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ABSTRACT

Background. Neuroblastoma (NB) is a disease of pediatric population, which is the commonest solid extracranial tumor, accounting for 3rd commonest childhood cancer, beyond 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: To our knowledge, this study is the first study conducted in Iraq discussed the clinical outcomes of radiotherapy to the primary site in of metastatic NB post induction chemotherapy. Suprarenal masses of NB is the most common site of primary. The most common sites of metastasis of NB are bone marrow and bone. Early diagnosis, and aggressive management of NB may be enhance better outcomes. Skeletal relapse and bone marrow involvement are common. No difference in relapse-free survival and OS in relation to sex, age, site of primary tumor, chemotherapy, RT, surgery and RT doses.

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

Introduction

Rudolf Virchow, a German physician, was the first person who described neuroblastoma (NB) in 1864. Through his research he said that these tumors found in the abdomens of children as gliomas. In 1910, James Homer Wright made great efforts to map the origin and development of tumor cells, and he named the tumors of neuroblasts, as "blastoma" refers to a collection of immature, undifferentiated cells. His meticulous study showed that these tumors originated from an immature, primitive form of neural cell [1]. This set of tumors is considered as a disease of pediatric population. NB is the commonest solid extracranial tumor, accounting for 3rd commonest childhood cancer, beyond leukemia and brain tumors. NB account for 15% of all pediatric cancers. White race children displayed more incidence than black infants. Males have higher incidence rate relative to females (M:F ratio of 1.3:1) [2].

NB is thought to occur sporadically, with 2% of cases are familial [3]. NB in the abdomen are the commonest form that arise in 65% of cases, and 50% arise from the adrenal glands (adrenal NB), and 1/3 are from paravertebral ganglion (extra-adrenal NB) [4].

Symptoms of NB are abdominal pain/fullness and abdominal mass (firm and fixed mass). Characteristic nodularity of abdominal NB is similar to palpating a bag of potatoes which differentiate it from a NB. In some cases, hepatomegaly, splenomegaly and intestinal obstruction may be seen [5].

More than 50% of cases present with metastatic disease. NB is associated with lymphatic and hematogenous spreading. Commonest hematogenous metastatic sites are the bone marrow (70.5%), bones (skull, long bones, ribs and vertebrae), liver and skin, Rarely metastasized to the brain or lungs. Thirty-five percent of cases had regional LN metastases with localized tumors [6]. Long bone involvement cause pain and limping with raise the risk of pathological fractures which is known as Hutchinson syndrome [7]. Periorbital ecchymoses, swelling, and proptosis (raccoon eyes) occur due to sphenoid bone and retrobulbar tissue involvement [7].

Painless proptosis, periorbital edema and ecchymosis of the upper lid are akin with trauma or child abuse. Irritable and fussy infant needs attention. Bone marrow involvement may result in pancytopenia. Huge involvement of the liver in metastatic condition is common in infants with stage Ms/4S and may cause Pepper syndrome (PS), which induce the respiratory distress, quoted by W. Pepper [7].

Some infants with stage (4S) NB die of massive hepatomegaly, respiratory failure, and overwhelming sepsis. Non-tender, bluish, and mobile skin and subcutaneous nodules are because of metastasis to these sites. This is known as "blueberry muffin sign." These nodules become prominently red once provoked and thereafter blanch for some minutes, due to release of

vasoconstrictive metabolic products. These nodules can be diagnostic of neuroblastoma and should be differentiated from metastatic skin leukemic infiltrates [7-10].

Paraspinal tumors in the thoracic, abdominal and pelvic regions often present with spinal cord compression due to spinal canal invasion through the neural foramina causing symptoms related to compression of nerve roots and spinal cord. There may be subacute or acute paraplegia, bladder or bowel dysfunction, or less commonly radicular pain. Cervical NB may present as Horner's syndrome [8].

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

Study design

A retrospective clinical-dosimetric study of 25 patients metastatic neuroblastoma (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.

Ethics

In compliance with the Helsinki declaration and its later amendments, all parents of participating patients had consented to participation in this work. The Institutional Ethical Board of the Department of Surgery, College of Medicine, University of Baghdad had approved the study (#No.1674 in 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 subsequently delivered to the primary sites using CT-based planning to delineate target volumes. The GTV is defined as the post-chemotherapy but pre-surgical volume shown by CT scanning. An additional 1.0 to 1.5 cm CTVm margin was created to account for microscopic disease, followed by a 0.5 to 1.0 cm PTVm margin to account for set-up uncertainties. Beam

sizes will be at least six cm. Equipment are LINEAR ACCELERATOR (linac), CT simulator, XIO workstation and MONACO.

