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Case report: successful treatment of primary intradural extramedullary extraskeletal Ewing sarcoma in adult patient with intralesional surgery, chemotherapy, and proton beam therapy of the cerebrospinal axis

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***Abstract*:** Ewing sarcoma is a rare malignant neoplasm that primarily affects bone in children. Extraskeletal location is less common, while intradural extramedullary Ewing sarcoma (IEES) in adults is a casuistic phenomenon. Due to its rarity, a standardized treatment strategy for IEES has not been established. The clinical use of proton beam therapy (PBT) for craniospinal irradiation (CSI) in the treatment of IEES has not been reported in the literature. A 41-year-old previously healthy man presented with disabling gluteal and lower extremity pain, decreased sensation, and progressive paraparesis without sphincter dysfunction. Imaging showed intradural extramedullary spinal lesions. The patient underwent urgent surgery. Histology and immunohistochemistry suggested a poorly differentiated neuroendocrine tumor. Negative chromogranin staining and a high Ki67 index prompted further investigation. Next-generation sequencing later confirmed an *EWSR1/FLI1* translocation, leading to the diagnosis of extraskeletal Ewing sarcoma. The patient received standardized chemotherapy with marked clinical improvement. PBT CSI was initiated but was interrupted due to COVID-19 and other complications. At 20 months follow-up, no recurrence was observed, and the patient reported an active life. Despite intra-spinal spread and multiple complications, intensive chemotherapy combined with PBT CSI led to a favorable outcome. CSI rather than focal radiotherapy should be considered for patients with IEES limited to the cerebrospinal axis. PBT may be used as an alternative to photon radiotherapy to better spare organs at risk.

Keywords: case report, Ewing sarcoma, extramedullary, extraskeletal, proton beam therapy, radiotherapy

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Introduction

Extraskeletal Ewing sarcoma (EES) is much less common than the classic Ewing sarcoma of bone (ESB).[1–3] The occurrence rate of EES stands at 0.4 per million, making it 10-fold less frequent than ESB. It occurs mainly in people aged between 10 and 30 years with a 1:1 male-to-female ratio.[4–6] EES can manifest in various areas, including the paravertebral region, meninges, chest wall, lower limbs, and pelvis.[7,8] Primary intradural extramedullary Ewing sarcoma (IEES) is extremely rare. The lumbar and sacral regions are the most common sites for IEES.[9]

Symptoms accompanying the disease depend on the localization and volume of EES. It usually

manifests as a rapidly growing mass.[10] The diagnostic process includes advanced imaging, namely computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET), as well as complex pathological assessment in tertiary sarcoma centers.[11]

The mainstay of treatment for EES is multiagent chemotherapy, which should be combined with local treatment for localized EES. Surgery remains the method of choice for local treatment, which may be combined with perioperative radiotherapy (RT) to improve local efficacy. For unresectable tumors, RT remains the only definitive local treatment.[12–15] Disseminated disease may benefit from chemotherapy. Due to the rarity of intradural IEES, there is no consensus on its management.[16] However, multidisciplinary treatment of IEES is challenging due to its localization close to the spinal cord. According to the literature, patients who do not receive adjuvant treatment have a worse prognosis than those who receive a combination of RT, chemotherapy, or both after surgery.[17] Other primary rare round cell spinal cancers such as atypical teratoid/rhabdoid tumors are also treated with intensive chemotherapy with local treatment, whereas the main treatment for meningiomas or nerve sheath tumors is surgery and/or radiotherapy.[18,19]

The prognosis in EES is better than in ESB, although prognostic factors are similar.[4,6] The negative prognostic factors at diagnosis include larger primary tumor size, older age, localization within the pelvis, low hemoglobin level, lower white blood cell count, and elevated lactate dehydrogenase.[20–23] Among predictive factors, the strongest is the pathological response to chemotherapy.[15] Nevertheless, IEES has the worst prognosis among all EES. Two-year event-free survival is 60% after multimodal treatment.[24] The most frequent failure is a relapse within the cerebrospinal axis.[25]

We report a case of an adult male patient diagnosed with primary IEES of the spine who was successfully treated by a multidisciplinary team (MDT) with treatment including subtotal laminectomy, chemotherapy, and proton beam therapy (PBT) of the cerebrospinal axis. The case report was presented according to the CARE guidelines.[26,27] The completed CARE checklist is available in Supplemental File A. The timeline of the events is shown in Figure 1.

