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Case Report

Case Report - Repeat Craniospinal Irradiation for Medulloblastoma

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Abstract

Medulloblastoma (MB) is the most common malignant central nervous system (CNS) tumour in children. Risk profile guides multidisciplinary intervention which includes surgery, radiation and chemotherapy. The clinical benefits of re-irradiation for relapsed disease have been described but seldom undertaken in fear of exceeding the tolerance of important organs at risk. We present a case of recurrent medulloblastoma in a 37-year-old patient who was originally diagnosed and treated 29 years prior.

We treated her with chemotherapy followed by re-irradiation of the craniospinal axis and consider benefits of this approach versus potentially life-threatening toxicity. VMAT was used to optimize conformity, homogeneity and minimize dose to surrounding organs at risk. We discuss the rationale of this management approach in context of the literature.

Keywords: Paediatric brain tumour, Medulloblastoma (MB), craniospinal irradiation (CSI), re-irradiation, relapse MB, re-treatment MB

Introduction

Medulloblastoma is a posterior fossa tumour of primitive neuroectodermal origin [1]. Seventy percent of cases present before the age of 20 and is rare in adults [2,3]. The following four histological variants exist: classic, desmoplastic or nodular, MB with extensive nodularity (MBEN) and large cell anaplastic (LCA) histology. In addition, four molecular subgroups exist including wingless (WNT), sonic hedgehog (SHH), Group 3 and Group 4, and harbour both prognostic and therapeutic significance.

The risk stratification using the modified Chang system identifies standard- and high-risk groups. Standard risk is defined as: age ≥ 3 years at presentation, <1.5cm^2 residual tumour after resection, cerebrospinal fluid (CSF) negative for tumour cells, absence of leptomeningeal spread on computed tomography (CT) or magnetic resonance imaging (MRI) and classic or desmoplastic histology. High-risk disease is defined when any of the following are present: age < 3 years, residual tumour of >1.5cm^2 after surgery, CSF positive for tumour cells, leptomeningeal spread on CT/MRI or LCA histology.

Despite technological advances, outcomes for those with disease recurrence are dismal and treatment options are limited.

Case Report

Presentation

A 37-year-old female, previously treated for medulloblastoma at age 8 years, now presented with diplopia, balance problems, associated hallucinations, nausea, fatigue, poor appetite, and functional decline.

We were unable to ascertain previous risk group constituents and treatment details were largely unavailable, including dose distribution to tumour volumes and critical organs at risk (OAR). The patient confirmed undergoing a craniotomy with tumour excision followed by complete craniospinal irradiation (CSI) at a state facility in 1991.

Physical Examination

On examination she was short statured with features suggestive of midbrain pathology; lateral nystagmus, poor pupil constriction, unable to sit up unassisted and raised intracranial pressure- bilateral lateral rectus paralysis eyes and papilledema. Infraoccipital alopecia, telangiectasia and atrophy of the posterior neck and back region was observed, consistent with long term sequelae of previous CSI. Pre-morbid ECOG performance status (PS) was 3.

Laboratory Investigations

Histological features of the pathology at diagnosis were unavailable. At the time of relapse, the decision was made not to acquire histology. CSF analysis was inconclusive but did reveal atypical small round blue cells suspicious for recurrent metastatic MB. Further immunohistochemical assessment was inconclusive. Baseline bloods were within normal parameters.

Imaging

MRI revealed a poorly defined T2 weighted high lesion encasing the 4th ventricle and associated extensive supra- and infratentorial ependymal and leptomeningeal enhancement, including involvement of the entire spinal cord and nerve roots of the cauda equina with two foci of apparent nodular extension into the spinal cord. These features were consistent with recurrent leptomeningeal metastatic disease (Figure 1).

