Exp Biomed Res 2022; 5(3): 303-318
Doi: 10.30714/j-ebr.2022.148

Experimental Biomedical Research **Systematic review article**

Do repeated surgical interventions in patients with lumbar paraspinal Ewing's sarcoma increase survival by supporting pharmacological treatment? A comprehensive systematic review

Ibrahim Yilmaz[1,2], Numan Karaarslan[3], Yasin Emre Kaya[4], Hakan Somay[5]

[1]Unit of Pharmacovigilance, and Rational Use of Drugs, Republic of Türkiye, Ministry of Health, Doctor Ismail Fehmi Cumalioglu City Hospital, Tekirdag, Türkiye.

[2]Department of Medical Services and Techniques, Istanbul Rumeli University, Vocational School of Health Services, Istanbul, Türkiye.

[3]Department of Neurosurgery, Halic University School of Medicine, Istanbul, Türkiye.

[4]Department of Orthopaedics and Traumatology, Bolu Abant Izzet Baysal University, School of Medicine, Bolu, Türkiye

[5]Department of Neurosurgery, Kadikoy Medicana Hospital, Istanbul, Türkiye

ABSTRACT

Aim: To present the medical and surgical treatment of a patient who was diagnosed with Ewing's sarcoma (EWS) in the paraspinal region and was operated on, in line with a comprehensive systematic literature review.

Method: A comprehensive and systematic literature search of electronic databases was performed. Keywords used were "EWS" and "EWS treatment". Randomized, controlled clinical trials were included in the study. Letters to the editor, bibliographies, reviews, and meta-analyses were excluded. In addition, our EWS case was presented in full detail.

Results As a results of a comprehensive and systematic literature search of electronic databases, the full texts of the appropriate 323 studies conducted between the years 1786 to 2021 were retrieved and evaluated. In the case we present here, the expandable mass was largely excised together with the invasive skin tissue. Immunohistochemical examination of the excised tumor tissue using vimentin antibody revealed that the mass was compatible with EWS, a mesenchymal malignant tumor.

Conclusion: Many different pharmacological agents can be administered in different posologies and different combinations before and after paraspinal/paravertebral lumbar surgery of EWS. Further studies containing more cases from different races, gender must be performed to comprehensively evaluate the effects of repeated surgical interventions of patients with EWS due to recurrence and/or residue, which may positively contribute to patient's survival and prognosis by giving more time to standard chemotherapy.

Key words: Ewing's sarcoma, paraspinal/paravertebral, lumbar surgery, repeated surgery, pharmacological drugs.

✉ *Dr. Ibrahim Yilmaz, Ministry of Health, Dr. Ismail Fehmi Cumalioglu City Hospital, Tekirdag, 59020, Türkiye*
E-mail: dryilmazi@yahoo.com

Received: 2022-05-06
Accepted: 2022-05-21 / Published: 2022-07-01

Introduction

Ewing's sarcomas (EWS) are solid-malignant tumors that usually develop in the bone structures [1]. The tumors develop directly from the bone tissue cells and are described as primary bone tumors [2]. They have distinctive

features and are separate from metastatic malignant tumors that develop in other organs [3]. EWS may be rarely observed in the connective tissue, adipose tissue, muscle tissue, or peripheral nerve tissues [4]. Although very rare, this can be seen in infants of breastfeeding age, school-aged children, adolescents, and older adults [5].

EWS is derived from indifferent mesenchymal stem cells [6]. Classical Ewing sarcoma is classified as peripheral malignant primitive neuroectodermal tumours, a skin tumors of the chest wall, and the soft tissue tumours part according to the tissue characteristics and origin of the tumour [7-9].

Surgery and/or radiotherapy and chemotherapy treatment protocols are applied to patients diagnosed with EWS [10]. Positive results have been obtained in the cure and survival of EWS cases with the intensive combined chemotherapies and standard treatments carried out within the framework of therapeutic adaptation studies during the last decade [11,12].