Case description

A previously healthy 41-year-old man with good performance status (Eastern Cooperative Oncology Group Performance Status 1) was referred to the National Research Institute of Oncology in Warsaw in December 2020 because of disabling pain in the gluteal area and both lower limbs with decreased sensation and progressive paraparesis without sphincter disorders. Physical examination revealed motor weakness of the lower limbs with 40% strength loss bilaterally, decreased sensation, and paraparesis. Upper extremity strength and tone and anal sphincter tone were within normal limits. MRI of the spine showed intradural extramedullary lesions measuring $38 \times 20 \times 15$ mm involving the thoracic and lumbosacral spinal cord with homogeneous contrast enhancement and compression of the medullary cone.

The patient was referred for urgent surgery. In December 2020, a laminectomy of Th11-L1 and removal of the spinous processes of Th11-12 were performed. The surgery resulted in macroscopically complete tumor resection and satisfactory decompression of the lumbar spinal cord with no intraoperative complications. The patient's neurological functions gradually improved, but he had a severe postoperative pain syndrome.

Postoperative histology showed the presence of small round blue cells within poorly differentiated tissue. Immunohistochemistry showed up to 95% positive expression of synaptophysin, bcl-2, GFAP, and Ki67 (paraganglioma-like structures). Microscopic margins were positive. Negative markers included the following: chromogranin, EMA, AE1/AE3−, CK20, CD3, CD10, bcl6, and MUM. The above results suggested poorly differentiated paraganglioma with neuroendocrine tumors or embryonal tumors not otherwise specified. Negative chromogranin staining, high proliferative index, and lesion localization did not support the diagnosis of paraganglioma. In addition, whole-body scintigraphy with labeled somatostatin analogs, ultrasound of the testes, alpha-fetoprotein, and human chorionic gonadotropin analysis were performed and showed no abnormalities.

In February 2021, next-generation sequencing (NGS) was ordered to confirm the diagnosis. Pending the NGS results and suspecting a poorly differentiated high-grade malignant neoplasm,

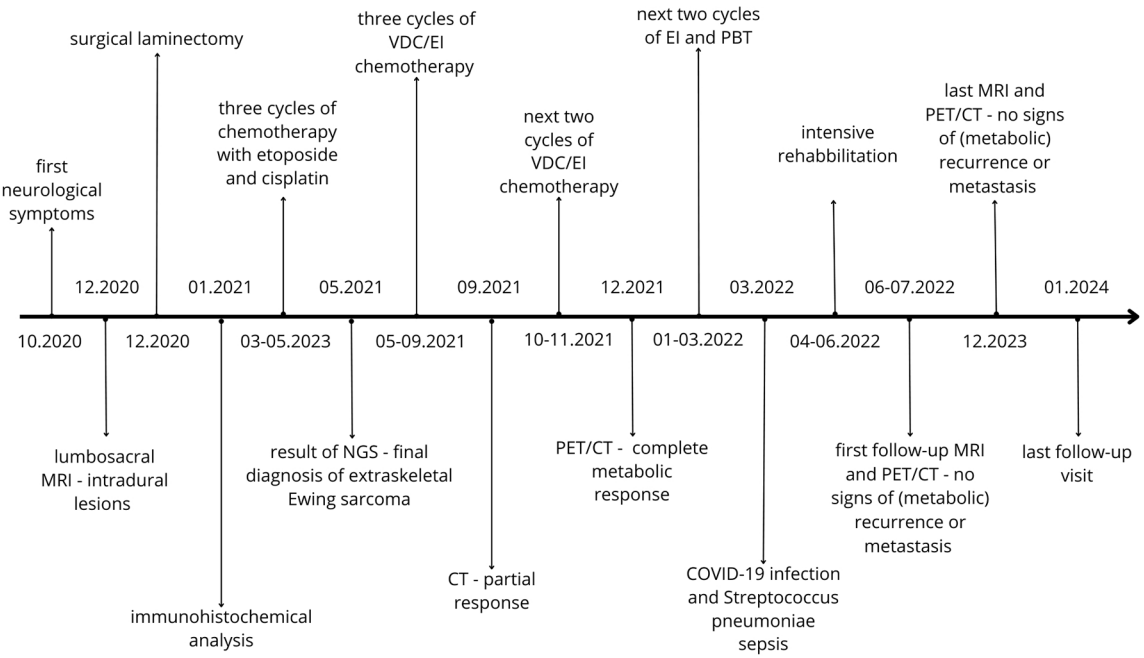

Figure 1. The timeline of the events.

