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# Local Control and Clinical Outcome of High-risk Pediatric Neuroblastoma Patients After Receiving Multimodality Treatment and Helical Tomotherapy

GUANN-YIING CHEN[1], JASON CHIA-HSIEN CHENG[1,2], YU-HSUAN CHEN[1], MENG-YAO LU[3], HSIU-HAO CHANG[3], YUNG-LI YANG[3], SHIANN-TARNG JOU[3], WEN-MING HSU[4] and SUNG-HSIN KUO[1,2,5,6]

*[1]Division of Radiation Oncology, Department of Oncology, National Taiwan University Hospital and National Taiwan University College of Medicine, Taipei, Taiwan, R.O.C.; Departments of [3]Pediatrics and [4]Surgery, National Taiwan University Hospital and National Taiwan University College of Medicine, Taipei, Taiwan, R.O.C.; [2]Graduate Institute of Oncology, [5]Cancer Research Center, and [6]National Taiwan University Cancer Center, National Taiwan University College of Medicine, Taipei, Taiwan, R.O.C.*

**Abstract.** *Background/Aim: The local control and clinical outcome of pediatric patients with high-risk neuroblastoma treated with tomotherapy as part of a modern multimodality paradigm was assessed. Patients and Methods: Twenty-four high-risk neuroblastoma patients who received radiotherapy (RT) to the primary site using helical tomotherapy (median 21.6 Gy) were included. Local failure (LF) was correlated with biological and clinical prognostic factors. Event-free survival (EFS) and overall survival (OS) were estimated using Kaplan-Meier analysis. Results: After a median follow-up of 43.5 months, the 3-year cumulative incidence of LF, EFS, and OS were 21.1%, 45.8%, and 62.9%, respectively. Elevated serum lactate dehydrogenase ≥1,500 U/l was associated with worse LF (p=0.02). There was no 3-year LF noted for patients with gross residual disease (GRD) who received more than 21.6 Gy. Conclusion: We demonstrated favorable local control of tomotherapy for the treatment of high-risk neuroblastoma. Dose escalation of RT for patients with GRD should be investigated.*

Neuroblastoma is the most common pediatric extracranial solid tumor, accounting for 15% of cancer-related deaths during childhood. Risk stratification with clinical and biological factors determines the subsequent treatment plans for this disease, known for its broad spectrum of clinical behavior (1, 2). Patients older than 18 months with metastatic disease and patients with *MYC-N* amplification at any age comprise the majority of high-risk cases under the revised stratification scheme used by the Children's Oncology Group (COG) (2).

Regarding these high-risk neuroblastomas, several studies have demonstrated the benefit of multimodality treatment, including induction chemotherapy in attempting chemoreduction followed by surgical resection of the primary tumor, consolidation high-dose chemotherapy with autologous stem-cell transplantation (ASCT), radiotherapy (RT) to the primary tumor site, and maintenance treatment (3-5). Recent advances have been attained by maximizing the intensity of myeloablative therapy in combination with stem cell rescue and tandem ASCT, followed by maintenance therapy with anti-GD2 antibody plus cytokines, further improving the event-free survival (EFS) and overall survival (OS) of patients with high-risk neuroblastoma (6-11).

A randomized study proved that the addition of local RT, as part of a consolidation therapy, to the primary tumor was beneficial in patients with high-risk disease in terms of disease control and survival (12). Several single-institution series also showed that consolidative RT provided excellent local control (13-20). However, the optimal dose and fractionation scheme of RT, and whether dose-escalation to gross residual disease (GRD) after operation or high-dose chemotherapy and ASCT is required, remain unclear, especially concerning the inherent toxicities of RT to pediatric patients.

In this retrospective study, we investigated the local control rate and clinical outcome of daily image-guided intensity-modulated radiation therapy (IMRT) using helical

*Correspondence to:* Sung-Hsin Kuo, MD, Ph.D., Division of Radiation Oncology, Department of Oncology, National Taiwan University Hospital, No. 7, Chung-Shan South Rd, Taipei, Taiwan, R.O.C. Tel: +886 223123456, ext.67144, Fax: +886 223711174, e-mail: shkuo101@ntu.edu.tw

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tomotherapy as part of a modern multimodality paradigm and its toxicity to children with high-risk neuroblastoma, treated at our institution.