Despite all the treatment protocols applied, the tumour can recur or metastasize [13]. For this reason, research has focused on different genetic pathways and/or drug combinations, and *in-vitro and in-vivo* trials on the use of small-molecule checkpoint kinase 1 inhibitors or siRNA knockdown in combination with gemcitabine have been performed to that effect. Such studies provided insight into candidate therapeutic target/drug combinations for the treatment of EWS [14]. Iron chelator drugs cause in-vitro apoptosis in EWS cells through inhibition of ribonucleotide and attenuate tumour growth in-vivo, in the xenograft model [15]. Ciclopirox, a synthetic antifungal agent used in the treatment of dermatomycoses, can inhibit EWS growth by affecting vasculature development and DNA replication [16]. Some studies using commercial cell lines have reported that the use of cyclin-dependent kinase (CDK) 4/6 pathway inhibitors in combination with insulin-like growth factor 1 receptor activation show promising results in the treatment of EWS [17]. Other than laboratory studies, a pharmacological agent named cabozantinib, which nonselectively inhibits c-Met, vascular endothelial growth factor receptor-2, AXL, and RET, is investigated in, a multicentre, single-armed, phase II study [2].

Although these pharmacological agents are tested experimentally or in phase II, they may be a promising treatment option in clinics in the future. In current treatment modalities, a few weeks of induction chemotherapy is administered before the surgical operation to achieve satisfactory treatment outcomes for tumours or metastases [18]. At this stage, combination infusions of cytostatic drugs such as doxorubicin, etoposide, ifosfamide, and vincristine are used [19,20]. Autologous stem cell transplantation can also be applied in this treatment process [21]. Local therapy can be applied with or after chemotherapy. Surgical operation is performed in some cases [22], and radiotherapy is applied instead of surgical operation or in addition to the operation [23].

However, no studies have investigated whether repeated surgery may positively contribute to standard chemotherapy. Moreover, no studies have examined whether repeated surgeries performed due to recurrence and/or residual tumour tissue may increase the survival of the patients treated with chemotherapy and whether repeated surgical interventions may have positive or negative effects on the prognosis of EWS. The present study aimed to systematically evaluate the pharmacological and surgical treatments of a case with paravertebral (paraspinal) EWS in line with the literature.

Materials and methods

Written consent of the hospital management and the patient was obtained for the use of patient data. The data of the patient, who applied to the outpatient clinic with complaints of low back and back pain for about two months, were extracted from the medical records.

Research strategy: A comprehensive and systematic literature search of numerous electronic databases, including Cochrane Collaboration, Cochrane Library, Ovid, Medline, ProQuest, the National Library of Medicine at the National Institutes of Health, and PubMed, was performed. A combination of keywords was used to retrieve studies broadly associated with the topic of interest. The search criteria were as follows: “surgery”, “pain”, “radiculopathy”, “lumbar”, “cabozantinib”, “checkpoint kinase 1 inhibitor”, “ciclopirox”, “cyclin-dependent kinase pathway”, “cyclophosphamide”, “dactinomycin”, “docetaxel (DTX/DLX)”, “doxorubicin”, “etoposide”, “gemcitabine”, “ifosfamide”, “irinotecan”, “paraspinal”, “paravertebral”, “ribonucleotide reductase inhibition”, “cytostatic drugs”, “temozolomide”, “tyrosine kinase”, “vincristine”, and/or “Ewing's sarcoma”.

The headings and abstracts of all studies on the pharmaceuticals used and surgeries performed for the treatment of EWS were reviewed. The full texts of the appropriate studies were retrieved according to the headings and abstracts, and then the decision of whether to include or exclude these studies was made after a comprehensive review [24].

Letters to the editor, bibliographies, reviews, and meta-analyses were excluded from the study. Critical appraisal checklists were used to assess and analyze the quality of the selected studies [24,25]. Experimental studies were excluded. Frequently cited articles were identified. References and citations of these articles were examined, and possible repetitions were avoided. Next, the obtained data were

