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Case Report

Palliative 3 D Conformal Radiotherapy of Children's Neuroblastoma Non-Resectable Liver Metastasis - Clinical Case with Literature Overview

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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. In 17% of high-risk cases symptomatic liver metastases are developed**.** We present a 6, 5-year-old child who was diagnosed with a metastatic paravertebral tumor from Th10 to L2 with a brain metastasis 3 years ago. Following the surgery of brain metastasis and primary tumor, the pathohistological analysis proved a neuroblastoma. For 2.5 years a complex multimodal therapy comprising high-dose chemotherapy, radiosurgery of brain metastasis with a single dose fraction 12 Gy, local RT of the whole lungs double-sided up to 15 Gy, local RT of the primary tumor up to TD 21 Gy were conducted. MRT reports residual pulmonary metastases, local recurrence, soft tissue cranial metastases, as well as non-resectable liver metastasis with diameter 7/7 cm. which after biopsy is pathologically verified.

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, myeloablative therapy with subsequent autologous bone marrow transplantation (ABMT), consolidating local radiotherapy (RT) of the primary tumor and distant metastases. Palliative RT in distant liver metastases may be treated with single doses 4-8 Gy or fractionated up to TD 21.6 Gy-30.6 Gy with a good effect.

Keywords: high-risk childhood neuroblastoma; liver metastasis; complex multimodal therapy; induction chemotherapy; palliative 3D conformal radiotherapy

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**]. At 75% was diagnosed in the abdominal cavity and at 30% in the adrenal medulla. The high-risk neuroblastoma group with unfavorable prognosis includes children over 18 months of age, those with distant metastases and tumor amplification of MyCN oncogene [**2**]. For MYCN-amplified tumors, complete resection led to a significant survival advantage that was not noted in the nonamplified group [**3**]. 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, myeloablative therapy with subsequent autologous bone marrow transplantation (ABMT), consolidating local radiotherapy (RT) of the primary tumor and distant metastases [**4**,**5**]. In this article we will present the capabilities of the consolidating local liver RT in metastatic NB after prolonged combined multimodal treatment.

Clinical case

We present a 6, 5-year-old child who was diagnosed with a metastatic paravertebral tumor from Th10 to L2 with a brain metastasis 3 years ago. Following the surgery of brain metastasis and primary tumor, the pathohistological analysis proved a neuroblastoma. For 2.5 years, complex multimodal therapy comprising high-dose XT, radiosurgery of brain metastasis with single dose fraction 12 Gy, local RT of the whole lungs double-sided up to 15 Gy, local RT of the primary tumor up to TD

21 Gy were conducted. Autologous Bone Marrow Transplantation (ABMT) has not been implemented. In the third year after intensive chemotherapy, MRT reports residual pulmonary metastases, local recurrence, soft tissue cranial metastases, as well as non-resectable liver metastasis with diameter 7/7 cm., which after biopsy is pathologically verified.