the patient was referred to radiation and medical oncologists. The MDT proposed definitive radiochemotherapy as the primary treatment. In March 2021, the patient was still in severe pain and had not fully recovered from the surgery. He was in a wheelchair and could not maintain a horizontal position due to increasing pain. The patient was unable to maintain the therapeutic position for RT. He started chemotherapy. Between March and May 2021, he received three cycles of chemotherapy based on etoposide and cisplatin (PE regimen with doses according to standard dosing: etoposide 100 mg/m^2 per day and cisplatin 30 mg/m^2 per day; days 1–3 for three cycles q21) with significant clinical improvement. The patient was able to walk unaided after the first cycle of chemotherapy, indicating a clinical response to treatment.

In May 2021, NGS results revealed a chromosomal translocation between *EWSR1* and *FLI1*. The *EWSR1*/*FLI1* gene rearrangement together with positive immunohistochemical staining for membrane expression of CD99 led to the diagnosis of EES. Because of the exclusively intra-spinal localization, the final diagnosis was IEES. Control thoracic and abdominal MRIs showed progressive disease with a contrast-enhancing tumor with a maximum transverse dimension of 22 × 17 mm located intrathecally at the level of the L1 and L2 vertebrae. The tumor at the L1 level filled almost the entire surface of the spinal canal. The tumor in the upper part seemed to be extramedullary, pushing the visible part of the spinal cord from the left to the right side. In addition, numerous enhancing infiltrates were visible on the surface of the spinal cord from the Th5 level down. The image suggested dissemination through the cerebrospinal fluid (CSF). The radiological evidence of dissemination through the CSF was the reason for not performing a CSF. The patient was referred for reconsultation by the MDT, which resulted in a change in the chemotherapy regimen. The patient received the first cycle of standardized VDC/EI chemotherapy as used for skeletal ES (VDC: vincristine 2 mg/cycle, doxorubicin 75 mg/m^2/cycle, and cyclophosphamide 1200 mg/m^2/

cycle; EI: etoposide 500 mg/m²/cycle, ifosfamide 9 g/m²/cycle q21) with premedication (aprepitant, ondansetron, and dexamethasone) and febrile neutropenia prophylaxis (filgrastim 48 million international units for 3 days after chemotherapy, starting 72 h after chemotherapy).[28] Chemotherapy was given every 3 weeks according to the institutional protocol for adult patients with ES, primarily because of the risk of significant hematologic toxicity with biweekly dosing.

The patient continued chemotherapy without significant treatment-related toxicity. However, in September 2021, the patient was diagnosed with a clinically silent pulmonary embolism based on a routine, assessing response to treatment CT with intravenous contrast.

Meanwhile, in October 2021, an MRI of the cerebrospinal axis showed partial response to chemotherapy, namely longitudinal enhancement along the spinal cord, located in the lower part of the thoracic and lumbosacral regions, without objectively measurable mass within the spinal canal. Additional PET/CT with 18F-fluorodeoxyglucose (18F-FDG) ruled out the presence of lesions with increased glucose metabolism. The patient continued chemotherapy according to the VDC/EI regimen until February 2022. In total, he received cumulative doses of cytostatics as follows: vincristine cumulative dose of 6 mg/m², doxorubicin cumulative dose of 410 mg/m², cyclophosphamide cumulative dose of 6.5 g/m², etoposide cumulative dose (together with PE) of 4.5 g, and ifosfamide cumulative dose of 67 g.

Regardless of the radiological spread within the cerebrospinal axis, the patient achieved a very good response to systemic treatment. Therefore, we proposed craniospinal irradiation (CSI) as a consolidative and definitive therapy. To obtain a better dose distribution, the patient was referred to another branch of our institute in Kraków to consider PBT CSI.

