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Original Article

Local control and toxicity outcomes following consolidative radiation therapy in patients with high-risk neuroblastoma: a 20-year experience at a single center

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ABSTRACT

Background. Intensive multimodal treatment can improve survival in patients with high-risk neuroblastoma, and consolidative radiation therapy has contributed to local control. We examined the clinical outcomes of patients who underwent consolidative radiation therapy at our institution.

Methods. We retrospectively reviewed the records of patients with high-risk neuroblastoma who underwent consolidative radiation therapy from March 2001 to March 2021 at Asan Medical Center. Patients underwent multimodal treatment including high-dose chemotherapy, surgery, stem cell transplantation, and maintenance therapy. Radiation (median, 21.0 Gy; range, 14–36) was administered to the primary site and surrounding lymph nodes.

Results. This study included 37 patients, and the median age at diagnosis was 2.8 years (range, 1.3–10.0). Four patients exhibited local failure, and 5-year free-from locoregional failure rate was 88.7%, with a median follow-up period of 5.7 years. The 5-year disease-free survival (DFS) and overall survival (OS) rates were 59.1% and 83.6%, respectively. Univariate analysis revealed that patients with neuron-specific enolase levels >100 ng/mL had significantly worse DFS and OS (P = 0.036, 0.048), and patients with no residual disease before radiation therapy showed superior OS (P = 0.029). Furthermore, patients with 11q deletion or 17q gain exhibited poor DFS and OS, respectively (P = 0.021, 0.011). Six patients experienced grade 1 acute toxicity. Late toxicity was confirmed in children with long-term survival, predominantly hypothyroidism and hypogonadism, typically < grade 3, possibly attributed to combination treatment. Four patients experienced late toxicity ≥ grade 3 with chronic kidney disease, growth hormone abnormality, ileus, premature epiphyseal closure, and secondary tumor, and recovered by hospitalization or surgical treatment.

Conclusions. In patients with high-risk neuroblastoma, consolidative radiotherapy to the primary tumor site resulted in excellent local control and a tolerable safety profile.

Key words: neuroblastoma, radiation therapy, combined modality therapy, treatment outcome, toxicity.

Neuroblastoma (NB) is one of the most common extracranial solid cancers in pediatric patients, with more than 90% of cases detected in children less than 10 years of age.[1] Patients with NB are classified into risk groups based on the Children's Oncology Group (COG) risk classification system, and approximately 55% of these patients are in the high-risk group.[2] Previously, overall survival (OS) rates of less than 15% had been reported.[3] However, patients with high-risk NB (HR-NB) currently undergo a multimodal treatment strategy, including

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induction chemotherapy, resection of the primary tumor, high-dose chemotherapy and stem cell transplantation (SCT), consolidative radiation therapy, and maintenance systemic therapy using cis-retinoic acid and/or immunotherapy.[4-6] The use of these intensive treatment courses has increased the survival rate up to 50%.[3] Among them, consolidative radiation therapy was proven to improve local control (LC) at the primary tumor site.[4,7]

Several studies on consolidative radiotherapy for patients with NB have been published and topics related to dose and toxicity are well established.[7-10] The evaluation of both acute toxicity, occurring during or within three months of treatment, and late toxicity, defined as events that occur more than 3 months or even decades after treatment, is crucial in pediatric populations, as demonstrated in the literature.[11,12] However, there are few studies on radiation therapy with domestic data, and since our institution is one of the largest centers in Korea, a review of the clinical results of these patients will add to our understanding of the role of local control with radiation for this disease.[13] Therefore, we aimed to report the clinical outcomes of patients with HR-NB who underwent consolidative radiation therapy at our clinic, with a 20-year experience.