## Patients and Methods

*Patients and multimodality treatment*. This was a retrospective analysis of patients with high-risk neuroblastoma, who were treated consecutively at the National Taiwan University Hospital between 2009 and 2015. The definition of high-risk neuroblastoma was based on the criteria of the International Neuroblastoma Risk Group (INRG) Classification System (2) and in accordance with the following COG studies. All children received *$^{18}$F-FDOPA* (6-[$^{18}$F]-L-fluoro-L-3, 4-dihydroxyphenylalanine) scan for detection of possible metastatic foci (21). All children, except two who underwent resection upfront, were treated using the Taiwan Pediatric Oncology Group (TPOG) N2002 risk-adapted protocol (22). They subsequently underwent radical surgery, if suitable, typically between 4 and 7 months after the initiation of chemotherapy, followed by hematopoietic stem cell transplantation (HSCT), if appropriate. RT to the primary site (and metastatic site(s), if applicable) was commenced within 1 to 2 months of HSCT. The children then underwent maintenance therapy with cis-retinoid acid, with or without maintenance anti-GD2 antibody.

In this study, patients who received IMRT to the primary tumor site, using helical tomotherapy as part of the modality treatment, were included. RT was administered in 1.75- to 1.8-Gy fractions, 5 days a week, to a total dose ranging from 21.6 to 35 Gy (median 21.6 Gy), with weekly concurrent vincristine. Daily image-guidance with cone-beam megavoltage computed tomography was employed to reduce day-to-day set-up error. Response to treatment was evaluated based on the International Neuroblastoma Response Criteria (23). Data were extracted from electronic medical records and imaging records.

*Statistical analysis*. The primary endpoint was local failure (LF). Secondary endpoints included the identification of prognostic factors affecting outcome, the pattern of failure, survival outcome, and toxicity. LF was defined as the time interval from the initiation of RT to the date of any local disease recurrence or progression. Distant failure was defined as the time interval from the initiation of RT to the date of radiologically-confirmed distant disease recurrence or progression. OS was calculated from the date of initiation of RT to the date of death from any cause or last follow-up for survivors, and EFS was calculated from the date of initiation of RT to the date of the first event (including disease recurrence, progression, or death) or to the date of the last follow-up for patients without events.

Variables collected included age at diagnosis/age at RT, sex, primary site (intra-abdomen or elsewhere), metastasis site, tumor size, lactate dehydrogenase (LDH), ferritin, International Neuroblastoma Staging System classification, International Neuroblastoma Risk Group classification, histology, grade, *MYC-N* amplification status, the use of surgery and lymph node dissection, the use of HSCT and maintenance therapy, and the presence of GRD at the start of RT. The cumulative incidence of LF was assessed using a competing-risks analysis with death as the competing risk. Cumulative incidences of LF among different subgroups were compared using Gray's method (24). Kaplan–Meier analysis was used to estimate the OS and EFS. Statistical analysis was performed with R, version 3.3.2 (Free Software Foundation, Inc. 51 Franklin St, Fifth Floor, Boston, MA, USA). Treatment toxicity was graded according to the Common Toxicity Criteria for Adverse Events, version 4.3.

## Results

*Patient characteristics and treatment modality*. Twenty-nine patients were identified in our database. Five patients, two with intermediate-risk disease, two lost to follow-up after completion of RT, and one deceased before subsequent imaging studies, were excluded. A total of 24 patients were included in the analysis. Patient characteristics are listed in Table I. Most patients had stage 4 disease (88%), and three patients with stage 3 disease either had *MYC-N* amplification or had unfavorable histology and were >1.5 years old. Twenty-one patients (88%) underwent surgery, and thirteen (54%) underwent additional lymph node dissection. Twenty-one patients underwent at least one course of HSCT (88%) (Figure 1). The median follow-up for the surviving patients was 43.5 months (range=25-100 months) from diagnosis, and 27.5 months (range=8-84 months) from starting RT.

