

The importance of surgery as part of multimodal therapy in rapid progressive primary extraosseous Ewing sarcoma of the cervical intra- and epidural space

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Abstract

Primary extraosseous Ewing sarcomas (EESs) are an extremely rare pathological entity. Less than 32 cases have been reported in the literature. Here we report an uncommon case with very rapid progression in the cervical region with extra- and intradural involvement. We present a thorough review of the literature and discuss possible treatment modalities. The Medline database was searched using the search terms: *Ewing sarcoma, extraosseous tumour, treatment, management, cervical spine*. A previously healthy 29-year-old man complained of right-sided radiculopathy (C7). Magnetic resonance imaging showed an enhancing foraminal, sandglass shaped neuroinoma-like lesion. Surgery revealed an intra- and extra-dural lesion, which was histologically diagnosed as Ewing sarcoma. Despite gross total resection, there was a massive symptomatic tumor recurrence within 6 weeks. A second gross total resection was realized. The patient was treated according to the EURO E.W.I.N.G.-Protocol (VIDE) and recovered very well (progression-free interval during therapy). Several decompressive re-surgeries were realized with adjuvant radio-chemotherapy. At the last follow-up (17 months after initial surgery) the patient was in remission with a good quality of life. This case is to illustrate that despite extensive therapeutic efforts, the progression-free survival in case of primary EES may be very short. To maintain neurological function and good quality of life as long as possible, a multimodal strategy seems to be adequate. Like in the present case this implies several surgeries and adjuvant chemo- and radiotherapy. Whether this improves overall survival remains unclear.

Introduction

The incidence of Ewing's sarcoma of bone (ESB) is 1.7 to 2.1 per million people in the United States (about 200 new cases/year).¹ Most often they occur in children or young adults. They usually occur in the skeleton (arms, legs, pelvis, chest wall) and may spread to the lungs or other bony sites.² These tumours rarely originate in the spine.^{3,4} Primary EES of the spine are even more rare and less than 32 cases (mostly adolescents) have been reported.^{5,6} The lumbosacral region was the most common location (50%), followed by the thoracic region (25%). For the cervical spine (including the cervico-thoracic junction) only 8 cases have been reported.^{6,7} At present, the 5 year survival rate is about 41%.⁸ Due to advancements in care survival for Ewing sarcoma of the spine has significantly increased (nearly 2-fold) since the 1980s. Nevertheless, prognosis is still dismal (3- to 4-fold reduced survival), if distant metastasis occurs.⁸ In general Ewing tumours are radio- and chemosensitive. Consequently, these modalities play a major role in a multimodal therapy concept. The role of surgery, especially with regard to local tumor control, is still under discussion. Unlike in extremities, Ewing sarcoma in the spinal epidural space or the spinal column cannot be resected with wide margins due to relevant structures such as major vessels, oesophagus, and the myelon. However, decompressive surgery - even multiple - may preserve neurological function and therefore maintain quality of life although it may not prolong overall survival. Based on an illustrative case, we discuss the relevant literature and try to work out a management algorithm based on preservation of neurological function and maintenance of quality of life.

Case Report

A 29-year-old man presented with a history of right C7-radiculopathy progressing over 3 months. Then a hemiparesis occurred. Magnetic resonance imaging (MRI) demonstrated a bright enhancing intraforaminal cervical tumour with intra- and extraspinal components. During surgery an intra- and extradural gross total resection was performed. Histology demonstrated a uniform population of small round blue cells with extensive mitoses and scattered necrosis. Immunohistochemistry showed bright expression for MIC-2, and partial expression for vimentin, cytokeratin and synaptophysin. The fluorescent *in situ* hybridization (FISH) detected the translocation of the EWS Gene on chro-

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mosome 22q12. The diagnosis was extraosseous Ewing sarcoma.