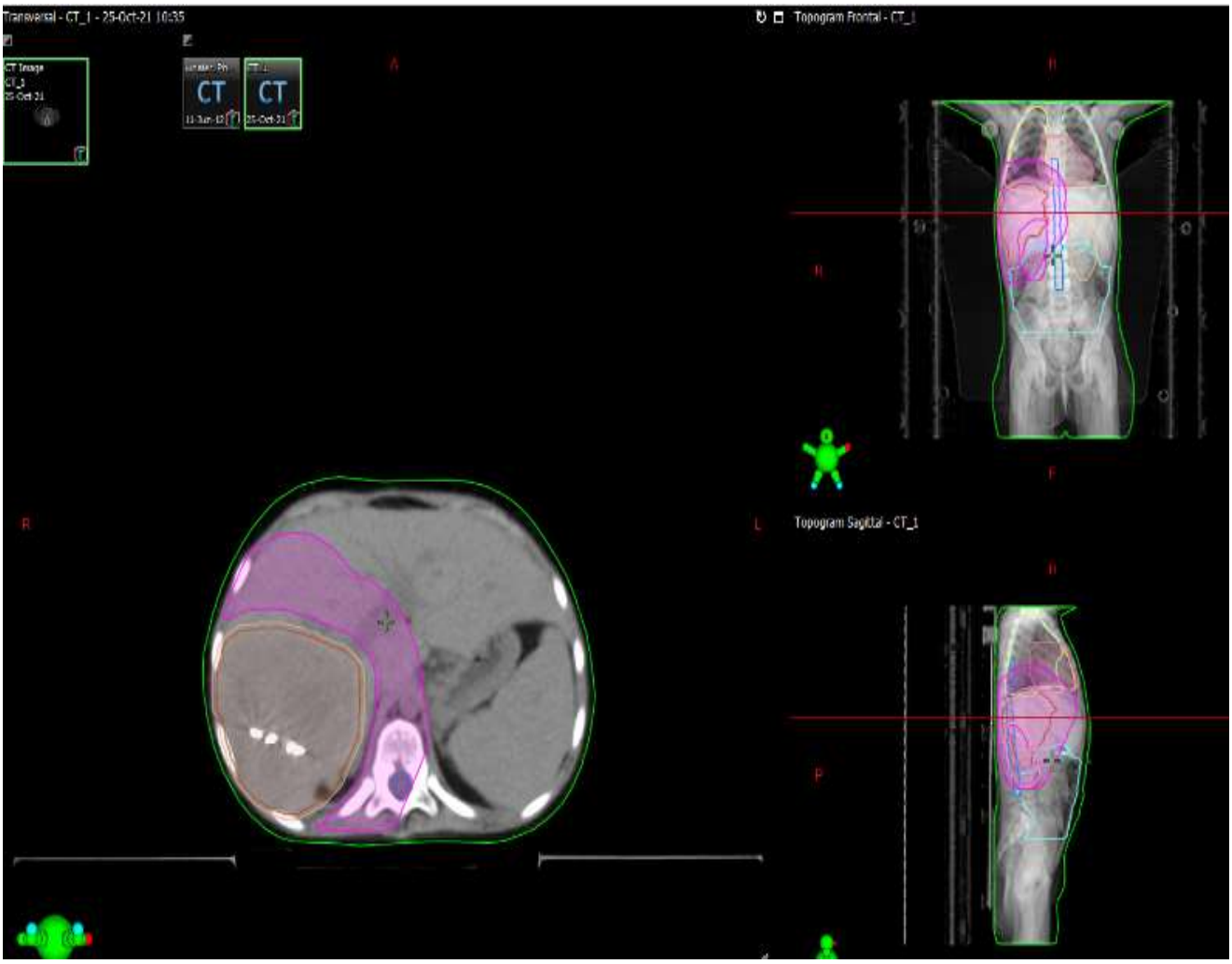

Fig. 1 *Planning of palliative hepatic metastasis radiotherapy raying by contouring of tumor volume and adjacent normal tissues and organs*

The child was presented for local palliative RT of hepatic metastasis. Laboratory results showed increased liver transaminases and LDH (ALAT 90 IU/l; ASAT 50 IU/l and LDH 600 U/I). The general state of the child was relatively good (HB 9 g/dL with normal peripheral blood count values). We planned and calculated the necessary palliative RT (**Fig.1, Fig.2**), but at the day of hospital admission, the child did not appear due to a worsened general state. For this reason, it was not possible to conduct palliative RT.

Discussion

Neuroblastomas, which account for 97 % of all neuroblastic tumors, are clinically heterogeneous, varying in location, histopathologic appearance, and biologic characteristics [**6**]. In 17% of high-risk NB symptomatic liver metastases are developed**.** The most common symptoms attributable to hepatic metastasis were abdominal enlargement, abdominal pain, respiratory difficulty due to upward pressure on the diaphragm and obstruction of the inferior vena cava [**1**]. The staging system should be referred to as the International Neuroblastoma Staging System and the response criteria as the International Neuroblastoma Response Criteria [**7**]. Neuroblastoma is a clinically heterogeneous disease which can have a benign, localized behavior or a rapidly progressive, widely disseminated, lethal character [**3**]. Attempts have been made to identify factors that can be used to risk stratify these patients and to characterize an "ultra-high-risk" (UHR) subpopulation with particularly poor outcome. However, among published data, there is a lack of consensus in the definition of the UHR population and heterogenity in the endpoints and statistical methods used [**8**]. Because the rate of surgical complications is higher when extensive tumors are removed at diagnosis[**9**], the standard approach for advanced stage tumors has become initial biopsy (using an open or minimally invasive approach such as obtainment of adequate tissue for biological studies) followed by clinical/pathologic/biological risk group assignment, chemotherapy and second-look surgery [**3**].