*Local control and failure pattern*. Five patients (20.8%) experienced LF, and the median time to LF was 9 months (range=3-17 months). Four of the five patients subsequently developed distant metastases (DM). Three patients had local relapse as their first event, and two were treated with salvage surgery. The cumulative incidence of LF was 16.7% [95% confidence interval (CI)=5.0-34.1%] at 1 year, 21.1% (95%CI=7.4-39.4%) at 2 years, and 21.1% (95%CI=7.4-39.4%) at 3 years (Figure 2A). Four of five patients had in-field relapse at a median of 8 months, while one patient had out-of-field failure at 11 months. His primary tumor was located in the left adrenal area, and the recurrent tumor was at the right liver tip.

Patients with serum LDH level ≥1,500 U/l at diagnosis had worse local control than those who had lower serum LDH (3-year cumulative incidence of LF: 50.0% *versus* 6.7%, $p$=0.02) (Figure 2B). Other factors were not significantly different in terms of LF (Table II). Remarkably, patients with stage 3 disease, favorable histology, or RT dose >21.6 Gy, demonstrated no LF, although the analysis was limited by the small numbers. Among the seven patients with GRD, an RT dose of 21.6 Gy resulted in a 3-year cumulative LF incidence of 25% *versus* 0% with >21.6 Gy ($p$=0.34).

In contrast, a total of 12 patients (50.0%) eventually progressed to have DM. The median time to DM was 7.5 months (range=2-28 months). In 8 patients (66.7%), DM developed without evidence of local recurrence. The cumulative incidence of distant failure from the start of RT was 33.3% (95%CI=15.5-52.3%) at 1 year, 45.8% (95%CI=25.0-64.4%) at 2 years, and 51.3% (95%CI=28.8-69.9%) at 3 years.

*Survival outcome*. The 3-year EFS was 45.8% (95%CI=25.6-64.0%) (Figure 3A). The OS at 3 years was 62.9% (95%CI=38.5-79.9%) (Figure 3B). Of the 24 patients, 16 (66.7%) were alive at the time of analysis. There was no

Table I. *Patient characteristics*.

| | Number (%) |
|---|---|
| Median age at diagnosis(y) | 3.3 |
| Range | 0.8-15.3 |
| Age >1.5 | 21 (87.5) |
| Age >4 | 11 (46) |
| Median age at RT(y) | 4.1 |
| Range | 2.2-16.1 |
| Gender | |
| Male | 13 (54) |
| Female | 11 (46) |
| Primary site | |
| Left adrenal | 13 (54) |
| Right adrenal | 8 (33) |
| Left thoracic paravertebral | 1 (4) |
| Right thoracic paravertebral | 1 (4) |
| Right lumbar paravertebral | 1 (4) |
| INSS | |
| Stage 3 | 3 (13) |
| Stage 4 | 21 (88) |
| INRG | |
| Stage L2 | 3 (13) |
| Stage M | 21 (88) |
| Histology | |
| Unfavorable | 16 (67) |
| Favorable | 1 (4) |
| Unknown | 7 (29) |
| Grade | |
| Differentiated | 3 (13) |
| Poorly-differentiated | 7 (29) |
| Undifferentiated | 6 (25) |
| Unknown | 8 (33) |
| MYC-N amplification | |
| Yes | 5 (21) |
| No | 9 (38) |
| Unknown | 10 (42) |
| Risk group | |
| High | 24 (100) |
| Metastatic site | |
| Bone | 15 (63) |
| Bone marrow | 20 (83) |
| Lymph node | 15 (63) |
| Liver | 2 (8) |
| Lung | 0.8-15.3 |
| LDH at diagnosis (U/l) | |
| Mean (SD) | 2,140 (3,534) |
| Median (IQR) | 1,041 (842) |
| ≥1,500 | 6 (25) |
| <1,500 | 15 (63) |
| N/A | 3 (13) |
| Ferritin at diagnosis (ng/ml) | |
| Mean (SD) | 677.1 (491.2) |
| Median (IQR) | 608.5 (632.25) |
| ≥400 | 8 (33) |
| <400 | 4 (17) |
| N/A | 12 (50) |
| Response to induction chemotherapy | |
| CR | 1 (4) |
| VGPR | 3 (13) |
| PR | 12 (50) |
| MR | 2 (8) |
| NR | 5 (21) |
| PD | 0 (0) |
| Debulking surgery | |
| Yes | 21 (88) |
| No | 3 (13) |
| Lymph node dissection | |
| Yes | 13 (54) |
| No | 11 (46) |
| HSCT | 21 (88) |
| Cis-RA | 22 (92) |
| Anti-GD2 antibody | 2 (8) |
| Gross residual after surgery | 11 (46) |
| Gross residual at start of RT | 7 (29) |
| Median RT dose | 2,160 cGy |
| Range | 2,160-3,500 cGy |
| RT dose >2,160 cGy | 5 (21) |
| Patients with gross residual disease at RT | 2 (29) |
| Patients without gross residual disease at RT | 3 (14) |
| RT to metastatic site(s) | |
| Yes | 12 (50) |
| No | 9 (38) |
| Not applicable | 3 (13) |