Statistical analysis

All analyses done by using SPSS version 25.0 for Windows (SPSS Inc., Chicago, Illinois, USA). The relapse-free survival (LRS), median survival (MS) and OS were calculated and plotted according to the Kaplan– Meier curves. Patients were censored at the time of last follow-up if they had no event. Qualitative data consist of numbers and percentages were measured. Mean and SD for quantitative data also calculated. A two-sided *P*-value of <0.05 and 95% confidence interval (95%CI) were considered 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).

Kaplan–Meier analysis of RFS according to sex shown in Figure (2 (A)). 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 (2 (B)). 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 (2 (C)). 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). 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 (2 (D and 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 (2 (E)). 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 (2 (G)). 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 (2 (H)). 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).

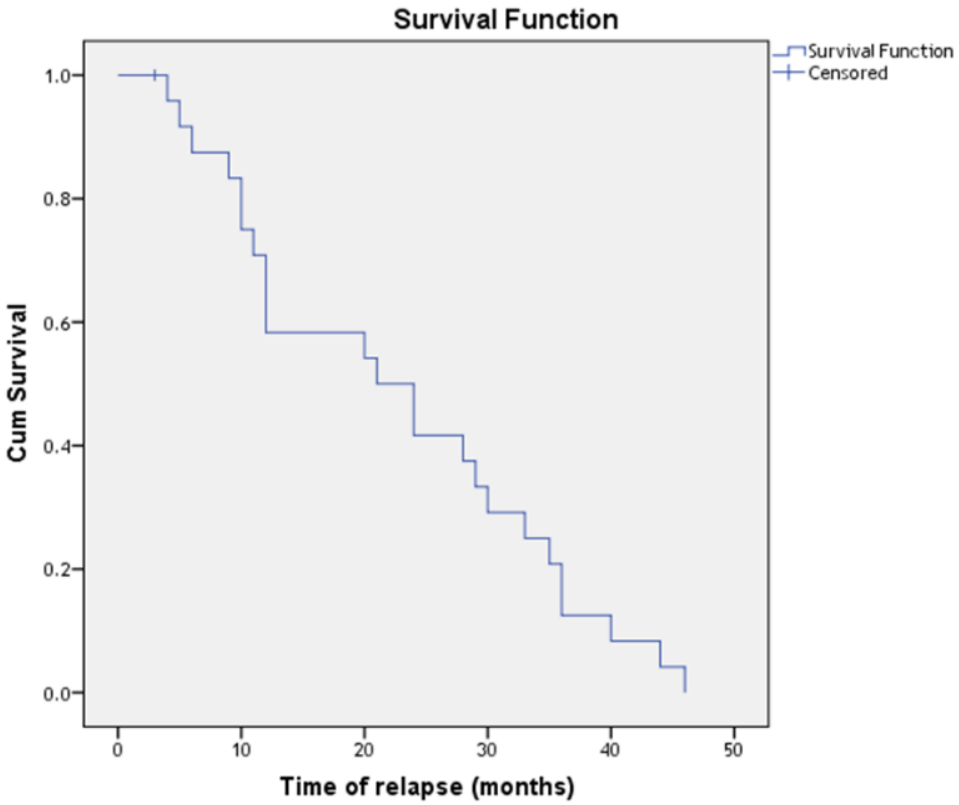

Figure 1. Kaplan–Meier curve of relapse-free survival (RFS).