Materials and methods

Patients

This study was approved by the Institutional Review Board of Asan Medical Center. From March 2001 to March 2021, 50 patients with NB received radiation therapy at Asan Medical Center, with 42 patients treated for consolidation and 8 patients treated with a palliative aim. Among the 42 patients to recieve consolidative radiation therapy, 39 were patients with HR-NB, defined by the following COG Neuroblastoma Risk Stratification System: (i) International Neuroblastoma Risk Group (INRG) stage L1, *MYCN* amplified disease patient <12 months with incomplete resection, (ii) INRG stage L1, *MYCN* amplified disease patient ≥12 months with incomplete resection, (iii) INRG stage L2, *MYCN* amplified disease patient, (iv) INRG stage L2, *MYCN* non-amplified, unfavorable histology (UH) disease with age 18 months to <5 years, (v) INRG stage L2, *MYCN* non-amplified, undifferentiated, or poorly differentiated histology disease with age 18 months to <5 years, (vi) INRG stage M patients, except for those with *MYCN* non-amplified disease with age <12 months or age 12 month to <18 months with UH and DNA index >1, (vii) INRG stage MS, *MYCN* amplified disease patient <12 months without MS-related symptom, (viii) INRG stage MS, *MYCN* amplified disease patient age 12 to <18 months, (ix) INRG stage MS, *MYCN* non-amplified disease patient age 12 to <18 months with any unfavorable biology.[2] Finally, we analyzed the medical records of 37 patients <18 years of age with a sufficient follow-up period of at least 3 months after treatment.

Treatments

All patients underwent induction chemotherapy, surgery, and consolidative radiation therapy. Topotecan-containing induction therapy was used, and surgery was performed after a median of 5 cycles of chemotherapy. Gross total resection (GTR) was defined as the complete removal of any visible or palpable primary tumors and lymph nodes at the regional lymph node station and was evaluated based on the operation note description and pathology reports. If GTR was not acquired and residual lesions remained at the primary site or regional lymph node station after surgery, it was evaluated as subtotal resection (STR).

The delineation of the tumor bed was done with reference to the CT or magnetic resonance imaging (MRI) taken between the period of induction chemotherapy and surgery. The primary tumor bed, residual tumor, and regional lymph nodes were targeted, and clinical target volume (CTV) was delineated with a margin of 1.0 to 1.5 cm from the initial tumor bed and lymph node, and planning target

volume was set with a margin of 5 to 7 mm from the CTV. Radiation was delivered once or twice daily (five times per week), and treatment verification was performed by weekly kV X-ray or cone beam CT imaging guidance using set-up correction based on the bony anatomy.

Follow-up and outcomes

Patients were regularly evaluated for tumors by contrast-enhanced CT, MRI, or ^{123}I-meta-iodobenzylguanidine scan at intervals of 2 to 3 months, with bone marrow biopsy and positron emission tomography CT performed if new lesions appear, or progression is suspected. After induction chemotherapy, tumor response was evaluated according to the International Neuroblastoma Response Criteria, and the presence of residual disease was evaluated right before radiation treatment.[14]

The purpose of this study is to report the LC rate, disease-free survival (DFS), OS, and toxicity of patients with HR-NB who underwent radiation therapy. Freedom-from locoregional failure (FFLRF) was defined as the time from the first day of radiation therapy to the local recurrence. Also, we reviewed whether recurrence occurred within or outside the radiation field. DFS was calculated as the period from the initiation of induction chemotherapy to any disease progression (locoregional recurrence or distant metastasis) or death, and OS was defined as the time from the initiation of induction chemotherapy to death from any cause. Three months before and after terminating radiation therapy, we reviewed treatment-related acute and late toxicity based on Common Terminology Criteria for Adverse Events version 5.0.

Statistical analysis

Statistical analyses were performed using SPSS version 21.0 (SPSS Inc., Chicago, IL, USA). FFLRF, DFS, and OS were all calculated using the Kaplan–Meier method, and factors affecting each LC and survival were assessed using logistic regression analysis. Additionally, Fisher's exact test was used to identify factors that increase the risk of ≥ grade 3 late toxicity.