y: Years; RT: radiotherapy; INSS: International Neuroblastoma Staging System; INRG: International Neuroblastoma Risk Group; LDH: lactate dehydrogenase; SD: standard deviation; IQR: interquartile range; N/A: not available; CR: complete response; VGPR: very good partial response; PR: partial response; MR: mixed response; NR: no response; PD: progressive disease; HSCT: hematopoietic stem cell transplantation; Cis-RA: cis-retinoic acid.

difference in OS between patients with and without GRD (3-year OS 71.4% *versus* 56.3%, $p$=0.67), or patients who received RT to metastatic sites and the primary site and those who received RT only to the primary site (3-year OS 36.5% *versus* 88.9%, $p$=0.055).

*Toxicity.* RT was well-tolerated, and all patients completed the planned RT course with a median treatment interruption of 0 days (range=0-3 days). Fifteen patients (62%) experienced transient grade >3 neutropenia, and 3 patients (13%) had grade >3 thrombocytopenia. A total of 20 patients (83%) had grade >1 hematological toxicity. RT-associated dermatitis, nausea, and vomiting were generally mild, and no patient experienced skin or gastrointestinal toxicity greater than grade 2. One patient which was followed for a longer period had probable growth suppression due to treatment related toxicity. None of the surviving patients developed impaired renal function. No secondary malignancy was observed.

## Discussion

In our cohort of children treated for high-risk neuroblastoma with curative intent, we observed a favorable local control with tomotherapy. The cumulative incidence of LF was 21% at 3 years. The 3-year OS of 62.9% was also encouraging. This is in sharp contrast with the overall poor distant control rate, as the cumulative incidence of distant failure was 51% at 3 years.

RT to the primary site has become an essential component for consolidation treatment of high-risk neuroblastoma (25). Furthermore, the contribution of local control from RT to the primary site to improve OS has increasingly been recognized (26). Whether the commonly used RT dose of 21-24 Gy is sufficient for treating patients with GRD remains unanswered, as some series proposed that the extent of surgery and unresected disease impacts local control or even survival (27-29). In our series, two (28.6%) of seven patients with GRD received doses higher than 21.6 Gy, and did not experience local recurrence. In comparison, we observed a 3-year LF rate of 25.0% in patients with GRD receiving standard RT with 21.6 Gy. Recently, Casey *et al.* also reported that among 19 patients with GRD after resection, the 5-year LF rates for patients receiving <30 Gy and those receiving 30-36 Gy were 30% and 0%, respectively (30).