Immediately after surgery, the patient's neurological status improved. Further metastases were ruled out. 4 weeks later, just before starting the adjuvant therapy according to EURO-E.W.I.N.G. 99 protocol, a massive recurrence of the tumour lead to acute re-deterioration. An intradural and extradural debulking of the tumour was performed. Postoperatively, the patient recovered and was able to walk with minor assistance, however the arm remained paretic. Histology confirmed recurrence of the Ewing sarcoma with a high Ki-67 labelling index (30%). The planned chemotherapy was started shortly after surgery (vincristine, ifosfamide, doxorubicin, etoposide; six cycles). During the cycles the patient responded well. But after termination of the last one, the tumour progressed again. At this time spinal metastasis occurred. Debulking surgery followed twice to relief the patient's neurological symptoms. The interdisciplinary tumour-board decided to administer a salvage chemotherapy (topotecan and cyclophosphamide, two cycles) combined with radiotherapy (local boost and the whole spinal canal, 36 Gy). Afterwards he received high-dose busulfan and mephalan and autologous stem cell transplantation. Besides the dysfunction of fine motor skills by a distal paresis of the upper extremity and some degree of spinal ataxia he was able to walk with little assistance. Eighteen months after treatment, the patient had no worsening of his neurological symptoms and is free of local and distant recurrence (Figures 1-3).

Discussion

Commonly it is thought that prognosis of Ewing sarcoma is mainly dependent on the presence of metastases at initial diagnosis and

not by tumour site, volume or local therapy modality.⁹ For Ewing sarcoma of the spine there are only limited data about survival, especially for the primary ones. In their analysis Mukherjee and colleagues found a 5-year survival rate of 41% in Ewing sarcoma's

patients with primary spine involvement. For PNET/EES in the spinal canal a 5-year survival rate between 0% and 37.5% was reported.¹⁰ There are no data about quality of life.

In general Ewing tumour is diagnosed by needle biopsy and then chemotherapy is initi-

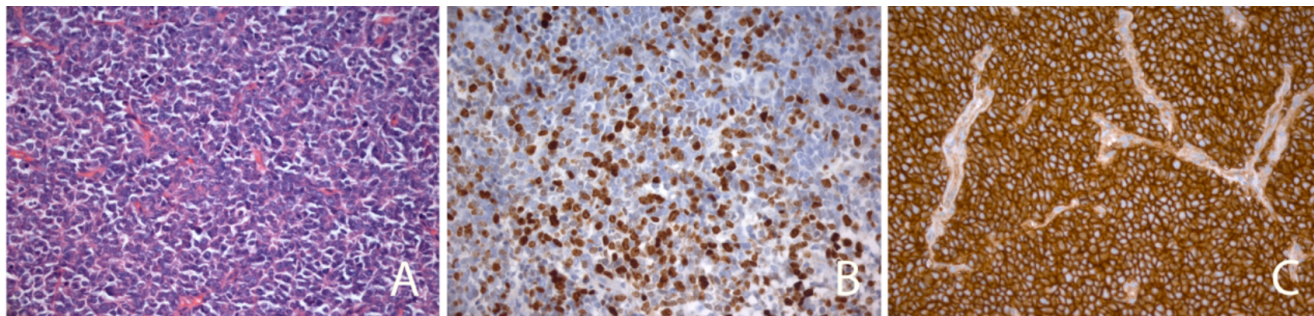


Figure 1. Histology - First surgery: hematoxylin and eosin-stained tissue sections demonstrated a highly cellular, uniform population of small round blue cells with extensive mitoses (A). Ki67 immunostaining revealed an increased proliferation rate (B), and the tumor was strongly immunopositive for MIC-2 (C) (400x).

Table 1. Showing the literature review for primary extraosseous Ewing sarcomas in the cervical spine and the management and outcome.

