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Case Report

Consolidating Local and Palliative Radiotherapy of High -Risk Neuroblastoma in Childhood- Clinical Case with A Literary Review

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Abstract

Neuroblastoma (NB) is the most common extracranial solid childhood neoplasm originating in the adrenal gland or from any part of the sympathetic plexus. Radiotherapy (RT) to the tumor bed after surgical resection in high-risk NB contributes significantly to local disease control and prevention of local relapse. We present a 6-year-old child, which with multiple bone metastases on the vertebrae, sacrum and cranial bones were diagnosed. For 2.5 years, complex multimodal therapy comprising high-dose Chemotherapy (Ch), surgery of the primary tumor in the right adrenal gland, myeloablative therapy with subsequent Autologous Bone Marrow Transplantation (ABMT), palliative fractionated sacral bone metastasis RT up to Total Dose (TD) 21 Gy and local tumor bed RT up to TD 21 Gy, were conducted. CT and MRI reports residual bone metastases, which were left for observation by PET/CT at an interval of 3 months. Children's IV stage NB is subject to prolonged combined multimodal treatment, including initial tumor resection or biopsy, aggressive induction Chemotherapy (Ch), surgery to achieve Local Tumor Control (LTC) or tumor volume reduction, myeloablative therapy with subsequent ABMT, consolidating local tumor bed RT and palliative RT of distant metastases.

Keywords: High-Risk Childhood Neuroblastoma, Bone Metastases, Consolidating Tumor Bed Radiotherapy, Palliative Radiotherapy, Combined Multimodal Treatment.

Introduction

Neuroblastoma (NB) is the most common extracranial solid childhood neoplasm originating in the adrenal gland or from any part of the sympathetic plexus [1]. The high-risk neuroblastoma group with unfavorable forecast includes children over 18 months of age, those with distant metastases and tumor amplification of MYCN oncogen [2]. For MYCN-amplified tumors, complete resection led to a significant survival advantage [3] The greatest problem is posed by children with metastatic disease or amplified MYCN gene, who continue to do badly despite intensive treatments [4]. Radiotherapy (RT) is usually administered to both the primary tumor bed and persistent metastatic sites after myeloablative therapy for high-risk neuroblastoma [5]. Children's IV stage NB is subject to prolonged combined multimodal treatment, including initial resection or biopsy, aggressive induction Chemotherapy (Ch), surgery to achieve Local Tumor Control (LTC) or tumor volume reduction, consolidating local Radiotherapy (RT) of the primary tumor bed and palliative RT of distant metastases [6,7]. After prolonged combined multimodal treatment, in this article we present the capabilities of the consolidating local Radiotherapy

(RT) of the primary tumor bed and of the bone metastases.