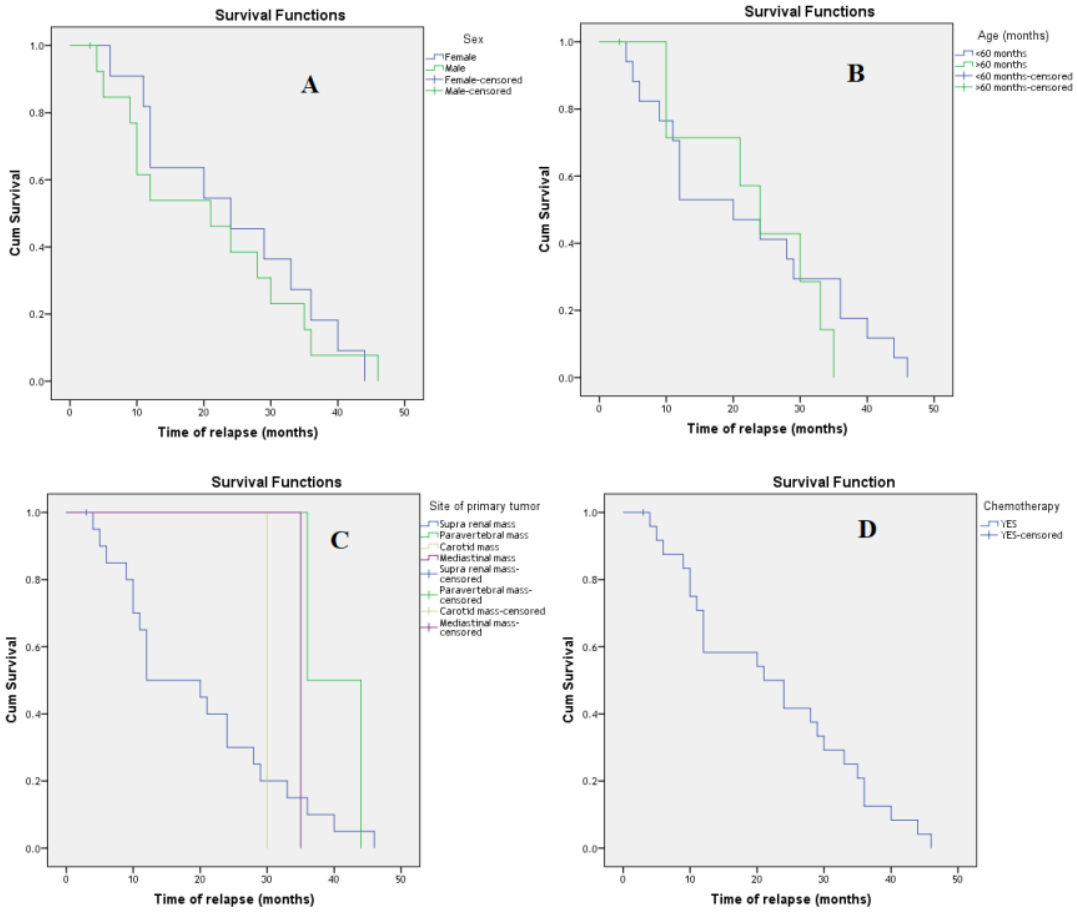

Figure 2. Kaplan–Meier curves of relapse-free survival (RFS) for (A) sex, (B) age, (C) site of primary tumor, (D) chemotherapy, (E) surgery, (F) radiotherapy, (G) doses of RT and (H) year of diagnosis