| Case No. | Reference | Age | Level of C-spine | Surgery | Localization | Ctx | Rtx (Gy) | Outcome (months) | Gender |
|----------|--|-----|------------------|---------|----------------------------|--|--|--|--------|
| 1 | Shin <i>et al.</i> ¹⁴ | 22 | C7-T1 | Partial | Intra-, extradural | YVAD-C (Cyclophosphamide, vincristine, adriamycin, decarbazine, two cycles) | No | NED (4 years) | F |
| 2 | Shin <i>et al.</i> ¹⁴ | 38 | C6-C7 | Partial | N/A | Mesna, adriamycin, ifosfamide, dacarbazine | No | AWD (5) | M |
| 3 | Kennedy <i>et al.</i> ⁵ | 24 | C | Partial | Extradural | Intergroup Rhabdomyosarcoma Study II (isophosphamide, vincristine, adriamycin, alternating with actinomycin D, six courses) | Intergroup Rhabdomyosarcoma Study II (4600 cGy), administered in 200-cGy fractions | NED (13) | M |
| 4 | Mukhopadhyay <i>et al.</i> ⁵ | 29 | C | Partial | N/A | VAC (vincristine, adriamycin and cyclophosphamide) alternating with ICE (ifosfamide, cisplatin and etoposide) least six cycles | Radiotherapy (50 Gy) | Follow-up period is 21.2 months (range 11-32 months) | F |
| 5 | Mukhopadhyay <i>et al.</i> ¹⁵ | 13 | C | Partial | N/A | VAC (vincristine, adriamycin and cyclophosphamide) alternating with ICE (ifosfamide, cisplatin and etoposide) least six cycles | Radiotherapy (50 Gy) | Follow-up period is 21.2 months (range 11-32 months) | M |
| 6 | Kogawa <i>et al.</i> ⁶ | 7 | C2-C4 | Partial | Extradural | Yes and PBSCT | 40 | NED (60) | F |
| 7 | Ozturk <i>et al.</i> ¹⁰ | 18 | C-T | N/A | N/A | N/A | | M | |
| 8 | Harimaya <i>et al.</i> ⁷ | 30 | C2-C4 | Partial | Intradural, extramedullary | Yes (VAIA) | 50 | DOD (14) | F |
| 9 | This case | 30 | C7-T1 | Partial | Intra-, extradural | Yes | 40 | AWD (18) | F |

AWD, alive with disease; DOD, dead of disease; NED, no evidence of disease; PBSCT, peripheral blood stem cell transplantation; VAIA, vincristine, adriamycin, ifosfamide, and actinomycin-D.

ated. For local control this may be followed by radiation and/ or surgery. At present, the role of surgery remains unclear. For instance, Bacci *et al.*¹¹ concluded that surgery with adequate surgical margins is better than RT in cases of extremity ES, but patients are better treated with full-dose RT from the start, when inadequate surgical margins are expected. Ozaki *et al.*¹² concluded that surgery adds to the safety of local control in patients with Ewing sarcoma. Interestingly, however, they reviewed also the 10-year overall survival and found a not significant relationship concerning the amount of surgical resection (radical, wide, marginal, and intralesional).

In comparison, treatment of (primary) Ewing sarcomas of the spine has special characteristics. Firstly, radiotherapy is limited by the tolerance of the spinal cord (55Gy). Secondly, achieving tumour free surgical margins or *en bloc-resection* may be difficult to obtain due to essential anatomic structures. However, decompressive surgery may be well indicated for spinal cord decompression and maintenance or restoration of neurological function. As in the presented case, the treatment may become very aggressive with multiple surgeries, chemo-/radiotherapy and peripheral blood stem cell transplantation (PBSCT).

Harimaya⁷ described a similar case in a 30-year-old woman, who died of intramedullary dissemination 14 months after the surgery. After subtotal resection the patient was treated by chemo-, and radiotherapy (VAIA, 50Gy). In contrast Kogawa⁶ reported a still complete remission 60 months after surgery for his patient, a 7-year old child with a primary epidural Ewing sarcoma. Postoperative radiotherapy (40 Gy) and chemotherapy was given including PBSCT. Others reported that consolidation with high-dose chemotherapy combined PBSCT failed to improve overall survival-rates in patients with high-risk ES.¹³

In the English literature, 8 cases of EES arising primarily within the cervical spinal canal have been reported (Table 1).^{5-7,10,14,15} 50% were

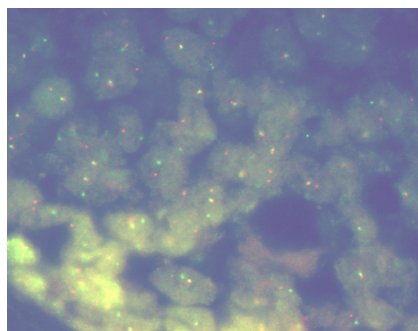


Figure 2. Break-apart FISH, showing chromosomal translocation (of Chromosome 22q12) in 25/40 nuclei of the tumour cells (wide gap between red and green dots).

female. The mean age of these patients at diagnosis was 26 years (range 7-30 years). Most patients (75%) were between 20 and 30 years old, 12.5% even in the first decade of life.