Results

Table I summarizes the patient characteristics. The median age at diagnosis was 2.8 years (range, 1.3–10.0), and 29 patients (78.4%) were diagnosed at age ≥18 months. The most common primary site was the adrenal gland, presented in 27 patients (73.0%), followed by the central abdominal compartment with six patients (16.2%) and thorax with four patients (10.8%). Six patients (16.2%) were categorized as INRG stage L2, 28 (75.7%) as stage M, and three patients (8.1%) as stage MS, and all the patients had INSS stage III or higher. At the time of initial diagnosis, 31 patients (83.8%) exhibited metastases to distant organs, and the most common sites (in order of occurrence) were bone marrow, skeletal bone, liver, lung, chest wall, and dura mater. The median levels of lactate dehydrogenase (LDH), neuron-specific enolase (NSE), and ferritin were 923.5 U/L (range, 223.0–5461.0), 170.9 ng/mL (range, 12.0–912.3), and 230.0 ng/mL (range, 19.9–941.3), respectively, and *MYCN* amplification was detected in 18 patients (48.6%).

Supplementary Table I presents the concise treatment scheme of patients with HR-NB who received multimodal treatment. Five patients (13.5%) could not receive SCT and/or maintenance therapy during the course of treatment due to intolerance to each treatment. Thirty-two patients (86.5%) received SCT, and three patients (8.1%) underwent total body irradiation (TBI) with a median of 8 Gy per four fractions (range, 5.25–10.5 Gy/ 4–7 fractions) before SCT. With radiation therapy, the median total dose for all patients was 21.0 Gy (range, 14.0–36.0) delivered by using 1.5–2.0 Gy per fraction. Patients who achieved GTR and STR received radiation doses ranging from 14.0 to 22.5 Gy and 18.0 to 36.0 Gy, respectively, with a median total dose of 21.0 Gy being the same for both groups. Twenty-nine patients (78.4%) were treated with three-dimensional conformal radiation therapy (3D-CRT) or intensity-modulated radiation therapy (IMRT), and eight (21.6%) received two-dimensional (2D) radiation therapy in the early 2000s.

Table I. Characteristics of patients with high-risk neuroblastoma having consolidative radiation therapy (n = 37).

Characteristics	No. of patients (%)
Sex	
Male	17 (45.9)
Female	20 (54.1)
Median age at diagnosis, years [range]	2.8 [1.3–10.0]
Age <18 months	8 (21.6)
Age ≥18 months	29 (78.4)
Primary site	
Adrenal gland	27 (73.0)
Central abdominal compartment	6 (16.2)
Thorax	4 (10.8)
INRG	
Stage L2	6 (16.2)
Stage M	28 (75.7)
Stage MS	3 (8.1)
INSS	
Stage III	6 (16.2)
Stage IV	31 (83.8)
Skeletal metastasis at diagnosis	
Yes	22 (59.5)
No	15 (40.5)
Bone marrow involvement at diagnosis	
Yes	23 (62.2)
No	14 (37.8)
Metastatic sites at initial diagnosis	
Bone marrow	23 (62.2)
Skeletal bone	22 (59.5)
Distant lymph node	15 (40.5)
Liver	5 (13.5)
Lung/ Chest wall	3 (8.1)
Dura mater	2 (5.4)
Median LDH at diagnosis, U/L [range]	923.5 [223.0–5461.0]
Median NSE at diagnosis, ng/mL [range]	170.9 [12.0–912.3]
Median Ferritin at diagnosis, ng/mL [range]	230.0 [19.9–941.3]
MYCN amplification	
Yes	18 (48.6)
No	17 (45.9)
Unknown	2 (5.4)
Shimada histopathology	
Favorable histology	12 (32.4)
Unfavorable histology	19 (51.4)
Unknown	6 (16.2)
Differentiation	
Well-differentiated	4 (10.8)
Poorly differentiated	18 (48.6)
Undifferentiated	3 (8.1)
Unknown	12 (32.4)
1p deletion	
Yes	6 (16.2)
No	31 (83.8)
11q deletion	
Yes	6 (16.2)
No	31 (83.8)
Trisomy 17q	
Yes	2 (5.4)
No	35 (94.6)

Abbreviations: INRG, International Neuroblastoma Risk Group; INSS, International Neuroblastoma Staging System; LDH, Lactate dehydrogenase, NSE, Neuron-specific enolase.
The sum of percentages may not be 100, rounded to one decimal place.