Volume definition and dose determination were performed in collaboration between Warsaw and Kraków. We prepared an individualized PBT plan with three clinical target volumes (CTVs). CTV1 covered the unaffected brain with a total dose of 36 Gy radiobiological equivalent (GyRBE) in 20 fractions. CTV2 covered the entire spinal canal with a total dose of 39.6 GyRBE in 22 fractions, the highest CSI dose reported in the literature. Due to their size and proximity to the spinal cord, we could not cover all suspicious lesions remaining after chemotherapy in the thoracic region with the higher dose because the risk of myelopathy would be unacceptable. CTV3 covered the spinal canal below the spinal cord, which was treated as the volume of the primary tumor, with a total dose of 54 GyRBE in 30 fractions. The dose distribution is shown in Figure 2. We used only posterior fields to spare healthy tissues located anterior to the spine. The dose-volume histogram is presented in Figure 3. For example, the dose received by the lungs and kidneys is neglectable.

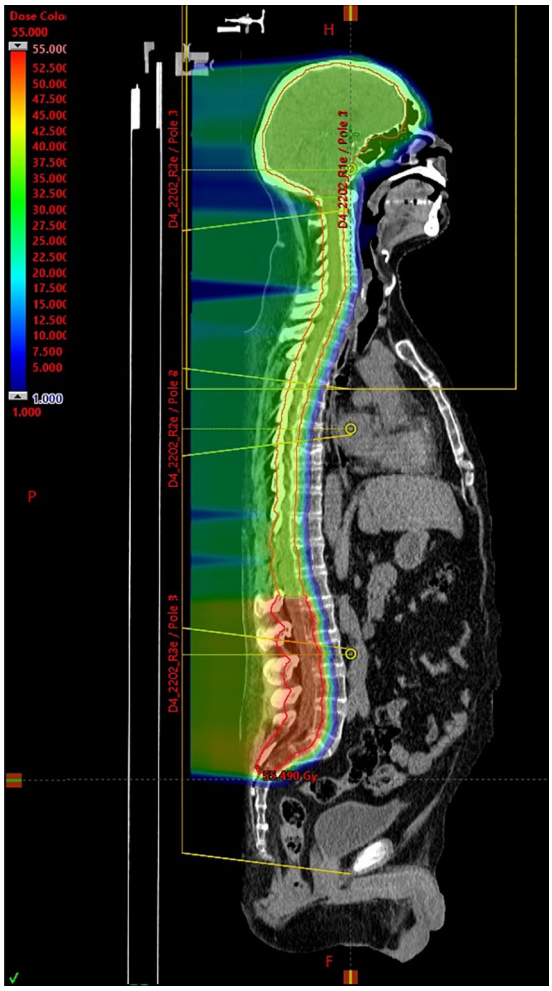

Figure 2. Dose distribution.

The start of the treatment was hampered by difficulties in positioning the patient, who was unable to lie flat due to back pain, but this was overcome by changing the pain medication. PBT CSI began