It is difficult to draw strong conclusions from the presented case and the small number of cases reported in the literature. Nevertheless, we believe that in case of spinal primary EES an aggressive surgical resection may improve local tumor control, maintain neurological function, preserve quality of life and may result in prolonged overall survival.¹¹

Conclusions

Despite extensive therapeutic efforts the prognosis of Ewing Sarcoma is still dismal. The therapy is based on a multimodal concept of chemo-/radiotherapy and surgery. In cases with primary EES with spinal involvement, the role of surgery is important in order to maintain neurological function and quality of life. Whether this improves overall survival remains to be shown by larger series.

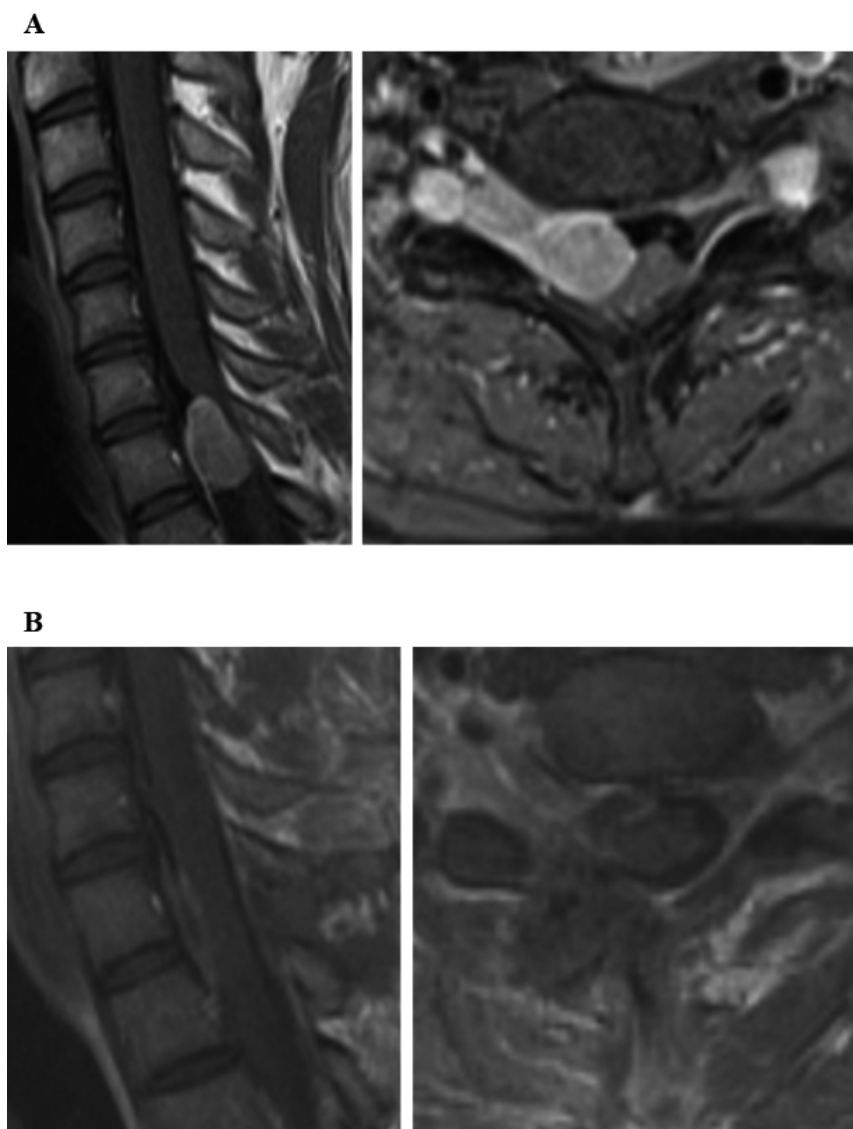


Figure 3. A) Preoperative (first surgery) T1-weighted magnetic resonance images showing a well-circumscribed, sandglass shaped contrast enhancing mass in the right foramen compressing the spinal cord without bony involvement. B) Postoperative (first surgery) T1-weighted magnetic resonance images after gross total resection (intra-, and extradurally) with a decompressed myelon (Right: sagittal views, left: transverse views).

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