Management

Due to the systemic nature of disease progression, we opted to initiate emergency up-front chemotherapy: Carboplatin AUC 6 Day 1 and etoposide 100mg/m2 D1-3 every 21 days. She completed 6 cycles following which our MDT convened to discuss repeat CSI. Correspondence with the previous head of department at the original treatment facility suggested that the patient most likely received 40.00Gy to the craniospinal axis and a 14.00Gy boost to the entire posterior cranial fossa using 2D-planning and a Cobalt-60 radiotherapy machine. After detailed discussion with the patient and family, addressing diagnostic uncertainty, limited data, conflicting opinions, and possible acute and late cumulative toxicities of re-irradiation; the patient and partner decided to accept, and informed consent was obtained.

We explored a three-isocenter Linac-based volumetric modulated arc therapy (VMAT) approach for CSI compared to a standard intensity modulated radiation therapy (IMRT) or three-dimensional conformal radiotherapy (3DCRT) plan. A single planning target volume (PTV) included meninges, cribriform plate, skull base, spinal meninges, and roots of the spinal nerves to the bottom of the sacrum. The boost volume included the central part of the cerebellum and posterior part of the brainstem, midbrain and fourth ventricle. The patient was scanned supine with a 5-point immobilisation mask. Daily cone beam CTs were performed to verify treatment position.

Dose Prescription: PTV 1,8Gy x 15 fractions= 27Gy, boost volume 2Gy x 13 fractions= 26Gy, using 10MV photons and VMAT technology implementing a 3-isocenter technique. Cumulative dose was 53Gy.

Treatment Outcomes

Following three chemotherapy cycles we observed significant clinical and radiological improvement. The patient exhibited a pronounced reduction in cerebellar signs and ECOG PS improved to 1. CSF cytology was negative, and MRI confirmed a dramatic near complete response as depicted in Figure 1. An additional three cycles of chemotherapy was undertaken, following which a planning CT scan was scheduled for repeat CSI using VMAT.