Clinical Case

We present a six -year -old boy with initial complaints of pain in the right shoulder and left lower limb. After abdominal CT, a heterogeneous tumor with dimensions 128/101/131 mm with origin from right adrenal gland was found (Fig.1). The aspiration tumor biopsy proves neuroblastoma. Due to the insufficient amount of biopsy material, no genetic examination was conducted. Urine test found increased levels of tumor markers Neuron Specific Enolase/ NST 225ug/l, Homovanillic Acid (HVA) 302 mg/g crea, Vanillylmandelic Acid (VMA) 296 mg/g crea. Bone-marrow trepanobiopsy proves metastases of neuroblastoma with positive immunohistochemical expression for Synapophazine, Chromographer and CD 56. On February 2021, Positron Emission Tomography/ Computed Tomography (PET/CT) with a marked 68 GA Somatostatin analogue (68 GA Dota- Toc) showed a large heterogeneous tumor located in the right abdominal half with an axial size of 121/97 mm and SUV max.14, as well as diffusely increase fixation of the specific radiopharmaceutical in bone marrow with SUV max. 11.5. After clinical discussion, it was found that it was about a high-risk neuroblastoma in a child over 18 months of age with bone marrow metastases. The child is subject to chemotherapy under a high -risk neuroblastoma scheme. Two Chemotherapy (Ch) courses were conducted with Topotean and Cyclophosphamide, the third Ch course with Vepezide and Cisplatin and the fourth Ch course with Vincristine, Doxorubicin and Cyclophosphamide. June 2021 control DOTA-TOC PET/CT reports a persistence of the right adrenal tumor with a slightly reduced size of about 18% and fixation of radiopharmaceuticals mainly on the periphery. Persistence of the diffuse bone- marrow engagement in places with a slightly reduced intensity of radiopharmaceutical accumulation. The tumor markers are significantly reduced/NST 36 UG/L, HVA 58 mg/g crea, VMA 76 mg/g crea. After the fourth Ch course, the florocytometry of the bone marrow biopsy reports about 1.5 % tumor cells from the study material. September 2021 control DOTA- TOC PET/CT reports a heterogeneous tumor with axial dimensions 95/106 mm and a caudal 108 mm, located dorsal from the liver, comparing it ventrally and to the left. The proximal tumar reaches the diaphragm and the distal to L2. Multiple bone metastases are reported throughout the body (Fig.2). The child conducts a fifth cytostatic course with Vepezide and Cisplatin. After consultation with a pediatric onco -surgeon, it is found that the primary tumor is inoperable, which requires continuation of intensive systemic chemotherapy, followed by autologous stem cell transplantation. October 2021 visibly radical extirpation of the primary tumor was performed. Histologically verified neuroblastoma with 85% necrosis. The child was directed for immunotherapy with Dinutuximab beta. January 2022 has been conducted control DOTA-TOC PET/CT, which takes into account a significant therapeutic effect on disseminated bone lesions, most of which have a full biological response. Persisted the bone marrow lesion in the left side of the sacrum on the C2-C3 level with SUV Max 8.6, as well as other areas of slightly increased supply fixation of radiopharmaceuticals in the area of cranial bones. The levels of tumor markers are NST 24 UG/L, HVA 8 mg/g crea and VMA 5 mg/g crea. It is recommended to continue immunotherapy and to conduct RT in the sacral bone metastatic area. In March 2022, we conducted palliative fractionated 3D Conformal Radiotherapy (RT) on the sacral metastasis up to TD 21 Gy (Fig 3). The control DOTA-TOC PET / CT through July 2022 reported a partial biochemical reduction of the traced hyperfixing area in the left sacral metastasis at the C2-C3 level with SUV Max 2.6 (before SUV max, 8.6), without a CT substract with a bone marrow lesion type. Two small areas are reported in the right parietal bone, located in its dorsal and near the coronar suture with a tendency to reduce radiopharmaceutical fixation - now SUV max 2.2, and before SUV max 3.0. August 2022 we performed consolidating fractionated Intensity Modulated radiotherapy (IMRT) by the VMAT method up to 21Gy of the primary tumor bed (Fig.4). The child suffered very well, without acute radiation changes from the surrounding healthy tissues and organs. After 3 months / January 2023, a Dota-Toc PET / CT was carried out, which again appeared on the two lesions of the cranial bones with SUV max up to 2.2 (Fig.5). The child is in good general condition, without bone lesions symptoms. Observation has been evaluated via a DOTA-TOC PET/CT after 3 months.

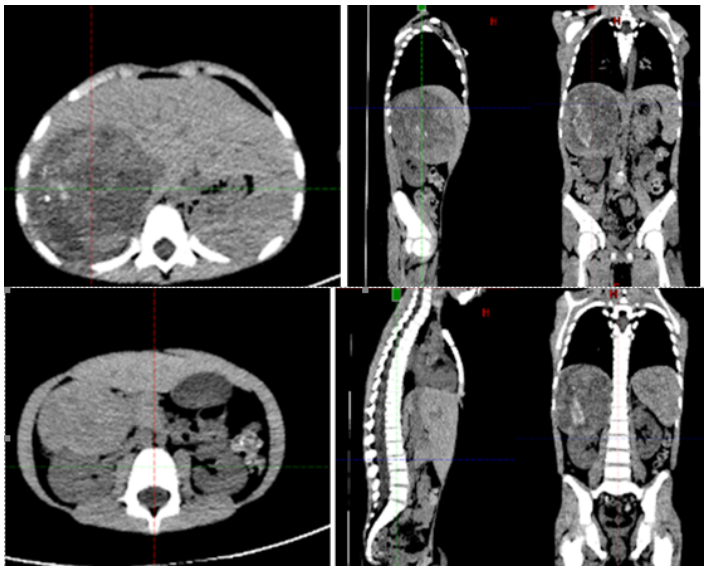

Figure 1: Abdominal CT from 19.01.2021-Heterogeneous tumor with dimensions 128/101/131 mm originating from right adrenal gland.