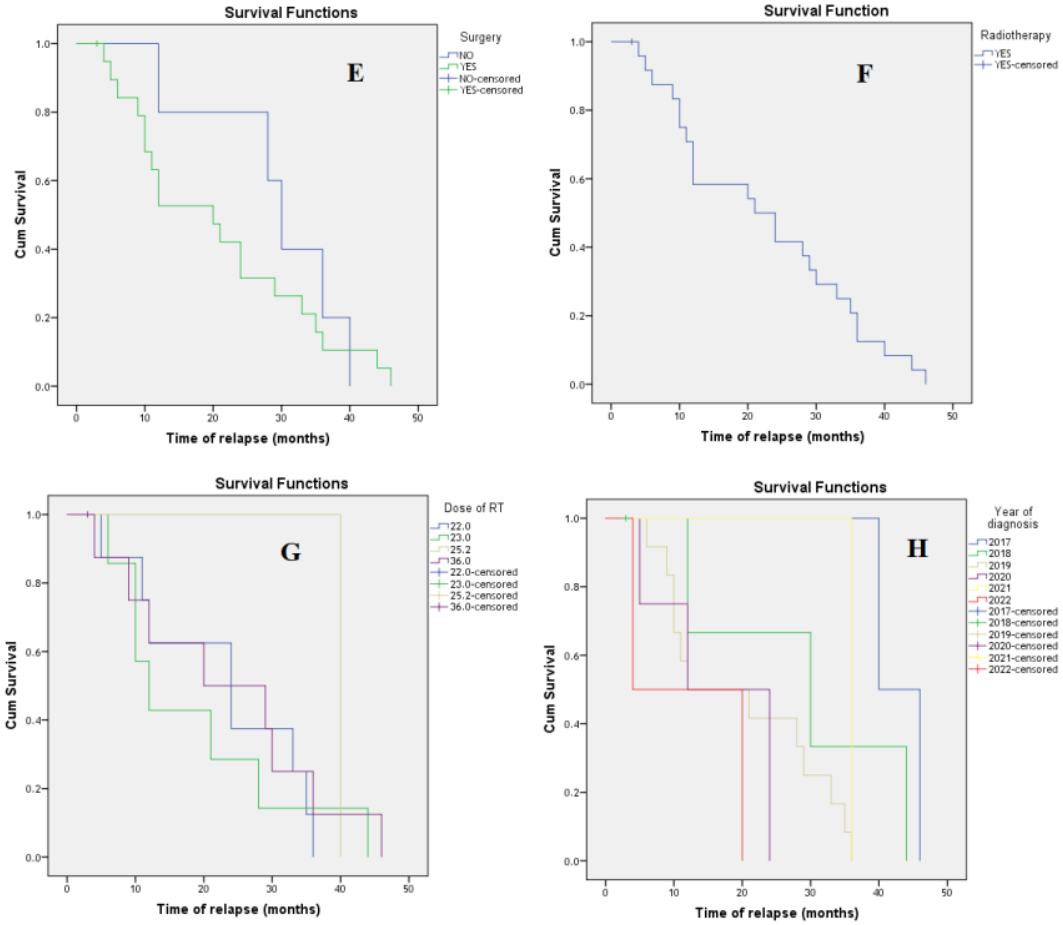

Figure 2. Continue

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.

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

Outcome	No.	%
Alive	5	20
Dead	20	80

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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, as shown in (Figure 3).

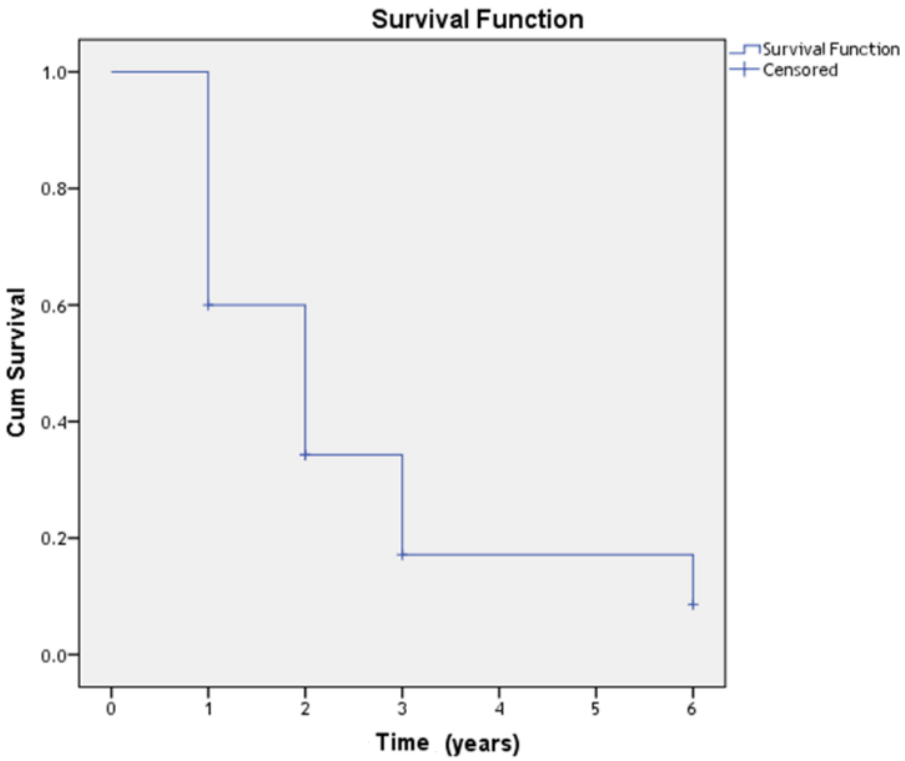


Figure 3. Kaplan–Meier curve of overall survival (OS)