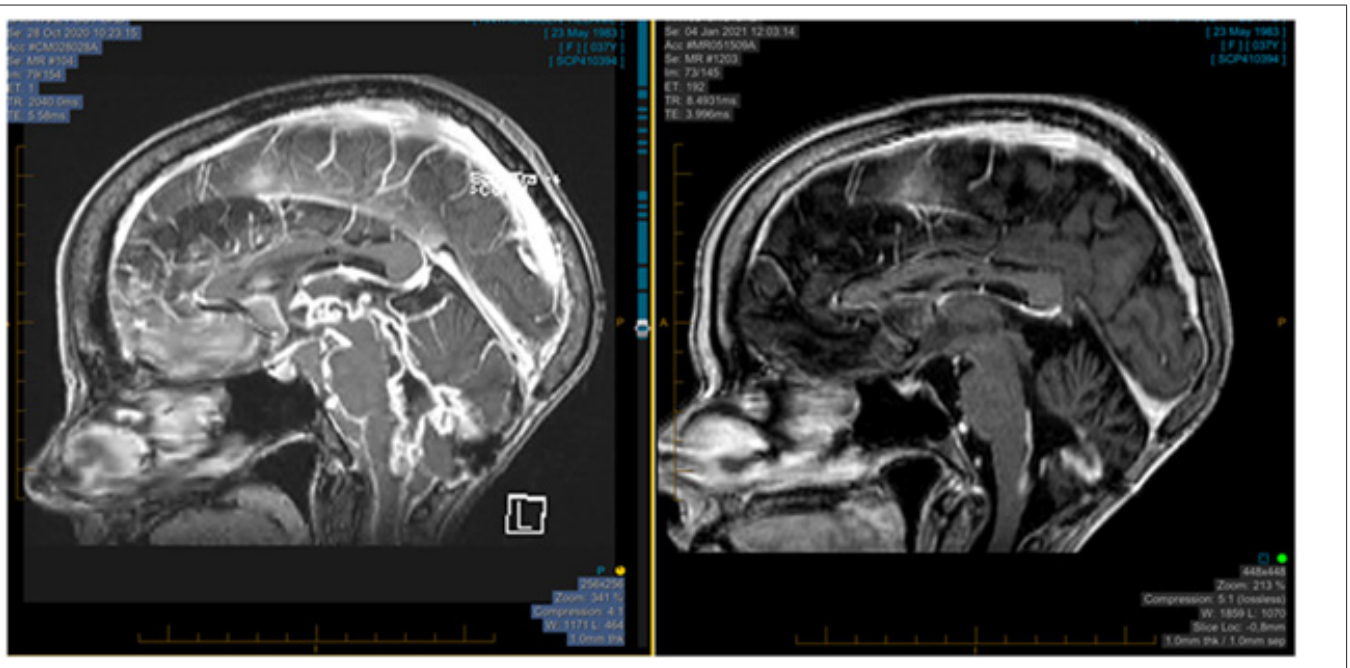

Figure 1: T1-contasted MRI performed prior to chemotherapy (a) and after 3 cycles (b).

Our patient tolerated radiotherapy well with mild acute toxicity, namely nausea and fatigue. There were no grade 3 or 4 acute RT-related toxicities. She developed a pancytopenia needing 2U blood transfusion, granulocyte-colony-stimulating factor and 1-week treatment break. She remained clinically stable 1 month after completion of RT with only mild residual fatigue and no severe toxicities or regressive neurology.

Discussion

Morbidity and mortality rates for patients with recurrent/relapse MB is poor, with few long-term survivors reported in literature [4]. Current treatment strategies include optimal safe re-resection where possible, combined with chemotherapy and/or re-irradiation. High-dose chemotherapy plus stem cell transplantation may be an option in patients with recurrent medulloblastoma contained within the CNS who may not benefit from conventional therapies [5].

Re-irradiation may be an effective therapeutic option in recurrent primary brain tumours, although it carries the risk of associated toxicities including radio-necrosis, leukoencephalopathy, endocrinopathies and secondary malignancies.

CSI of MB presents technical challenges owing to the involvement of large treatment volumes, adding further complexity with retreatment. Traditionally, the whole treatment length is covered with two different isocentric plans in which the junction is shifted after every five fractions to overcome the possibility of hot and cold spot, an approach referred to as feathering [6]. An alternative approach includes the use of proton therapy where the dose distributions that can be achieved and toxicity risks are usually better than conventional photon external-beam radiation due to of the Bragg-Peak effect. Due to lower cumulative lifetime doses to sensitive tissues such as the spinal cord and tissue distal to the PTV, re-irradiation with protons may be a safer option, however, is not an available approach in our setting.

The challenge our case presents includes the uncertainty of cumulative dose distributions; hot and cold spots given the lack of planning details; potential short and long-term toxicities involving re-irradiation, and the risk benefit ratio for incurable stage IV disease.

Traditional large field radiotherapy techniques have gradually been replaced by emerging techniques such as 3DCRT, IMRT and VMAT, offering better conformity, homogeneity indices, and a more reproducible and safer delivery with minimization of dose to surrounding critical structures [7].

We compared VMAT with dose distributions observed for IMRT and 3DCRT (Figure 2). The homogeneity index for VMAT was superior, and dose to the brain and spine is significantly more conformed with VMAT/IMRT, compared to the conventional 3D-CRT. This technique also simplified patient set up and eliminated the need for feathering/shifting junctions during treatment.