Table II summarizes the course of treatment and response or status after induction chemotherapy and surgery. Twenty-three patients (62.2%) showed a partial response on evaluation after induction chemotherapy, with no patient exhibiting a complete response or progressive disease. As a result of subsequent surgery, 24 patients (64.9%) were eligible for GTR, and the remaining 13 patients (35.1%) received STR with residual disease at the primary site which was also confirmed by postoperative imaging. In the imaging test performed before radiation therapy, 20 patients (54.1%) had no residual disease, nine (24.3%) presented with residual disease only at the primary site, four (10.8%) exhibited disease at distant sites, three (8.1%) had disease at both primary and distant sites, and one (2.7%) showed only bone marrow involvement. At the time of radiation therapy, the median age was 3.8 years (range, 2.0–11.3).

Table II. Course of treatment and response of patients with high-risk neuroblastoma having consolidative radiation therapy.

Characteristics	No. of patients (%)
Response to induction chemotherapy	
CR	0 (0.0)
VGPR	3 (8.1)
PR	23 (62.2)
MR	2 (5.4)
NR	9 (24.3)
PD	0 (0.0)
Extent of surgery	
Gross total resection	24 (64.9)
Subtotal resection	13 (35.1)
Stem cell transplant	
Yes	33 (89.2)
No	3 (10.8)
Maintenance therapy	
Yes	33 (89.2)
No	4 (10.8)
Total body irradiation	
Yes	3 (8.1)
No	34 (91.9)
Status before consolidative radiation therapy	
No residual disease	20 (54.1)
Residual at primary site	9 (24.3)
Residual at metastatic site	4 (10.8)
Residual at both primary and metastatic site	3 (8.1)
Bone marrow involvement only	1 (2.7)
Median age, at radiation therapy, years [range]	3.9 [2.0–11.3]
Total radiation dose, median, Gy [range]	21.0 [14.0–36.0]
Fraction size	
1.5 Gy/fx	21 (56.8)
1.8 Gy/fx	11 (29.7)
2.0 Gy/fx	5 (13.5)
Median BED*, Gy10, [range]	24.15 [16.80–42.48]
Radiation schedule	
Once per day (QD)	19 (51.4)
Twice per day (BID)	18 (48.6)
Radiation to metastatic site	
Yes	6 (16.2)
No	26 (70.3)
Not indicated	5 (13.5)

BED, Biologically effective dose; CR, Complete response; MR, Mixed response; NR, No response; PD, Progressive disease; PR, Partial response; VGPR, Very good partial response.
* Biologically effective doses are calculated using an α/β ratio of 10 Gy.
The sum of percentages may not be 100, rounded to one decimal place.

The median follow-up period was 69.0 months (range, 12.0–237.6) (Supplementary Table II). Among the 37 patients who received consolidative radiation therapy, four (10.8%) experienced locoregional failure and 14 (37.8%) had distant metastases; Among the four patients with locoregional failure, three patients (8.1%) also experienced distant metastases. The 1-, 3-, and 5-year FFLRF rates were 91.7%, 88.7%, and 88.7%, respectively. Table III presents the disease and treatment characteristics of four patients with locoregional failure. Two patients had INRG stage M disease, one presented stage MS, and the other had stage L2. Except for one unconfirmed patient, *MYCN* amplification was detected in all patients. All surgeries at the primary site were performed once, and all but one patient underwent STR. The total radiation dose ranged between 19.5 and 22.5 Gy. The 2D technique was performed on three patients who were treated before 2010, and one patient underwent 3D-CRT in 2014. All patients had in-field recurrence, and the median time until local failure was 2.75 months (range, 1.03–16.77). In three patients, distant metastases were noted as the first event, followed by local failure. Among the 14 patients who later developed distant metastasis during follow-up, six received RT for metastatic sites for salvage or palliative purposes. The median RT dose administered was 22.5 Gy, and detailed dose information and locations can be found in Supplementary Table III.