LDH is known to reflect tumor burden. We identified a subgroup with high serum LDH levels (≥1,500 U/l) that had significantly worse local control (3-year cumulative incidence of LF 50.0%). Among those six patients with high serum LDH, five eventually failed long-term. Casey *et al.* also demonstrated a trend towards worse local control in patients with *MYC-N* amplification and LDH ≥1,500 U/l (13). This finding might provide the rationale for intensifying local treatment for those patients with larger initial disease burden.

Most patients with high-risk disease have metastases at presentation, and the optimal treatment for metastatic sites is less well-established (19, 31). In our study, 12 patients received synchronous RT to their metastatic sites. Significant differences in subsequent distant failure or survival compared to patients who received RT only to the primary site were not observed. The rate of distant failure in this patient population remained high, emphasizing the importance of effective systemic control for high-risk disease. Distant failure rates in modern series examining RT to the primary site ranged from 32%-55% (13, 14, 17), similar to our data. Synergistic effect by adding poly (ADP-ribose) polymerase (PARP) inhibitor (MK-4827) to RT had shown promise to improve outcome in the setting of metastatic disease of neuroblastoma (32). Recent studies found that tachykinin receptor 1 (TACR1), also known as neurokinin-1 receptor or substance P receptor, is ubiquitously expressed in tumor cells of neuroblastoma; and inhibition of TACR1 can hamper the growth of neuroblastoma cell lines

Table II. *Prognostic factors for local failure.*

| | 3 y-local failure (%) (SE) | *p*-Value |
|---|---|---|
| Age (y) | | 0.53 |
| Age <4 | 15.4 (10.4) | |
| Age >4 | 27.3 (14.2) | |
| Gender | | 0.53 |
| Male | 15.4 (10.5) | |
| Female | 27.3 (14.2) | |
| Primary site | | 0.35 |
| Abdominal | 24.2 (9.7) | |
| Non-abdominal | 0 (0) | |
| INSS | | 0.35 |
| Stage 3 | 0 (0) | |
| Stage 4 | 24.2 (9.7) | |
| Histology | | 0.53 |
| Unfavorable | 31.3 (12.1) | |
| Favorable | 0 (0) | |
| Grade | | 0.61 |
| Differentiated | 33.3 (33.3) | |
| Poorly-differentiated/Undifferentiated | 23.1 (12.2) | |
| MYC-N amplification | | 0.26 |
| Yes | 40.0 (24.9) | |
| No | 11.1 (11.1) | |
| Metastatic site | | 0.74 |
| Skeletal/lung | 19.3 (10.4) | |
| Others | 25.0 (16.5) | |
| LDH at diagnosis | | 0.02 |
| ≥1500 U/l | 50.0 (23.1) | |
| <1500 U/l | 6.7 (6.7) | |
| Ferritin at diagnosis | | 0.3 |
| ≥400 ng/ml | 25.0 (16.5) | |
| <400 ng/ml | 0 (0) | |
| Response to induction chemotherapy | 0.63 | |
| CR/VGPR/PR | 18.6 (10.1) | |
| MR/NR/PD | 28.6 (18.8) | |
| Lymph node dissection | | 0.54 |
| Yes | 23.1 (12.2) | |
| No | 12.5 (12.5) | |
| HSCT | | 0.35 |
| Yes | 24.2 (9.7) | |
| No | 0 (0) | |
| RT dose | | 0.21 |
| >21.6 Gy | 0 (0) | |
| 21.6 Gy | 26.7 (10.6) | |
| Gross residual at start of RT | 0.61 | |
| Yes | 28.6 (18.6) | |
| No | 17.7 (9.5) | |
| RT to metastatic site(s) | | 0.55 |
| Yes | 25.0 (13.1) | |
| No | 17.6 (12.0) | |

y: Years; SE: standard error; INSS: International Neuroblastoma Staging System; LDH: lactate dehydrogenase; CR: complete response; VGPR: very good partial response; PR: partial response; MR: mixed response; NR: no response; PD: progressive disease; HSCT: hematopoietic stem cell transplantation; RT: radiotherapy.