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

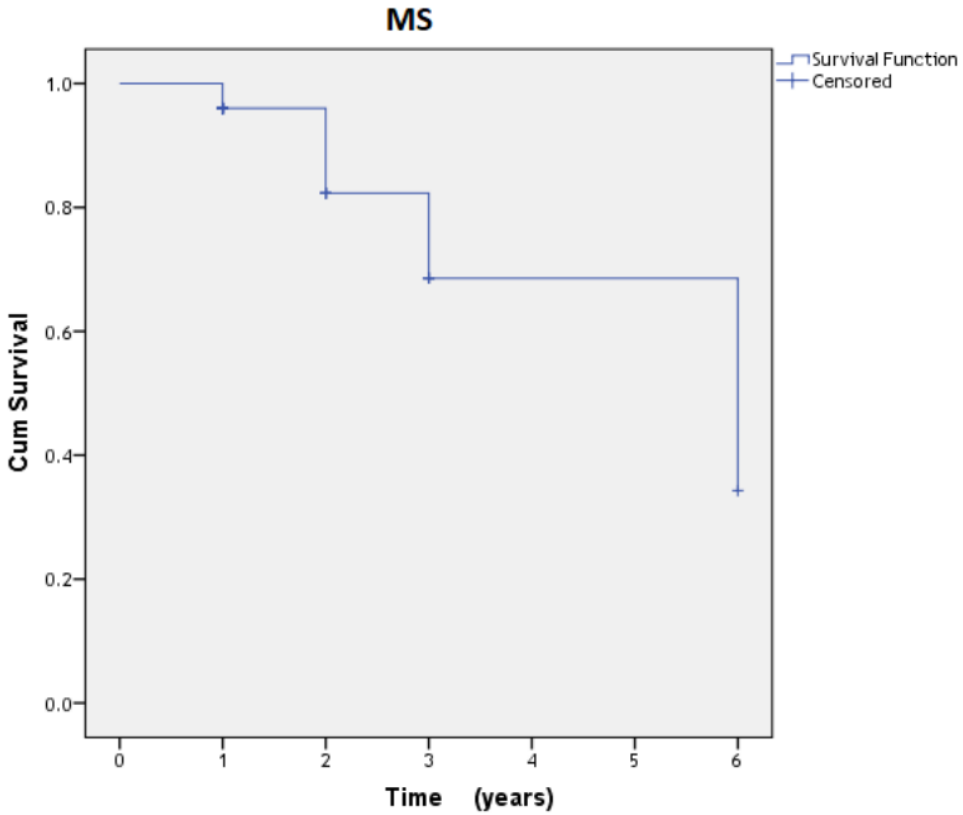


Figure 4. Kaplan–Meier curve of median survival (MS)

Kaplan–Meier analysis of OS according to sex shown in Figure (5 (A)). 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 (5 (B)). 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 (5 (C)). 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 (5 (E and 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 (5 (F)). 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 (5 (H)). 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 (5 (I)). 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.