Also, the 1-, 3-, and 5-year DFS rates for all patients were 91.9%, 70.3%, and 59.1%, respectively. Eleven patients (29.7%) deceased during the follow-up period, with six deaths (54.5%) attributed to tumor progression, and five (45.5%) were due to sepsis during salvage or palliative chemotherapy for recurrent disease. The 1-, 3-, and 5-year OS rates were 100.0%, 83.6%, and 83.6%, respectively.

A univariate analysis was performed, and the results are shown in Supplementary Table IV. DFS and OS were both superior for patients with an NSE level <100 ng/mL (NSE ≥100 ng/mL vs. <100ng/mL; 3-year DFS, 52.5% vs.

Table III. Patients with local failure at the primary site.

Case number/Sex	1/Male	2/Male	3/Female	4/Male
Age at diagnosis, years	2.49	1.89	1.25	2.66
Disease characteristics				
INRG	M	L2	MS	M
INSS	4	3	4	4
MYCN amplification	Unknown	Yes	Yes	Yes
Primary site	Adrenal gland	Adrenal gland	Adrenal gland	Adrenal gland
Skeletal metastasis	Yes	No	No	Yes
Treatment characteristics				
Extent of surgery	GTR	STR	STR	STR
SCT	No	Yes	Yes	Yes
TBI	Yes	No	No	No
Radiation therapy				
Age, years	3.12	2.82	2.07	4.07
Total dose, Gy	19.5	22.5	21.0	21.0
Fraction size, Gy	1.5	1.5	1.5	1.5
Radiation technique	2D	2D	2D	3D
Radiation schedule	QD	BID	BID	BID
Result of treatment				
Response to initial chemotherapy	PR	PR	PR	PR
Residual disease before irradiation	Primary site	(-)	Metastatic site	(-)
Local failure	In-field	In-field	In-field	In-field
Time to local failure (months)	1.03	3.00	2.50	16.77
Distant metastasis	Yes	No	Yes	Yes
Site of distant metastasis	Mediastinal LN	(-)	Liver	Lung, Liver, Bone, BM
Survival	Death	Death	Death	Death

2D, Two-dimensional; 3D, Three-dimensional; BM, Bone marrow; GTR, Gross total resection; INRG, International Neuroblastoma Risk Group; INSS, International Neuroblastoma Staging System; LN, Lymph node; PR, Partial response; SCT, Stem cell transplantation; STR, Subtotal resection; TBI, Total body irradiation.

100.0%, $p = 0.036$; 3-year OS, 73.4% vs. 100.0%, $p = 0.048$). Also, patients who had no evidence of any residual disease at primary and distant sites before radiation therapy demonstrated a higher OS rate (no residual disease vs. residual disease, 3-year OS, 95.0% vs. 70.6%, $p = 0.029$), but not with FFLRF or DFS (no residual disease vs. residual disease; 3-year FFLRF, 89.5% vs. 88.2%, $p = 0.807$; 3-year DFS, 75.0% vs. 64.7%, $p = 0.496$). *MYCN* non-amplified disease seemed to provide marginally superior LC (*MYCN* amplification vs. *MYCN* un-amplification, 3-year FFLF, 81.4% vs. 100.0%, $p = 0.070$); however, no clinical factor demonstrated statistically significant results for FFLRF. Additionally, in the analysis of another important genetic or chromatin change in neuroblastoma associated with a poor prognosis, it was found that patients with 11q deletion or 17q gain exhibited poor DFS and OS, while there was little association with 1p deletion.