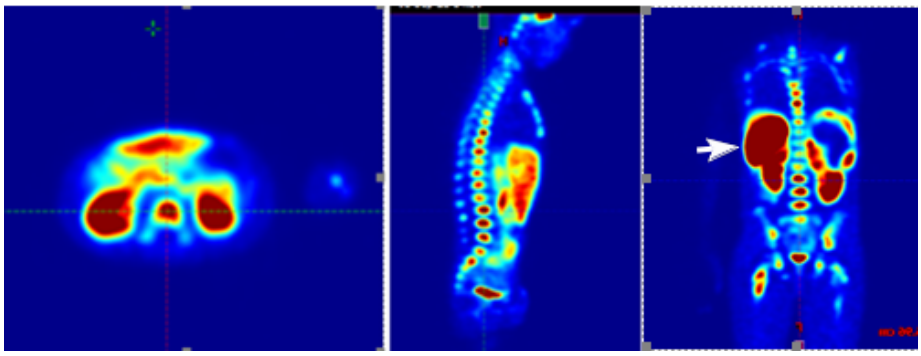

Figure 2: Preoperative DOTA-TOC PET/CT / CT of September 2021-Multiple bone metastases on the vertebrae bodies and large adrenal tumor on the right shown with the white arrow.

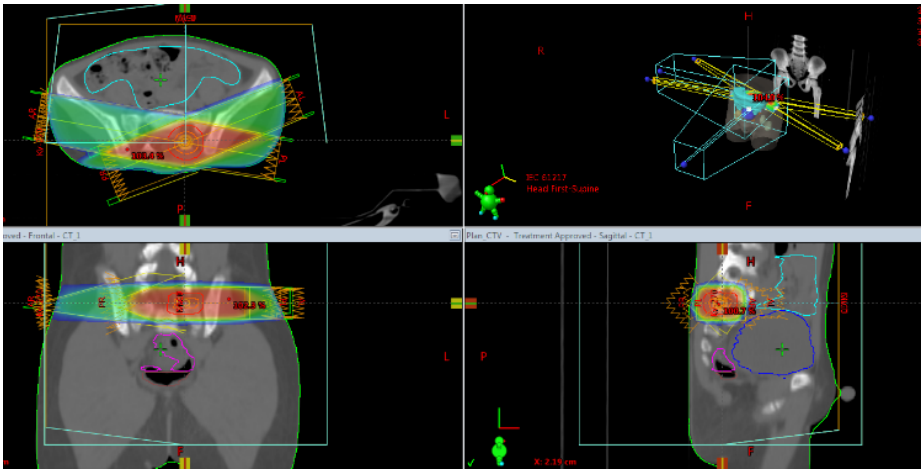

Figure 3: Palliative fractionated 3D Conformal RT of sacral metastasis up to TD 21 Gy.

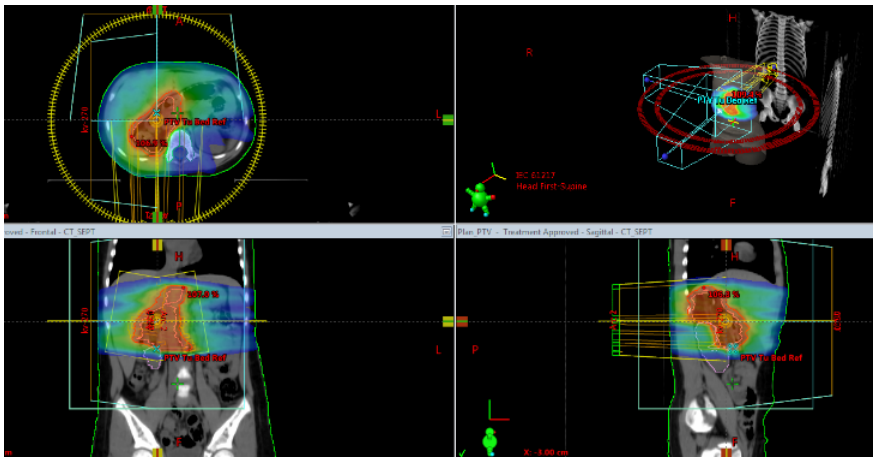

Figure 4: Consolidating fractionated Intensity Modulated RT by the VMAT method up to 21Gy of the primary tumor bed.

