authors demonstrated a low rate of event-free survival, mostly attributed to a high mortality rate resulting from insufficient supportive care, lack of access to critical care units, absence of bone marrow transplant facilities, and treatment abandonment [27].

CONCLUSION

Most NB main sites are suprarenal. NB metastasizes mostly to bone marrow and bone. Early diagnosis and aggressive NB treatment may improve outcomes. Common are skeletal recurrence and bone marrow involvement. NB survivors have a 22.38-month RFS and 2.46-year OS. Relapse-free survival and OS are unaffected by sex, age, original tumor site, chemotherapy, RT, surgery, and RT dosages.

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REFERENCES

1. Kelly EB. Neuroblastoma: Cancer in Very Young Children. The 101 Most Unusual Diseases and Disorders. 2015;1:253. https://www.pcrf.net/information-you-should-know/types-of-cancer-in-children.html?gad_source=1&gclid=Cj0KCQjwurS3BhCGARIsADdUH527EXZP5GnI1ocxWE06mUBDjY4d_Y_invM9XPk0XkonupfO_pRNMuAaAubUEALw_wcB
2. Goodman MT, Gurney JG, Smith MA, Olshan AF. Sympathetic nervous system tumors, chap IV. In: Ries, LAG, Smith MA, Gurney JG, Linet M, Tamra T, Young JL, Bunin GR (eds). Cancer incidence and survival among children and adolescents: United States SEER Program 1975–1995, National Cancer Institute, SEER Program. NIH Publ no 00–4649. Bethesda, MD; 1999; p. 35.
3. Maris JM. Recent advances in neuroblastoma. *N Engl J Med.* 2010;362(23):2202-11. doi: 10.1056/NEJMra0804577

Chu CM, Rasalkar DD, Hu YJ, Cheng FW, Li CK, Chu WC. Clinical presentations and imaging findings of neuroblastoma beyond abdominal mass and a review of imaging algorithm. *Br J Radiol.* 2011;84(997):81-91. https://doi.org/10.1259/bjr/31861984. PMID: 21172969; PMCID: PMC3473807.

4. Hadley L, Lakhoo K. Neuroblastomas: Pediatric Surgery: A Comprehensive Text for Africa. 2011;2:610. chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/http://www.surgicalneed.nl/wp-content/uploads/2016/08/help_pedsurgeryafricavolume02.pdf
5. DuBois SG, Kalika Y, Lukens JN, Brodeur GM, Seeger RC, Atkinson JB, et al. Metastatic sites in stage IV and IVS neuroblastoma correlate with age, tumor biology, and survival. *J Pediatr Hematol Oncol.* 1999;21(3):181-9. https://doi.org/10.1097/00043426-199905000-00005
6. Hu HM, Zhang WL, Li J, Wen Y, Li F, Zhi T, Huang DS. Report of seven children with undifferentiated embryonal sarcoma of the liver. *Chin Med J (Engl).* 2019;132(18):2244-5. https://doi.org/10.1097%2FCM9.0000000000000429
7. Malis J. Clinical Presentation of Neuroblastoma. Chapter 1, IntechOpen. 2013:3-12. https://doi.org/10.5772/55921
8. Bhagat P, Vij M, Raju LP, Gowrishankar G, Menon J, Shanmugam N, Kaliamoorthy I, Rammohan A, Rela M. Update on the Pathology of Pediatric Liver Tumors: A Pictorial Review. *Diagnostics (Basel).* 2023;13(23):3524. https://doi.org/10.3390/diagnostics13233524
9. Lucas B, Ravishankar S, Pateva I. Pediatric Primary Hepatic Tumors: Diagnostic Considerations. *Diagnostics (Basel)*. 2021;11(2):333. https://doi.org/10.3390/diagnostics11020333
10. Jazmati D, Butzer S, Hero B, Doyen J, Ahmad Khalil D, Steinmeier T, et al. Long-term follow-up of children with neuroblastoma receiving radiotherapy to metastatic lesions within the German Neuroblastoma Trials NB97 and NB 2004. *Strahlenther Onkol.* 2021;197(8):683-9. https://doi.org/10.1007%2Fs00066-020-01718-5
11. Wei Z, Li J, Jin Y, Liu Y, Wang P, Cao Y, Zhao Q. The application and value of radiotherapy at the primary site in patients with high-risk neuroblastoma. *Br J Radiol.* 2022;95(1134):20211086. https://doi.org/10.1259%2Fbjr.20211086
12. Lucas JT Jr, Wakefield DV, Doubrovin M, Li Y, Santiago T, Federico SM, Merchant TE et al. Risk factors associated with metastatic site failure in patients with high-risk neuroblastoma. *Clin Transl Radiat Oncol.* 2022;34:42-50. https://doi.org/10.1016/j.ctro.2022.02.009
13. Albrecht F, Wolters H, Ziert Y, Timmermann B, Kortmann RD, Matuschek C et al. Evaluation of treatment-associated eye toxicity after irradiation in childhood and adolescence-results from the Registry of the Evaluation of Side Effects after Radiotherapy in Childhood and Adolescence (RiSK). *Strahlenther Onkol.* 2021;197(8):700-10. https://doi.org/10.1007%2Fs00066-021-01793-2
14. Casey DL, Pitter KL, Kushner BH, Cheung NV, Modak S, LaQuaglia MP, Wolden SL. Radiation Therapy to Sites of Metastatic Disease as Part of Consolidation in High-Risk Neuroblastoma: Can Long-term Control Be Achieved? *Int J Radiat Oncol Biol Phys.* 2018;100(5):1204-9. https://doi.org/10.1016/j.ijrobp.2018.01.008
15. Kandula S, Prabhu RS, Nanda R, Switchenko JM, Cash T, Qayed M et al. Outcomes After Radiation Therapy to Metastatic Sites in Patients With Stage 4 Neuroblastoma. *J Pediatr Hematol Oncol.* 2015;37(3):175-80. https://doi.org/10.1097%2FMPH.0000000000000264
16. Polishchuk AL, Li R, Hill-Kayser C et al. Likelihood of bone recurrence in prior sites of metastasis in patients with high-risk neuroblastoma. *Int J Radiat Oncol Biol Phys.* 2014;89:839-45. https://doi.org/10.1016/j.ijrobp.2014.04.004
17. Kushner BH,Wolden S, LaQuaglia MP et al. Hyperfractionated low-dose radiotherapy for high-risk neuroblastoma after intensive chemotherapy and surgery. *J Clin Oncol.* 2001;19:2821-8. https://doi.org/10.1200/jco.2001.19.11.2821
18. Mazloom A, Louis CU, Nuchtern J et al. Radiation therapy to the primary and postinduction chemotherapy MIBG-avid sites in high-risk neuroblastoma. *Int J Radiat Oncol Biol Phys.* 2014;90:858-62. https://doi.org/10.1016/j.ijrobp.2014.07.019
19. Casey DL, Kushner BH, Cheung NK, et al. Local control with 21-Gy radiation therapy for high-risk neuroblastoma. *Int J Radiat Oncol Biol Phys.* 2016;96:393-400. https://doi.org/10.1016/j.ijrobp.2016.05.020
20. Kushner BH, Cheung NK, Barker CA, et al. Hyperfractionated low-dose (21 Gy) radiotherapy for cranial skeletal metastases in patients with