Treatment-related toxicity is shown in Table IV. Acute toxicity occurred in six patients (16.2%) with grade 1. Late toxicity occurred in 24 patients (64.9%). The most frequent adverse events were hypothyroidism, chronic kidney disease, and growth hormone abnormalities.

Table IV. Treatment-related toxicity in patients with high-risk neuroblastoma who received multimodality treatment.

	No. of patients (%)				
	Grade 1	Grade 2	Grade 3	Grade 4	Total
Acute toxicity	6 (16.2)	0 (0.0)	0 (0.0)	0 (0.0)	6 (16.2)
Anorexia	3 (8.1)	0 (0.0)	0 (0.0)	0 (0.0)	3 (8.1)
Nausea	3 (8.1)	0 (0.0)	0 (0.0)	0 (0.0)	3 (8.1)
Vomiting	1 (2.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.7)
Late toxicity	3 (8.1)	17 (45.9)	3 (8.1)	1 (2.7)	24 (64.9)
Chronic kidney disease	2 (5.4)	6 (16.2)	2 (5.4)	0 (0.0)	10 (27.0)
Diabetes	0 (0.0)	1 (2.7)	0 (0.0)	0 (0.0)	1 (2.7)
Gait disturbance	1 (2.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.7)
Growth hormone abnormality	2 (5.4)	4 (10.8)	1 (2.7)	0 (0.0)	7 (18.9)
Hypercholesterolemia	0 (0.0)	4 (10.8)	0 (0.0)	0 (0.0)	4 (10.8)
Hypertrophic hypogonadism	1 (2.7)	4 (10.8)	0 (0.0)	0 (0.0)	5 (13.5)
Hypothyroidism	0 (0.0)	17 (45.9)	0 (0.0)	0 (0.0)	17 (45.9)
Mechanical ileus	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.7)	1 (2.7)
Premature epiphyseal closure	0 (0.0)	0 (0.0)	2 (5.4)	0 (0.0)	2 (5.4)
Secondary tumor	0 (0.0)	0 (0.0)	1 (2.7)	0 (0.0)	1 (2.7)
Scoliosis	3 (8.1)	0 (0.0)	0 (0.0)	0 (0.0)	3 (8.1)

Toxicity ≥grade 2 occurred in 21 patients (56.8%), which was detected at a median of 21.0 months (range, 4.2–201.2) from the end of radiation therapy until event occurrence. A total of four patients (10.8%) experienced ≥grade 3 adverse events, including chronic kidney disease, growth hormone abnormality, premature epiphyseal closure, secondary tumor, and mechanical ileus. One patient with grade 4 ileus recovered after laparoscopic adhesiolysis and exploration. Only one patient presented with a secondary malignant neoplasm (SMN), and papillary thyroid cancer developed, necessitating removal by thyroidectomy. The fisher's exact test was used to detect factors related to ≥grade 3 late toxicity; however, no factors with significantly increased toxicity were documented (Supplementary Table V).

Discussion

In the last decade, consolidative radiation therapy in patients with HR-NB was shown to have LC rates of 78.9–100.0% with a radiation dose of 21.0 Gy (range, 18.0–36.0 Gy).[7-10] At our center, we documented a 5-year LC rate of 88.7%, with a median follow-up period of 69.0 months in 37 patients, which was consistent with research conducted in recent years. Casey et al.[8] have reported that LDH, *MYCN* amplification, number of surgeries, and the presence of skeletal metastases could be risk factors associated with local failure. However, none of the factors, including total radiation dose and surgical extent, were significantly associated with LC in the present study. It remains unclear about the appropriate radiation dose in several studies for patients with STR.[7,8,15] Although we identified STR in three of four patients with in-field recurrence, univariate analysis revealed that surgical extent was not associated with LC. Casey et al.[16] have performed a dose escalation study for patients with HR-NB presenting gross residual disease. For 19 patients, RT doses of 21, 30, and 36 Gy with a local failure rate of 0.0% were recorded in the 30 and 36 Gy groups and 30% in the 21 Gy group, thereby showing a tendency for improved LC at higher doses (p = 0.12). In contrast, in the ALBL0532 study[17], a prescription dose of 21.6 Gy was administered to patients who had undergone complete resection, while