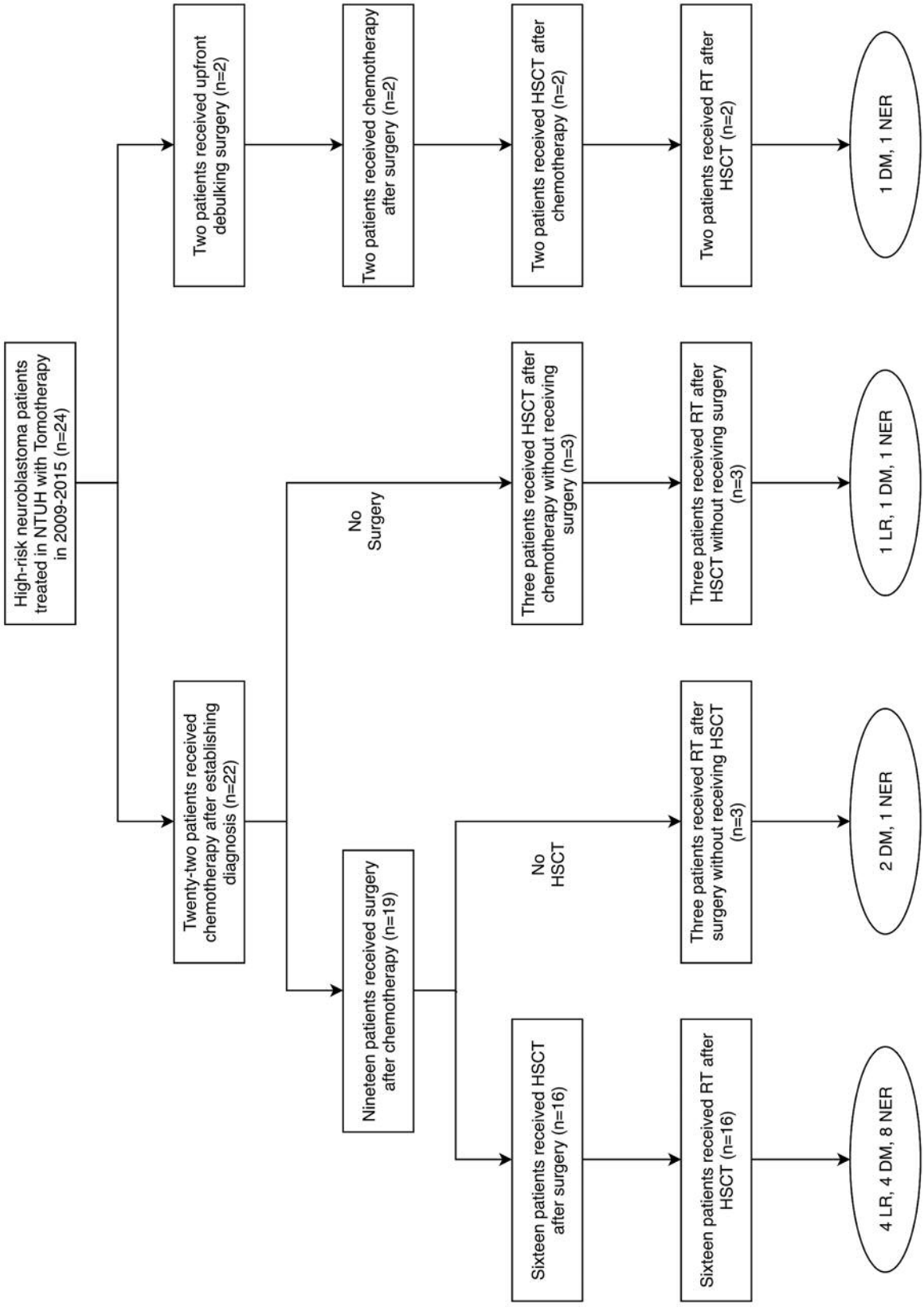


Figure 1. *Treatment modality and clinical outcome of the included patients. HSCT: Hematopoietic stem cell transplantation; RT: radiotherapy; LR: local recurrence; DM: distant metastases; NER: no evidence of recurrence.*