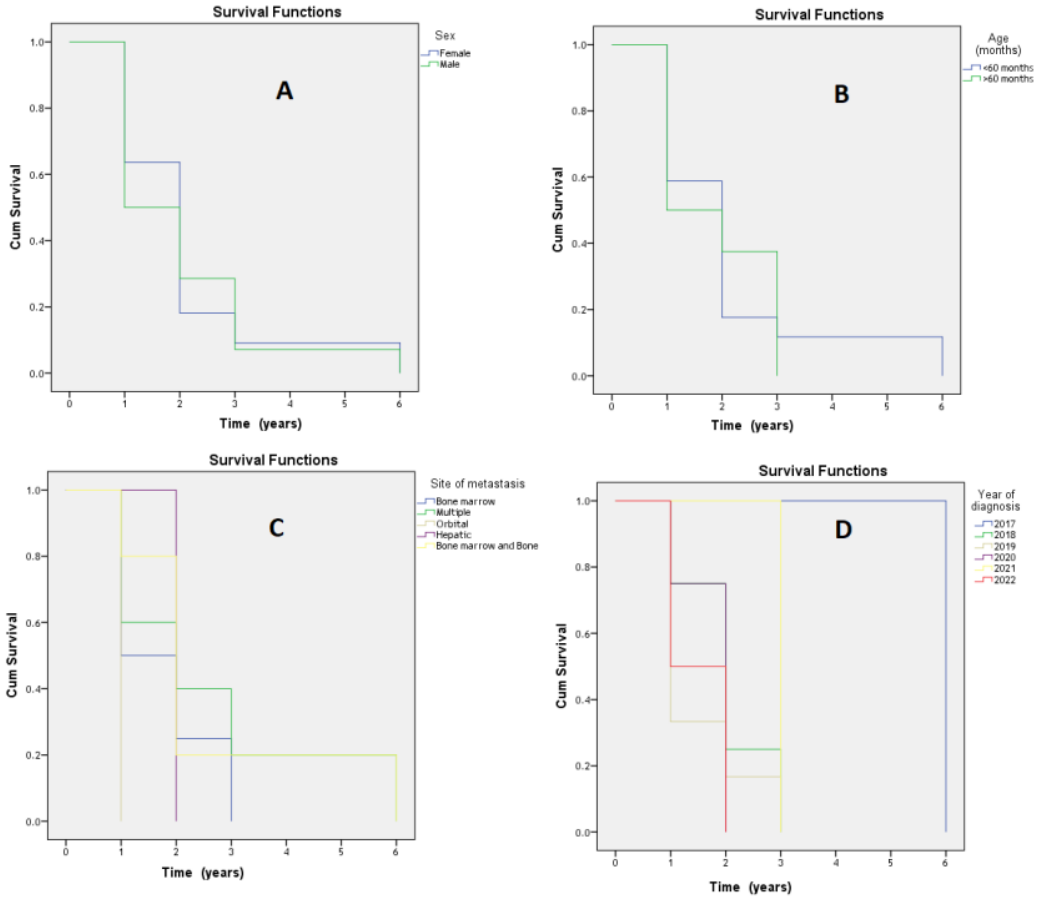
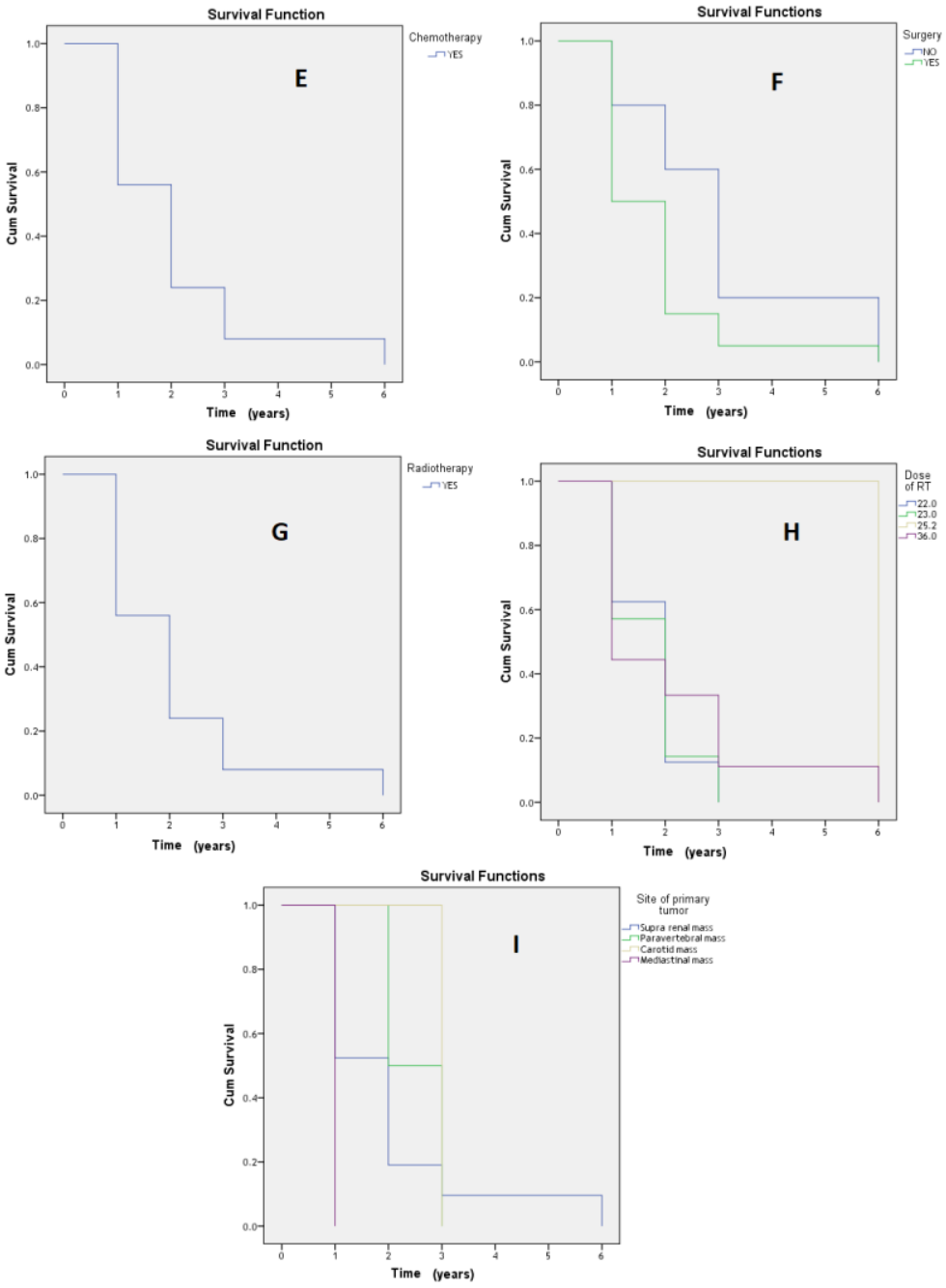


Figure 5. Kaplan–Meier curves of relapse-free survival (RFS) for (A) sex, (B) age, (C) site of metastasis, (D) year of diagnosis, (E) chemotherapy, (F) surgery, (G) radiotherapy, (H) doses of RT and (I) site of primary tumor