patients with incomplete resection received 36.0 Gy. The 5-year cumulative incidence of local progression showed a marginal difference between the two groups, with rates of 11.2% versus 7.1%, respectively (p=0.059). A study assessing only patients with GTR documented an excellent LC exceeding 90% with hyper-fractionated RT at 21 Gy after intensive systemic therapy and debulking surgery.[8] Based on the results of the present study, an RT dose of 21 Gy could be considered sufficient for LC, and efforts to reduce the dose have been recently proposed owing to concerns regarding potential late toxicity, which needs to be confirmed in future investigations. In one study[18], it has been proposed to consider de-escalation of radiation for patients with no image-defined risk factors and those with over 90% resection.

In the present study, the 3-year DFS and OS were 70.3% and 83.6% respectively, which was superior to those of other studies presented in Supplementary Table II. These favorable outcomes can be attributed to the implementation of systemic therapies both in the pre- and post-surgical phases, alongside the inclusion of SCT, with most of our patients demonstrating strong compliance.[19,20] Furthermore, while the number of patients is not large, it is believed that maintenance treatments, including interleukin-2 for 10 patients (27.0%) and anti-GD2 monoclonal antibodies for two patients (5.4%), may have contributed to longer survival to some extent.[21] Nevertheless, fourteen patients experienced distant recurrence, of which seven presented lesions at the same site as those at diagnosis, which remained invisible during the treatment course owing to intensive systemic therapy. Herein, six patients underwent palliative radiation therapy at the metastatic site after recurrence. Conversely, in a study by Chen et al.[9], 12 patients with metastatic lesions detected at initial diagnosis were treated with synchronous radiation treating the primary tumor; however, no significant difference in distant failure or survival was noted compared with those who did not receive this treatment course. No standardized treatment for distant lesions has been established, considering that most metastatic lesions are multiple and widely distributed and respond well to maintenance chemotherapy in some cases; however, radiation as a salvage or palliative strategy is recommended when warranted, rather than as an early treatment strategy.

Using univariate analysis, we found that the NSE level at diagnosis was related to poor DFS and OS. NSE is expressed in patients with NB and various cancers, including small cell lung cancer and melanoma, and has been described as a factor indicating poor prognosis. Georgantzi et al.[22] found that elevated levels of chromogranin A (CgA) and NSE were found in advanced-stage patients, with NSE correlating with outcomes and tumor size. They highlighted the clinical significance of NSE as a tumor marker in NB, while CgA merits further investigation in prospective, multicenter clinical studies. Furthermore, a study by Cangemi et al.[23], which included 505 patients with NB, has also demonstrated the prognostic value of NSE levels, in addition to ferritin, lactate dehydrogenase, catecholamine metabolites, consistent with the findings of our current study. Therefore, NSE levels at diagnosis or during treatment could be used as useful serum markers to aid in treatment-related decisions.

In addition to the biomarker changes in serum, there are several well-known genetic factors associated with poor prognosis in NB. Among them, aberrations in 11q and 17q were also confirmed to be associated with poor prognosis in our study. Regarding this, efforts are still ongoing, from the preclinical stage onwards, to understand the roles of these factors and to develop cancer treatments targeting them.[24-27]