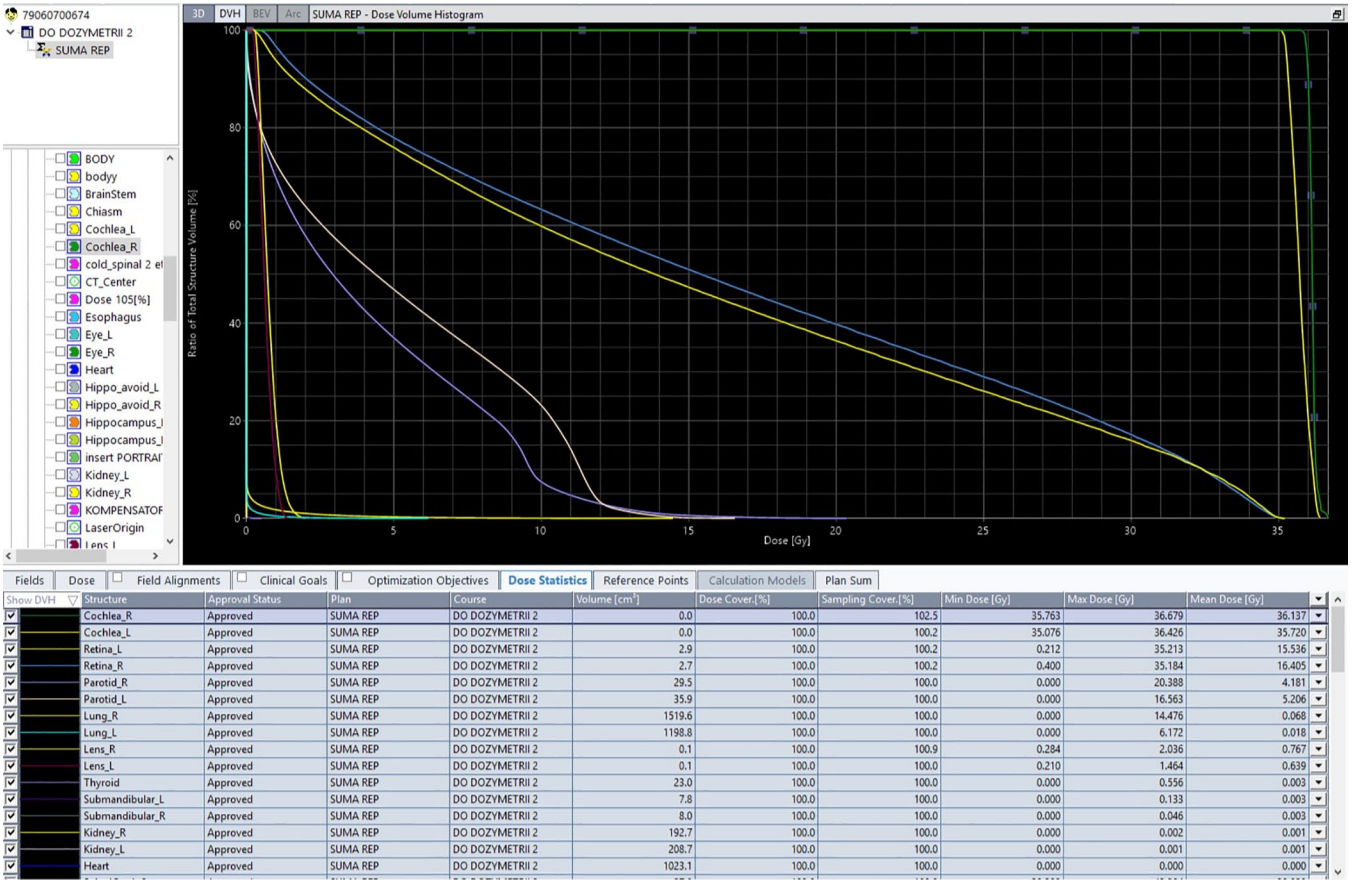

Figure 3. Dose-volume histogram; most organs at risk receive very limited doses.

on February 16, 2022, and continued until March 15, 2022. During the treatment, the patient developed compression fractures of the Th8 and L1 vertebrae, and the lower lumbar vertebral bodies were lowered, probably as a result of osteoporosis caused by chronic steroid use (see Figure 4). This situation forced PBT plan adaptation.

During PBT CSI, the patient continued EI chemotherapy. He received two more cycles on February 21 and March 17, 2022. Both resulted in grade 4 leukopenia according to the Common Terminology Criteria for Adverse Events 5.0. Because the treatment occurred during the peak of the COVID-19 pandemic, the patient tested positive for COVID and had his PBT CSI interrupted. He developed a severe secondary superinfection of bacterial bronchopneumonia. On March 30, 2022, he was admitted to an infectious disease hospital, where he also developed *Streptococcus pneumoniae* sepsis. After 2 weeks of hospitalization, the patient was slowly recovering and was scheduled to resume PBT; however, another vertebral fracture with symptomatic spinal cord compression occurred, resulting in the need for orthopedic treatment, and therefore PBT was eventually discontinued. The total doses received by the patient were 30.6 GyRBE in 17 fractions to the cerebrospinal axis and 41.4 GyRBE in 23 fractions to the lumbosacral region of the spine.

The patient slowly recovered from the adverse events. He underwent intensive rehabilitation. In June 2022, an MRI of the lumbosacral and thoracic spine showed no evidence of local progression. In August 2022, PET/CT with 18F-FDG showed no metabolic evidence of local or distant recurrence. Therefore, MDT decided to discontinue treatment and refer the patient for follow-up. He received a total of 14 cycles of VDC/EI. In November 2023, the patient reported no major symptoms, moved independently, and reported an active family and work life while continuing intensive rehabilitation. The last MRI and PET/CT performed in December 2023 showed no evidence of recurrent disease. Further improvement in quality of life was observed on the last follow-up visit in January 2024.