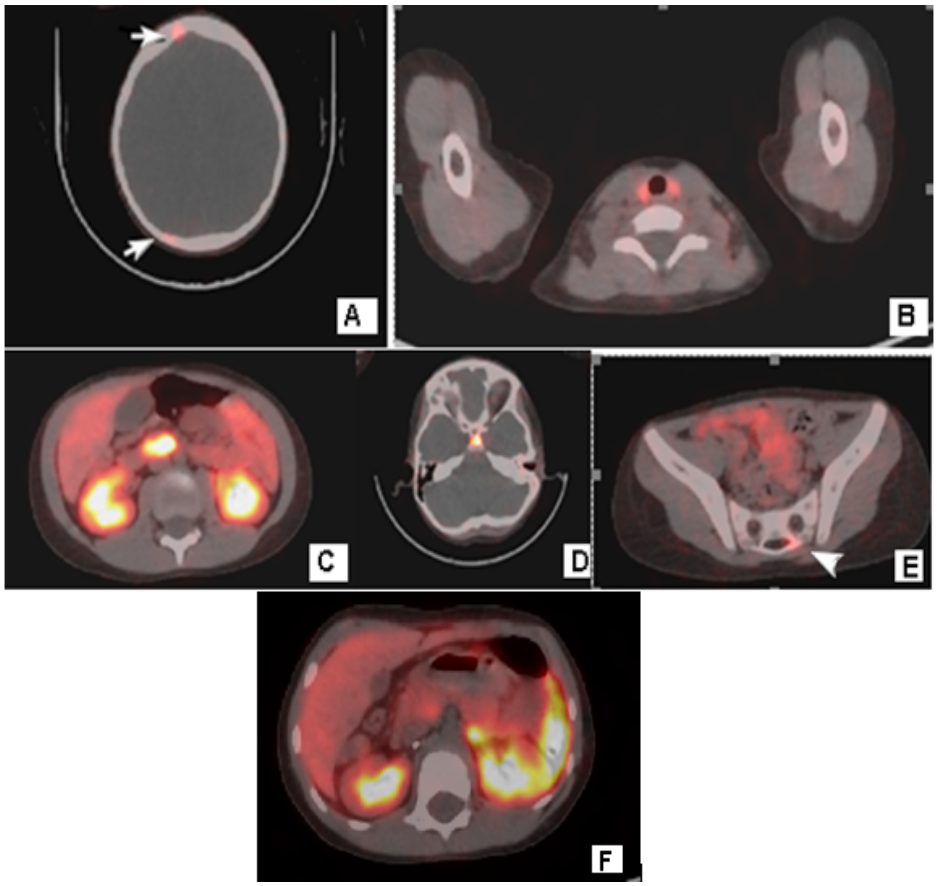

Figure 5: DOTA-TOC PET/ CT from January 2023- A/ Again, the two lesions of the cranial bones with SUV max 2.2; C/ Physiological accumulation of radiopharmaceuticals in the thyroid gland; C/ Physiological accumulation of radiopharmaceuticals in the pancreas; E/ Physiological accumulation of radiopharmaceuticals in the pituitary gland; E/ After RT- Partial biochemical reduction of the sacral metastasis at the C2-C3 level with SUV Max 3,0 (before SUV max, 8.6), shown with the white arrow. F/Physiological accumulation of radiopharmaceuticals in the spleen.