high-risk neuroblastoma. *Int J Radiat Oncol Biol Phys.* 2009;75:1181-6. https://doi.org/10.1016%2Fj.ijrobp.2008.12.026
21. Sangthawan D, DesRosiers PM, Randall ME, et al. Relapse in the skull after myeloablative therapy for high-risk neuroblastoma. *Pediatr Hematol Oncol.* 2003;20:23-30. https://pubmed.ncbi.nlm.nih.gov/12687750/
22. Mayer BFB, Schunn MC, Urla C, Schäfer JF, Fideler F, Neunhoeffer F et al. Trap-Door Thoracotomy and Clamshell Thoracotomy as Surgical Approaches for Neuroblastoma and Other Thoracic Tumors in Children. *Cancers (Basel).* 2024;16(2):373. https://doi.org/10.3390/cancers16020373
23. Mora J, Castañeda A, Gorostegui M, Varo A, Perez-Jaume S, Simao M, et al. Naxitamab Combined with Granulocyte-Macrophage Colony-Stimulating Factor as Consolidation for High-Risk Neuroblastoma Patients in First Complete Remission under Compassionate Use-Updated Outcome Report. *Cancers (Basel).* 2023 Apr 28;15(9):2535. https://doi.org/10.3390/cancers15092535
24. Bradfield SM, Douglas JG, Hawkins DS, et al. Fractionated low-dose radiotherapy after myeloablative stem cell transplantation for local control in patients with high-risk neuroblastoma. *Cancer.* 2004;100:1268-75. https://doi.org/10.1002/cncr.20091
25. Yu AL, Gilman AL, Ozkaynak MF, et al. Anti-GD2 antibody with GM-CSF, interleukin-2, and isotretinoin for neuroblastoma. *N Engl J Med.* 2010; 363:1324–1334. https://doi.org/10.1056/nejmoa0911123
26. Al-Maimory ST, Al-Darraji AF, Al-saeed RM, Al-Hadad S. Cancer in infancy: Experience of Children Welfare Teaching Hospital, Medical City Complex, Baghdad. *J Fac Med Bagdad* [Internet]. 2015 Apr. 5 [cited 2024 Jun. 21];57(1):1-5. https://doi.org/10.32007/jfacmedbagdad.571293