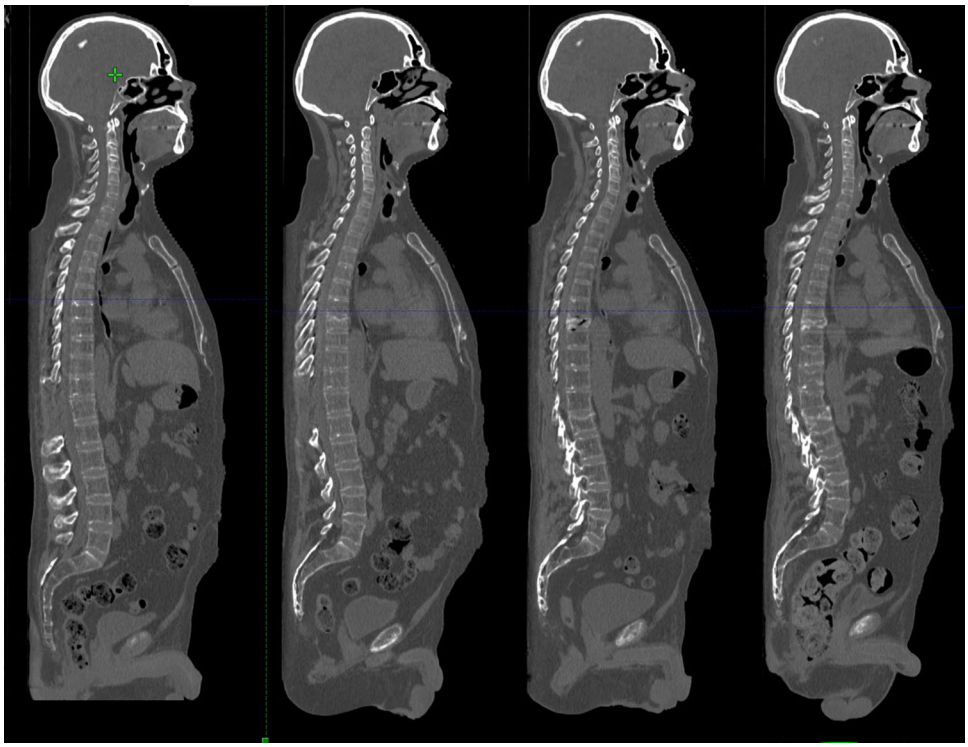

Figure 4. Consecutive fractures of the Th8 and L1 vertebrae that occurred during irradiation.

Discussion

Only 53 cases of primary IEES have been described in the literature, including our case.[9,29] Importantly, we present the first case of an adult patient treated for IEES with PBT CSI. In addition, the treatment resulted in a complete response with no evidence of disease recurrence at nearly 20 months of follow-up, despite intra-spinal spread, multiple complications, and CSI interruption. Multimodal treatment including a combination of intensive chemotherapy and local treatment seems to be the appropriate treatment option for IEES. Nevertheless, our case may help clinicians to answer some questions that may arise during treatment planning.

The first question is the intention of treatment. Intra-spinal spread may be an argument for purely palliative treatment with chemotherapy alone. However, CSI has provided very good intra-spinal control even in much more radioresistant cancers such as ependymoma.[30–33] There are some reports describing patients with intra-spinal spread or leptomeningeal metastases who benefit from CSI. Therefore, based on our case and the available data, we propose a statement that intra-spinal spread should not be a definition nor an indication for palliative RT alone.

The second question is related to the choice between focal RT and CSI. In their review of 20 cases of patients with IEES treated with focal RT and CSI, Chihak et al. found that only three patients received CSI.[34] Importantly, none of them experienced craniospinal axis failure, whereas 47.1% of patients treated with focal RT developed progression with poor survival. Of these, one had primary site failure, five developed distant craniospinal axis failure, and two had both. In another case report and a literature review reported by Izubuchi et al., a 35-year-old woman with IEES and meningeal metastases, who underwent surgery, chemotherapy, and spinal RT without whole brain RT, developed brain metastases 10 months after diagnosis.[16] The authors also summarized all IEES cases described in the literature between 1997 and 2019 and concluded that CSI might be more effective for local control than whole spine RT or focal RT. The case of our patient supports the conclusions driven by the authors of the above reports that CSI should be preferred to focal RT in IEES. However, this conclusion may be limited by the lack of CSF analysis before RT, and the good clinical outcomes achieved may have been due to chemotherapy alone.