Considering the recent development of systemic therapy and prolonged survival, late toxicity is particularly important in pediatric patients, especially as the number of long-term survivors has increased. During a 20-year follow-up period, Geurten et al.[28] reported

that 54% of patients experienced long-term adverse events, and 28% had endocrine complications. Additionally, it has been reported that 89% of patients with NB had at least one medical condition, with 50% showing abnormal endocrine function.[29,30] Furthermore, in a recently published review study[31], it was also highlighted that thyroid carcinoma and myeloid leukemia are the most commonly reported subsequent neoplasms in survivors of NB, and the risk of these neoplasms was found to be 2.8 to 10.4 times higher than in the general population. In the present study, 22 patients (59.5%) presented with endocrine dysfunction, with hypothyroidism noted most commonly, followed by growth hormone abnormality, hypercholesterolemia, hypogonadism, and diabetes. SMN occurred in one patient (2.7%) and was diagnosed as papillary thyroid cancer. The patient had a primary tumor located in the thorax with nodal metastasis involving the neck nodes, therefore including the supraclavicular lymph nodes and mediastinum within the radiation field. He received radiation therapy at the age of 3.5, with a dose of 21 Gy in 14 fractions using a 2D technique. Thyroid cancer developed approximately 10 years and 11 months after radiation therapy, and no TBI was done separately. According to the SEER data study by Applebaum et al.[32], 34 of 2,801 patients with NB developed SMN, accounting for 1.2%. Additionally, the 30-year cumulative incidence of SMN in HR patients who received intensive multimodal treatment was 10.4%. The median latency time for SMN was 38 months for all hematologic malignancies and 158 months for solid tumors. Herein, the median follow-up period for surviving children was 78.8 months (range, 16.5–240.8), which is considered insufficient time to detect SMN; hence, the incidence rate may have been low. Furthermore, since the occurrence of late toxicity in pediatric patients is presumed to be due to multifactorial attributes, special attention is required in determining the treatment for each department.

The major advantage of the present study is that we analyzed the treatment process and results of patients who received multiple treatments at a single institution with domestic data. Additionally, as seen in Supplementary Table II, the median follow-up period was 69.0 months, providing data for a markedly sufficient time to reveal treatment efficacy.

However, there are some limitations to our study. First of all, as this study is a retrospective study for a disease with a low incidence, the number of patients analyzed is small. In addition, because of the small sample size and only four patients with local failure, this study may not be sufficient to assess risk factors for local failure. Also, there were some heterogeneous approaches to radiation treatment dose or technique by setting a long recruitment period to analyze the data of as many patients as possible. For the same reason, we included patients who received radiation therapy using older techniques performed in the early 2000s. Furthermore, immunotherapy, including anti-GD2 antibodies, has recently been widely applied as maintenance therapy; however, only a small portion of patients in the present study were treated with interleukin-2 or anti-GD2 monoclonal antibodies.[33] Therefore, improved survival outcomes could have been achieved if more recent radiation technology and tailored systemic treatments were applied. Lastly, although the observation period was sufficient to observe treatment efficacy, it was deemed insufficient for late toxicity assessments. Therefore, conducting a toxicity study on the same set of patients after a longer observation period would be helpful in the future.

In conclusion, consolidative radiation therapy to the primary tumor site could provide excellent LC in patients with HR-NB. To reduce late toxicity caused by the cumulative side effects of various treatments, additional efforts are needed to reduce the total radiation dose. Additionally, controlling distant recurrence is essential for increasing the survival rate, thereby necessitating active monitoring and additional treatment, especially in patients with poor prognosis.

Supplementary Materials

Supplementary materials for this article are available online at https://doi.org/10.24953/turkjped.2023.575

Ethical approval

This study was conducted in accordance with the 1964 Declaration of Helsinki. This study was approved by the Institutional Review Board of Asan Medical Center (#2022-0772), and written informed consent was waived due to the retrospective nature of this study.

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: JY Jang, SD Ahn, YJ Kim.; data collection: JY Jang, HU Kim, HJ Im, KN Koh, HR Kim, SH Kang.; analysis and interpretation of results: JY Jang, HU Kim, JH Park, YJ Kim.; draft manuscript preparation: JY Jang. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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