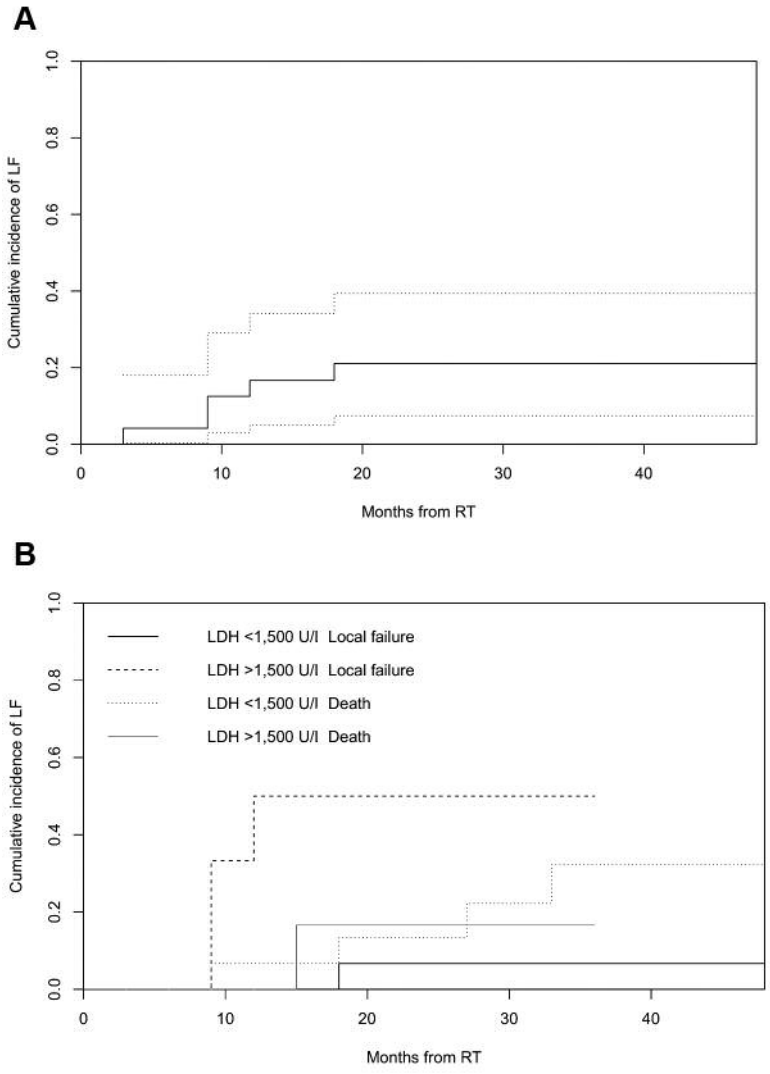


Figure 2. *Cumulative incidence of local failure. (A) Overall cumulative incidence of local failure (LF). The dotted line denotes confidence interval. (B) Cumulative incidence of LF with serum LDH >1,500 U/l (dashed line) versus serum LDH <1,500 U/l (solid black line). The dotted line and solid red line respectively represent their competing risk (death).*

(33, 34). These findings indicate that targeting TACR1 might serve as a potent new treatment strategy for neuroblastoma.

IMRT allows for higher conformity and better sparing of adjacent organs at risk (35), leading to its increasing utilization in clinical practice for pediatric cancers. The planning target volume margin could be further reduced using the IMRT technique by helical tomotherapy (36), which is useful for treating childhood neuroblastomas. Pai Panandiker *et al.* reported excellent local control with IMRT in a cohort comprising mostly high-risk neuroblastoma patients without GRD (17). However, seven (29.2%) of our patients had GRD, which might have contributed to the higher local recurrence rate. Dose escalation using IMRT might benefit these patients, while limiting doses to adjacent organs at risk.