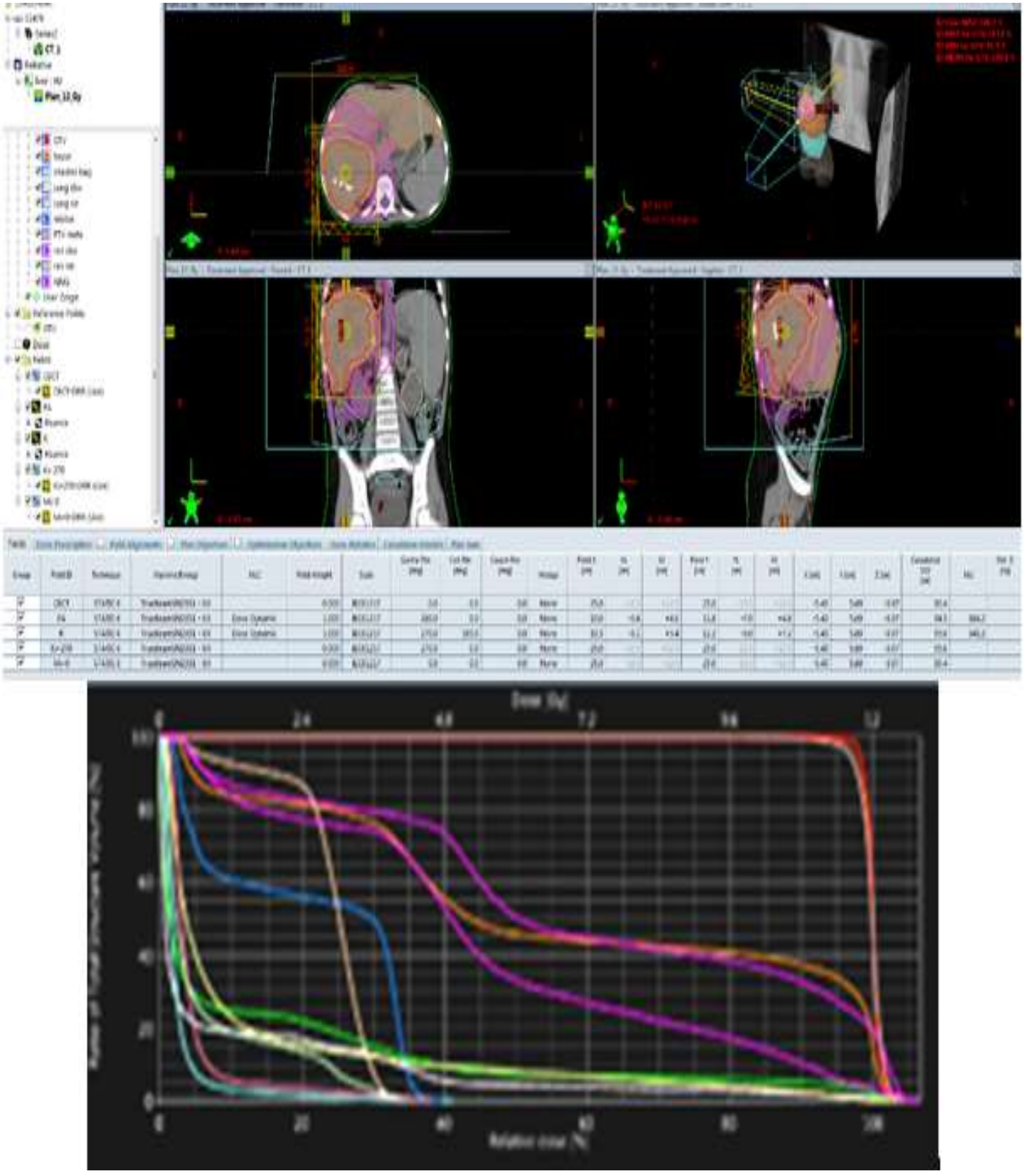

Fig.2 *3D Conformal Radiotherapy (3D CRT) of a hepatic metastasis, which covers more than 1/3 of the liver volume over one front and lateral field with DD 4 Gy/ three fractions implemented three times a week up to TD 12 Gy (Biologically Equivalent Dose 18 Gy). The histogram also presents the distribution of radiation doses in the critical adjacent normal tissues and organs and in target volumes.*

Gross total resection (GTR)

Gross total resection should be part of the management of stage 4 neuroblastoma in patients greater than 1 year of age [**10**]. In small cohort of patients with metastatic neuroblastoma, GTR at the time of diagnosis offered a survival benefit [**11**]. Although an independent effect of GTR on survival was not demonstrable because complete resection after chemotherapy correlated strongly with increasing protocol intensity, its association with improved overall survival was striking. These results support a continued role for GTR in high-risk neuroblastoma along with intensive chemotherapy [**12**]. Gross total resection prior to hematopoietic stem cell transplantation (HSCT) in high-risk NB patients is not associated with improved OS compared to <GTR; however, these results suggest that >90% resection is associated with improved OS compared to less than 90% resection [**13**]. For high-risk neuroblastomas that do not show a clinical response to induction therapy, surgical resection is important in predicting outcome, but the extent of resection is not [**14**].Treatment-specific complications were found in both the aggressive surgery and chemotherapy groups. These results should, therefore, be taken into account when developing future treatment protocols [**15**].