Discussion

Neuroblastoma (NB) is the most common extracranial solid tumor of childhood, and metastatic disease occurs in a majority of patients [8]. NB is a clinically heterogeneous disease which can have a benign, localized behavior or a rapidly progressive, widely disseminated [3]. Patient variables analyzed for impact on survival included age, anatomic location of the primary tumor, RT of the primary site, complete resection at diagnosis, Gross Total Resection (GTR) at any time in the course of therapy, and treatment protocol dose-intensity [9]. Combined multimodal treatment in high-risk children's IV stage NB include Polychemotherapy (PCh), operation and local RT. Randomized studies on RT role in the complex treatment of IV clinical stage NB reported improved Local Tumor Control (LTC) after local RT of the primary tumor [6,7]. The CCG-3891 study administered induction PCh, surgery and post-operative local RT in macroscopic residual tumor, and after second randomization continuation of PCh or Total Body Irradiation (TBI) with 10 Gy, followed by Autologous Bone Marrow Transplantation (ABMT). Local RT and ABMT at IV stage NB significantly reduce local recurrences ($p = 0.09$) and improve the Disease-Free Survival (DFS) compared to the PCh group without a local RT (50% DFS vs 18% DFS) [10]. A COG study at high -risk neuroblastoma (ANBL0532) aims to improve LTC and Disease- Free Survival (DFS), as well as evaluation of the effect of ABMT, followed by local RT to TD 21Gy with DD 1.5 Gy. This RT protocol is held during the 42-day period after AKMT, but not earlier than 28 days after it. Despite non -radical surgery, this combined approach achieves 5 years. 80% LTC [11]. After induction PCh and surgery, the CCG-321P3 study conducted a TBI with 10 Gy or a local RT of the postoperative extraabdominal residual tumor up to TD 20 Gy, and with an abdominal localization to RT 10 Gy. At 3 years after local RT, increased LTC was achieved [12]. Good selection for intensive PCh, surgery and local RT

achieves healing results similar to low risk NB [13]. The clinical case presented was diagnosed with a large volume of tumor and multiple bone metastases (Fig.1, Fig.2). After achieving a partial or complete remission, 47 children, ages 1-10 years, with Stage 4 neuroblastoma were treated with dose-intensive multi-agent chemotherapy, maximal surgical debulking, and hyperfractionated RT (1.5 Gy twice a day to 21 Gy). Radiotherapy fields encompassed the initial tumor volume and regional lymph nodes plus a 3-cm margin. This was followed by consolidation with either ABMT or immunotherapy [6]. There was a slight advantage in DFS among 539 high-risk patients, for those patients with complete gross resection of the primary tumor, although this was not significant. Resectability improved after neoadjuvant chemotherapy. After agressive induction Chemotherapy (Ch) and subsequent ABMT, a visibly radical tumor operation was performed, then we performed the local RT of the tumor bed to TD 21 Gy (Fig.4). There was a small survival benefit for complete resection. Incomplete resections received secondary resection or 10 Gy of external beam RT. This study suggests that complete resection may still be important in the current era of intense chemotherapy and transplant [14]. Total local radiation doses are evaluated depending on two factors: age and postoperative residual tumor (macroscopic or microscopic residual disease). For microscopic residual tumor after induction Ch and surgery, a local RT up to TD 21-24 Gy is required. In macroscopic residual tumor, it is necessary to increase the radiation dose by hyperfractionated RT (twice daily with DD 1.2 -1.5 Gy to TD 9-36Gy), and for microscopic or subclinical disease up to TD 18-30 Gy. [15, 16]. About the palliative RT in bone metastases a TD 15 Gy or more significantly increased response rate (100% vs. 57%; $p = 0.038$), compared with a dose smaller than 15 Gy. For the bone group and CNS metastases group, the overall response rates were 63.2% and 44%, respectively [8]. In our patient, a palliative fractionated RT was performed in the area of the sacral bone metastasis by fractionated 3 D conformal RT up to 21Gy (Fig.3), which reduced the activity of radiopharmaceuticals from the control PET/CT from SUV max.8.6 of SUV max. 3, 0 (Fig.5). Thanks to the complex multimodal treatment in high -risk neuroblastoma, we have achieved a 2 -year survival rate without disease progression and good quality of life.

Conclusion

Children's IV stage NB is subject to prolonged combined multimodal treatment, including initial tumor resection or biopsy, aggressive induction Chemotherapy (Ch), surgery to achieve Local Tumor Control (LTC) or tumor volume reduction, myeloablative therapy with subsequent Autologous Bone Marrow Transplantation (ABMT), consolidating local Rradiotherapy (RT) of the primary tumor and palliative RT of distant metastases. Consolidating local Radiotherapy (RT) of the primary tumor may be treated fractionated up to TD 21.6 Gy with a good effect. Palliative RT of the bone metastases may be treated with single doses 4-8 Gy or fractionated up to TD 21.6 Gy. Thanks to the complex multimodal treatment in high -risk neuroblastoma, we have achieved a 2 -year survival rate without disease progression and good quality of life.

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