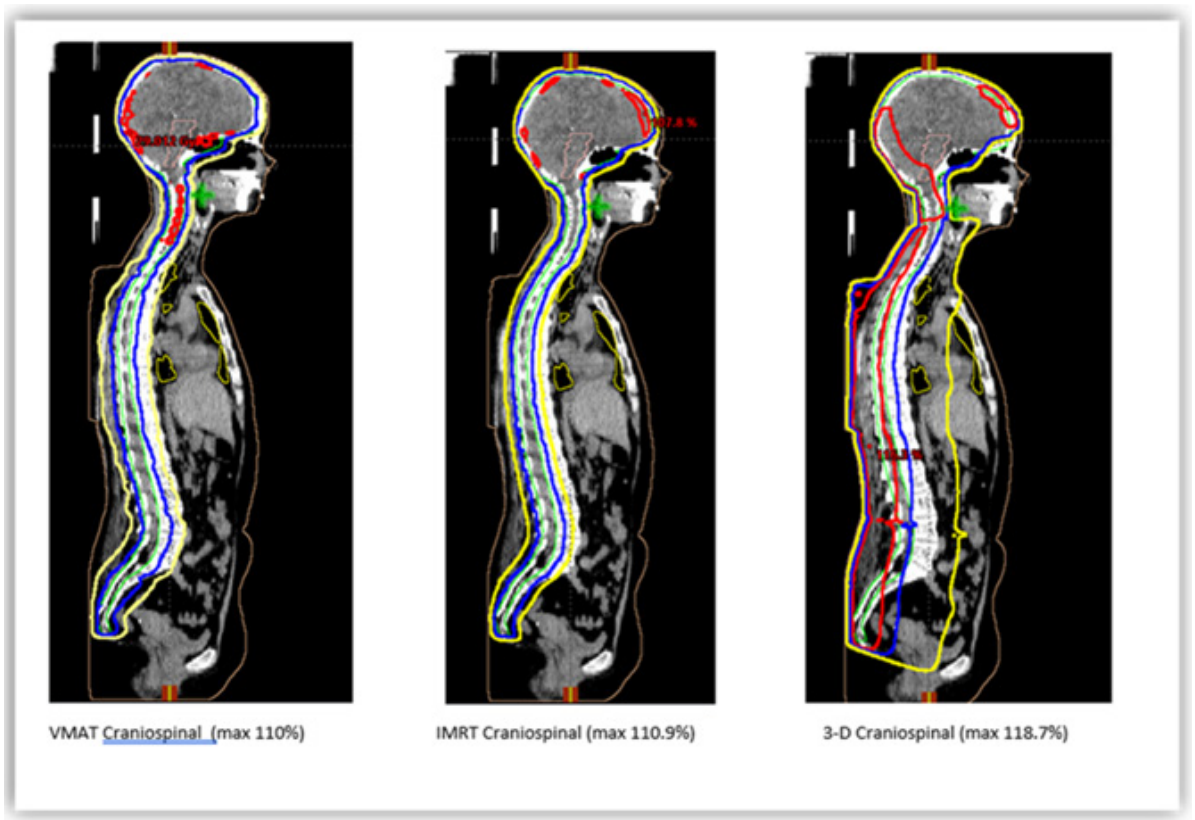

Figure 2: Comparison of the dose distribution observed between VMAT (left), IMRT (middle) and the conventional 3-D plan (right). Yellow = 70% isodose line, blue 95%, green PTV and red hot spots.

We further acknowledge recent literature exploring the use and safety of stereotactic radiotherapy as a re-irradiation option in the appropriate setting of CNS tumour relapse however this was not an appropriate option in the presented case study [8].

The risk of potential radio-necrosis with re-irradiation increases with cumulative doses exceeding 100Gy. If we consider the total dose from both treatments of our patient, the cumulative dose is approximately 54 Gy + 53 Gy = 107 Gy. A literature review on the outcomes of salvage re-irradiation in recurrent MB with a similar represented study group, concluded good local control and survival benefit with acceptable toxicity. In this review, there was one patient who developed symptomatic radionecrosis post re-irradiation, and this possibility was discussed and consented to by our patient [9].

Conclusion

We present a unique case of a rare disease entity where we explored the use of repeat CSI by means of VMAT. We were challenged by the lack of information regarding histological and molecular profiling, the uncertainty of whether this disease process was a case of late relapse or merely the occurrence of a unique second primary, as well as precise past treatment details. We explored the various techniques of RT available in our setting, offering the greatest benefit with least toxicity. Reports similar to what we describe is limited and we furthermore employ advanced VMAT-based radiotherapy techniques to ensure optimal treatment delivery.

We conclude that careful observation and surveillance for late toxicities including neurocognitive and endocrine status is needed. This, along with time to progression is essential to appreciate the outcome and benefit of retreatment.

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