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Outcome data

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

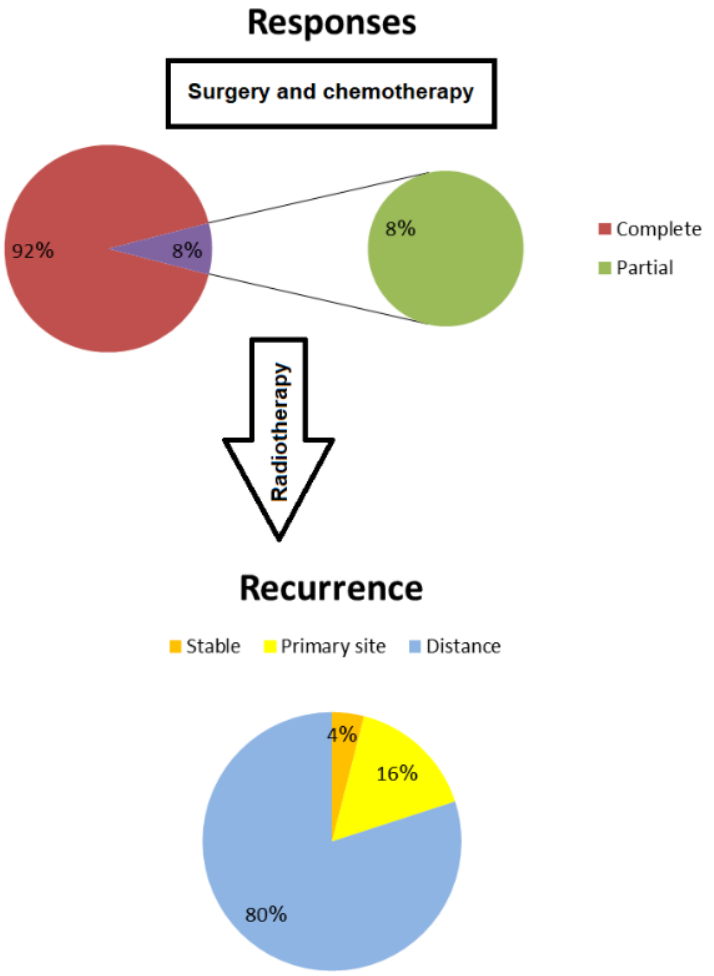

Figure 6. Responses and outcome after management of NB.

Discussion

To our knowledge, this study represent the first time study conducted in Iraq discussed the clinical outcomes in adjuvant setting radiotherapy to the primary site in of metastatic NB after complete remission to induction chemotherapy.

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). Cases of NB age below 60 months were 17(68%) whereas those above 60 months were 8(32%). 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. Orbital metastasis documented in two cases. All patients received chemotherapy and RT. Although, 80% of cases underwent surgery. Most of patients received RT at tumor bed (24, 96%). 9 out of 25 (36%) received 36Gy/20Fx RT dose. 8 out of 25 (32%) received 22Gy/12Fx RT dose. Seven out of 25 (36%) received 23Gy/13Fx RT dose. 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].

However, Jazmati and co-authors [11], studied 13 females and 5 males with S4 NB having received irradiation to a total of 24 metastatic lesions. The median age was 46 months. The irradiated metastatic sites were located either in the skull (n= 7), extremity (n= 10), spine (n= 5), or ribs (n= 2). Casey et al. [15] studied 159 NB cases. The median age at RT was 4 years. 62% received RT. 166 (68%) were bony metastases.

In 2015, Kandula et al. [16] studied 37 cases of NB with median age was 3.7 years. All patients underwent chemotherapy. The median RT dose to the primary site was 21.6 Gy. There were no significant baseline differences in case or tumor characters between the group did not receive RT to a metastatic site and the group that did receive RT.

In the present study, 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. The RFS was 22.38 months. It was 24.27 months for female whereas it was 20.77 months for male, with no significant difference (p=0.663). It was 22 months for those aged <60 months whereas it was 23.29 months for those aged ≥60 months with no significant difference (p=0.605). It was 19.6 months for supra renal masses whereas it was 40 months for paravertebral masses with no significant difference (p=0.456). It was 22.375 months for those received chemotherapy and/ or RT. It was 29.2 months for those underwent surgery while it was 20.579 months for those without surgery with no significant difference (p=0.421). It was 22.5 months for those received 22Gy, 18.71 months for those received 23Gy, and 23.25 months for those received 36Gy. Although, it 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 (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%) were alive with disease, and five (38%) died. Recurrence occurred in three cases (23%).

Polishchuck et al. [17] analyzed the pattern of metastatic recurrence in 43 NB cases. The majority of lesions were treated with a dose of 21.6Gy/12Fx. The risk for recurrence was not statistically lower in irradiated metastatic sites compared to non-irradiated metastatic sites. Similar data were found by Kandula et al. [16].