RT toxicity was generally mild in our series. Only one patient who received RT experienced growth suppression as the result of late toxicity of treatment. Endocrine abnormality might have also contributed to his growth suppression, considering he also received RT to skull base metastasis. None of the patients in our cohort developed a secondary tumor or hematologic malignancy in our relatively limited follow-up.

In summary, favorable local control was demonstrated in our cohort of high-risk neuroblastoma children treated with tomotherapy following multimodality treatment, including high-dose chemotherapy and HSCT. Patients with high serum LDH at presentation were at increased risk of local recurrence. Our study was limited by its retrospective nature, small patient number, and single transplant-based protocol

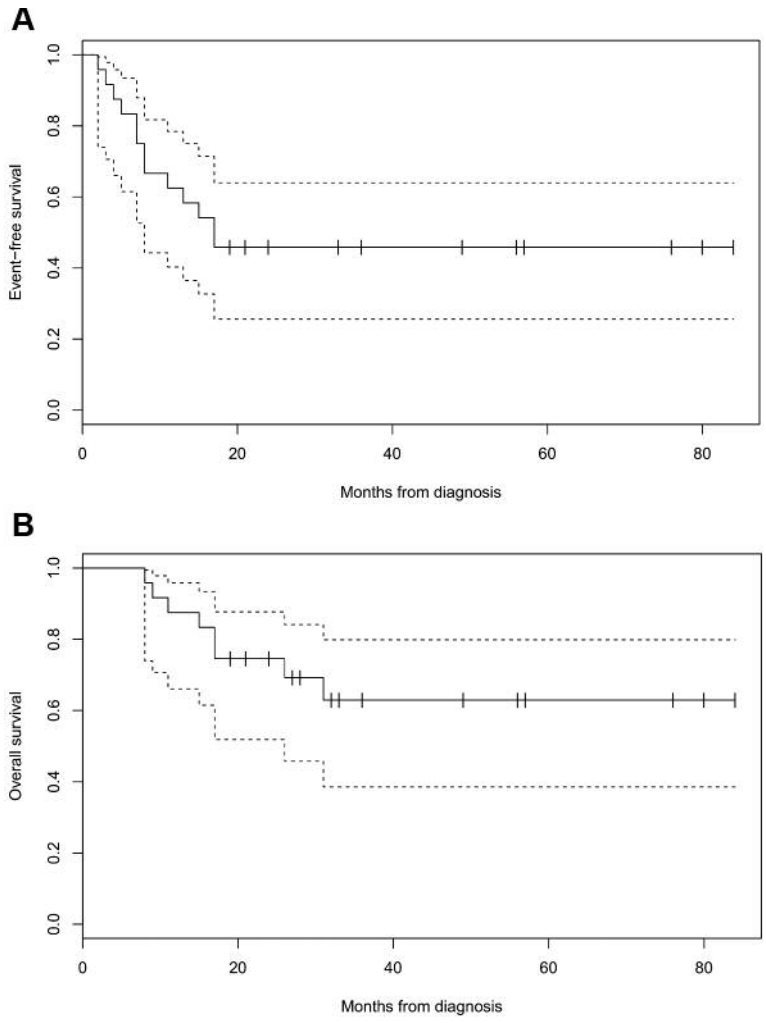


Figure 3. *Clinical outcomes of the total number of patients. (A) Event-free survival. (B) Overall survival. Dashed lines denote confidence intervals.*

typically without the use of anti-GD2 antibody. Nevertheless, our study adds to the growing body of evidence demonstrating the efficacy and safety of highly-conformal RT for the treatment of high-risk neuroblastoma. For patients with GRD after induction chemotherapy followed by surgery, the escalation of RT dose to GRD following the standard RT dose of 21.6 Gy after HSCT is warranted.

## Conflicts of Interest

The Authors have no conflicts of interest to declare in regard to this study.

## Authors' Contributions

GYC collected the data, conducted all statistical analyses and wrote the article; JCHC, YHC, MYL, HHC, STJ, and WMH contributed data, and SHK conceived, designed the work and revised the article. All Authors reviewed and approved the final article.

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