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 LTC after local RT of the primary tumor [**4,5**]. 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) [**16**]. Incomplete resections received secondary resection or 10 Gy of external beam radiation. This study suggests that complete resection may still be important in the current era of intense chemotherapy and transplantation [**17**]. After an induction PCh and surgery, the CCG-321P3 study conducted TBI with 10 Gy or local RT of a postoperative extraabdominal residual tumor up to total dose (TD) 20 Gy and in abdominal NB localization up to TD 10 Gy. 3 years after local RT an increased LTC was achieved [**18**]. Good selection for intensive PCh, operation and local RT achieves treatment results similar to low-risk NB [**19**]. R S Chamberlain et al/1995 evaluated the efficacy of complete surgical resection (CSR) versus partial surgical resection (PSR) using a strategy combining surgery with aggressive chemotherapy, radiation and bone marrow transplantation (BMT) for stage IV neuroblastoma. CSR is associated with prolonged mean and progression-free survival. BMT prolongs mean and progression-free survival in children with stage IV disease [**20**]. COG study at high-risk NB (ANBL0532) aims to improve the LTC and the DFS as well as an assessment of the effect of ABMT, followed by local RT up to TD 21Gy at daily dose (DD) 1.5 Gy. On this protocol, local RT was conducted during the 42-day period after ABMT, but not earlier than the 28th day after it. Despite an unradical operation, this combined approach achieves 80% LTC on the fifth year [**21**].

Local radiotherapy

Radical operation is possible at 2/3 of the non-resectable primary III-IV clinical stage neuroblastomas. After local RT of high- risk NB, local recurrences maintained a high level - 7% on 2nd, 10% on the 3rd and 16% on the fifth year, at low DFS / 48% - 45.7% - 40 % [**4,5,22**]. In local advanced primary tumors with metastatic regional lymph nodes (INSS IIB-III stage-pN1), postoperative positive resection lines and microscopic residual disease require more aggressive complex treatment. The adjuvant RT of the primary tumor with the regional lymph nodes at the pN1 increases the DFS and the overall survival [**23-25**]. In the radiotherapy of NB total local doses are judged depending on two factors: age and postoperative residual tumor (macroscopic or microscopic residual disease). In a microscopic residual tumor after induction Ch and surgery, local RT to total dose 21-24 Gy is required. In a macroscopic residual tumor, raising the total eradication dose is necessary by hyperfractioned RT (twice daily with DD 1,2 -1.5 Gy up to TD 9-36 Gy) and in microscopic or subclinical disease up to TD 18-30 Gy [**23,24**]. In case of non-translation, the multicentric study ANBLO532 applies local RT with clinical target volume (CTV), including pre-operative primary tumor up to TD 21.6 Gy with Boost in post-operative residual tumor up to TD 14.4 Gy (up to TD 36 Gy in macroscopy residual tumor).

Palliative radiotherapy for metastatic neuroblastoma

Metastatic disease occurs in a majority of patients, although radiotherapy plays an important role in the management of metastatic disease. Good response rates are achieved with palliative RT for symptomatic metastatic pediatric neuroblastoma, but survival is dismal [**26**]. Most of patients with neuroblastoma stage 4S (80%) have liver metastases. The appearance of hepatic dysfunction in these patients remains a serious problem especially for young children with excessive hepatic infiltration [**27**]. There were 26 soft tissue (group I), 19 bone (group II), 5 brain (group III), and 3 hepatic (group IV) treated sites. Median radiotherapy doses for groups I, II, III and IV sites were 2000, 2000, 2400, and 450 cGy, respectively. Radiotherapy is an effective treatment for palliation of symptomatic metastatic disease in children with neuroblastoma. The only patient who survived had a stage IV-S neuroblastoma with liver metastases and is alive 13 years after hepatic irradiation [**28**]. Palliative RT in distant metastases may be treated with single beam doses 4-8 Gy or fractionated up to TD 21.6 Gy-30.6 Gy with a very good effect on bone metastases. We present a clinical case where we planned locally palliative RT of a non-resectable liver metastasis with DD 4 Gy/ three fractions implemented three times a week up to TD 12 Gy (Biologically Equivalent Dose 18 Gy) (**Fig.1, Fig.2**). RT was not realized due to a deterioration of the child's overall condition.

Conclusion

Neuroblastoma (NB) is the most common extracranial solid childhood neoplasm originating in the adrenal gland or from any part of the sympathetic plexus. In 17% of high-risk NB symptomatic liver metastases are developed**.** 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, myeloablative therapy with subsequent autologous bone marrow transplantation (ABMT), consolidating local radiotherapy (RT) of the primary tumor and distant metastases. Palliative RT in distant liver metastases may be treated with single doses 4-8 Gy or fractionated up to TD 21.6 Gy-30.6 Gy with a good effect.

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