Both the Texas Children's Hospital and the Memorial Sloan Kettering Cancer Center (MSKCC), studied the effect of RT on NB survival. An local control (LC) rate of 74% at 5 years for irradiated metastatic lesions was reported in TCH [18] and 81% in MSKCC [15].

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

The combination of myeloablative therapy, immunotherapy, and differentiation therapy with 13-cis-retinoic acid has led to an improvement in survival for high-risk neuroblastoma. However, >50% of children will still undergo relapse systemically [19].

Although RT is routinely used to prevent local relapse, it is unknown whether irradiation to metastatic sites at risk of relapse can prevent disease recurrence and thereby increase long-term disease control [15].

The COG protocol ANBL0532 recommend irradiation to sites of metastatic disease that persist after induction chemotherapy. At our center, we have used 4 doses of RT to treat not only persistent sites of disease but also previous sites of measurable or bulky disease in complete response, especially those in emergence situations. The rationale for the latter approach stems from prior experiences showing that the majority of failures occur at previous sites of involvement, even those in complete response to induction therapy [17,20,21].

Similarly to this study data, the control rate in cases with gross disease at the primary site after induction chemotherapy and surgical resection is inferior [22,23]. Recently, data have suggested that 21 Gy to the primary site may not be a sufficient dose for these patients [15]. The modern protocols currently recommend 36 Gy postoperatively to the primary site for all cases with gross residual disease after resection [24].

In the study of Bradfield et al. [25], all initial sites of metastatic disease were irradiated after stem cell transplantation, regardless of the response to induction therapy. All patients received

RT, there were no local failures at irradiated sites. Polishchuk et al. [17] concluded that bone relapse tend to occur at anatomic sites of initial disease at diagnosis and that relapse are less common in the subset of metastatic sites that are irradiated.

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 and only one case still had stable disese. 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] reported that OS rates were 72.2 and 49.4%, respectively. At the time of analysis, 11 patients had deceased, nine due to tumor progression and two due to complications of the systemic therapy.

In the study of Kandula et al. [16], the median follow-up period without relapse was 61 months. The 5-year OS was 67%. For cases treated with and without RT to a metastatic site, the 5-year OS was 73% and 63%, respectively and the 5-year RFS was 46% and 55%, respectively.

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. The MS was 4.84 years. The OS was 2.09 yrs. for female whereas it was 2 yrs. for male). It was 2.12 yrs. for those aged <60 months whereas it was 1.875 yrs. for those aged ≥60 months with no significant difference (p=0.903). It was 1.75 yrs. for those with bone marrow secondaries. OS was 2.6 yrs. for those with multiple secondaries. It 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 (p=0.044). 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). It was 1.75 yrs. for those received 22Gy, 1.71 yrs. for 23Gy, and 2.11 yrs. for 36Gy. There was no significant difference among doses (p=0.23). 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 and colleagues [15] recorded the response to induction chemotherapy was prognostic of LC: The 5-year LC rate was 92% in sites that cleared with chemotherapy vs. 67% in persistent sites of disease (P<0.0001). However, on multivariate analysis, only persistence after induction chemotherapy remained significant (P < 0.0001).

Reports of primary site LC with RT have been excellent (84% to 100%); however, it appear that RT may not be as successful for control of metastatic sites [26,27].

Jazmati et al. [11] concluded that RT for children with high-risk NB metastases is feasible and highly tolerable, without any high-grade acute and late toxicity and no occurrence of secondary malignancies.

Yu et al., reported that the addition of immunotherapy with ch14.18 (a monoclonal antibody against the tumor-associated disialoganglioside GD2) to isotretinoin (standard therapy)and RT was associated with significantly improved event-free survival and OS outcomes in high-risk NB [28].

Local recurrence remain an obstacle in the treatment of NB and is a major cause of treatment failure. RT has become the standard practice in the treatment of high-risk NB and is typically administered to both the primary tumor bed with residual disease after surgical resection and persistent metastatic sites after induction chemotherapy. As a results, RT to the tumor bed post-surgical resection contribute significantly to local control and prevention of local relapse in high-risk NB. Palliative RT for metastasis is effective and safe [29].

Authors showed low event free survival due to high mortality rate due to lack of adequate supportive care, intensive care unit, BMT facility and abandonment of treatment [30].

Conclusion

Suprarenal masses of NB is the most common site of primary. The most common sites of metastasis of NB are bone marrow and bone. Early diagnosis, and aggressive management of NB may be enhance better outcomes. Skeletal relapse and bone marrow involvement are common. The RFS is 22.38 months and the OS of NB is 2.46 years for survivors. No difference in relapse-free survival and OS in relation to sex, age, site of primary tumor, chemotherapy, RT, surgery and RT doses.

Conflict of interesting

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