The third issue is the choice of the CSI technique. To date, photon RT has been the method of

choice for ES and IEES. There are several reports on the use of PBT in patients with ESB and only two reports on its use in EES.[35–39] However, PBT has never been used in IEES. The main advantage of PBT in CSI is a much better dose distribution outside the spinal canal and the brain due to the Bragg peak phenomenon, which allows a sharp dose drop behind the target volume.[40] The pediatric patient population benefits the most from CSI due to the reduction of significant late side effects of RT, which occur several years after RT and affect children more frequently than adults.[41–45] However, adult patients may also benefit from PBT. A report comparing proton and photon CSI in adult patients with medulloblastoma showed a benefit of protons in reducing acute hematologic and gastrointestinal toxicity.[46] Another study reported outcomes of 50 adult patients with various cancers treated with vertebral body-sparing CSI.[47] The authors reported a favorable acute toxicity profile and very low median doses to organs at risk, which may be associated with late toxicity. In our case, the use of PBT enabled good sparing of healthy tissues located anterior to the spine. Therefore, we can conclude that adult patients are also candidates for PBT CSI. However, the use of PBT for CSI may be limited by equipment availability and lack of reimbursement.

The fourth issue is the determination of target volumes and total dose. While it is obvious that the elective target volume in CSI should cover the entire cerebrospinal axis and the boost volume should cover the site of gross disease, the optimal dose remains unknown. We decided to prescribe doses similar to those used for medulloblastoma, namely 36 GyRBE in 20 fractions to the unaffected brain, 39.6 GyRBE in 22 fractions to the entire spinal canal, and 54 GyRBE in 30 fractions to the boost volume, defined as the spinal canal below the spinal cord. However, he received only 30.6 GyRBE in 17 fractions to the cerebrospinal axis and 41.4 GyRBE in 23 fractions to the lumbosacral region of the spine. Surprisingly, the suboptimal dose administered allowed for long-term disease control. We did not observe any significant neurotoxicity, so we can cautiously say that for potentially radiosensitive tumors, the commonly used total doses are an optimal approach.

Patient perspective

The most important question is the balance between the potential benefit and the risk of severe toxicity for the patient. Our patient underwent aggressive treatment with severe acute complications. On the other hand, after 19 months of follow-up, he is free of advanced disease and his quality of life is steadily improving with each follow-up visit. Some authors reported an even more aggressive approach in a 19-year-old female patient with a primary primitive neuroectodermal tumor of the thoracolumbar spinal cord who underwent surgical excision, CSI RT, and high-dose chemotherapy with autologous stem cell transplantation.[48] Our case highlights the importance of multidisciplinary care and collaboration between specialists in cancer treatment, as well as the potential benefit of advanced RT techniques.

Conclusion

Based on this case and available data from the literature, CSI rather than focal radiotherapy should be considered for patients with IEES limited to the cerebrospinal axis. PBT may be considered to avoid unnecessary irradiation of healthy tissues located anterior to the spine.

Declarations

Ethics approval and consent to participate

Each patient, at the beginning of treatment, provided routine informed consent for the use of their treatment and data processing. The study was conducted according to the guidelines of the Declaration of Helsinki. The paper does not report on the use of experimental or new protocols. This study, as part of a project series, was approved by the Local Ethics Committee at Maria Skłodowska-Curie National Research Institute of Oncology (approval number KB/9/2011).

Consent for publication

We obtained both oral and written consent of the patient for publication.

Author contributions

Mateusz Ziomek: Data curation; Formal analysis; Investigation; Methodology; Project administration; Resources; Software; Visualization; Writing – original draft; Writing – review & editing.

Joanna Placzke: Data curation; Formal analysis; Investigation; Methodology; Resources; Writing – original draft; Writing – review & editing.

Konrad Urbanek: Data curation; Formal analysis; Investigation; Methodology; Resources;

Visualization; Writing – original draft; Writing – review & editing.

Tomasz Skóra: Supervision; Validation; Writing – review & editing.

Piotr Rutkowski: Supervision; Validation; Writing – review & editing.

Mateusz Jacek Spałek: Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Resources; Software; Supervision; Validation; Visualization; Writing – original draft; Writing – review & editing.

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Competing interests
The authors declare that there is no conflict of interest.

Availability of data and materials
The data analyzed for this study can be found in the manuscript.

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Supplemental material
Supplemental material for this article is available online.

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