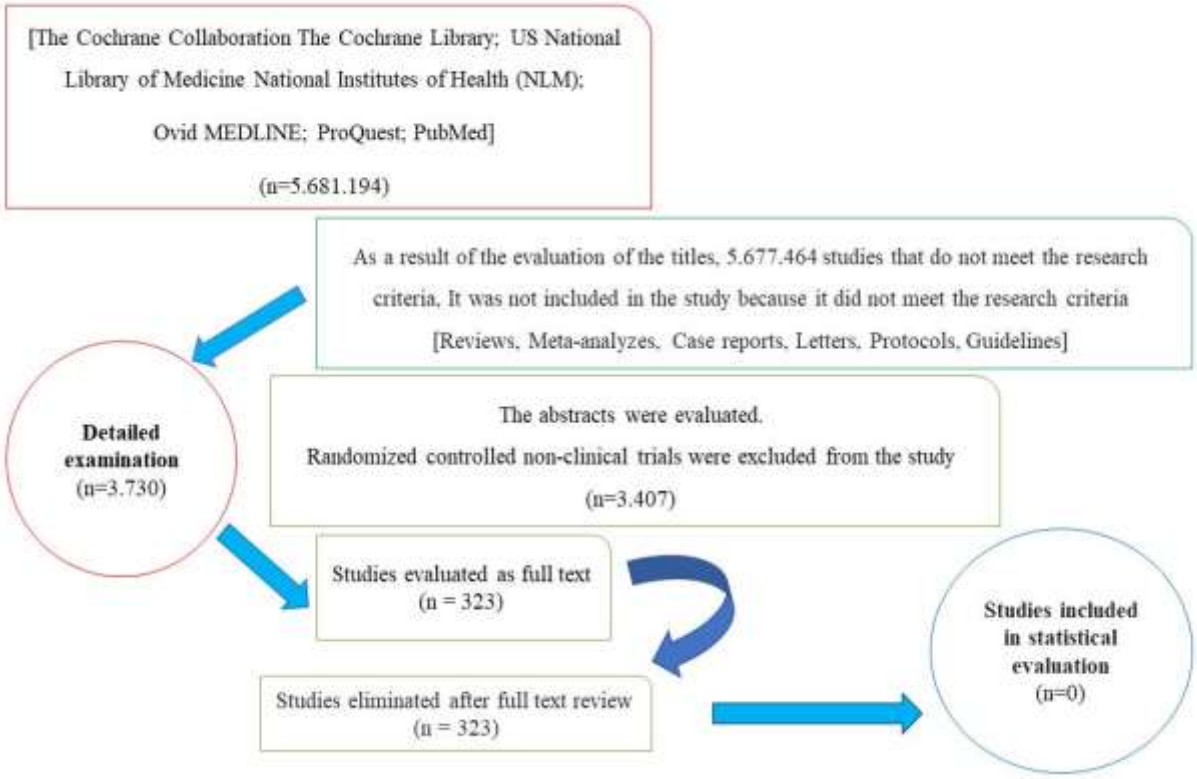

Figure 1. Systematic presentation of the inclusion criteria.

summarized, and the findings were compiled clearly and understandably using tables. The present study was conducted based on the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines [24-26].

Studies evaluated were selected independently. The risk of selection bias due to potential masking was also investigated. All studies were reviewed by two authors to ensure the accuracy of the data obtained. In cases where there was disagreement between two authors, all authors were consulted to reach a consensus.

The screening process of the studies that did not meet the inclusion criteria and therefore were left out of our systematic review is presented in Figure 1.

Results

A 31-year-old male patient who presented with the complaint of low back and back pain for about 2 months was evaluated. The patient did not have a history of any systemic disease and/or surgical intervention. In addition, the hematological and biochemical parameters of the patient, who had no history of smoking or alcohol use, were within normal limits.

The physical examination of the patient revealed a 5x5 cm painless mass lesion that slightly expanded the skin tissue in the lumbar region. Contrast-enhanced magnetic resonance imaging (MRI) of the lumbar spine was performed and the patient's neurological examination was normal.

A necrotic mass with a size of 84x48x49 mm was observed in the left paraspinal region between L2-L5 vertebrae, which was not related to osseous tissue and neural tissue and was in the muscle tissue (Figure 2).

The patient was preliminarily diagnosed with soft tissue sarcoma and then operated on. Tumor with fibrous pseudocapsule rich in vascular structures, and invading muscle tissue was grossly excised (Figure 3).

The immunohistochemical examination of the excised tumour tissue revealed that the mass was compatible with Ewing sarcoma, a mesenchymal malignant tumour (Figure 4).

The patient with no sign of recurrence in the follow-ups was discharged with normal neurological examination and was recommended to apply to the oncology clinic. The three-phase bone scintigraphy with Tc-99m methylene diphosphonate of the patient

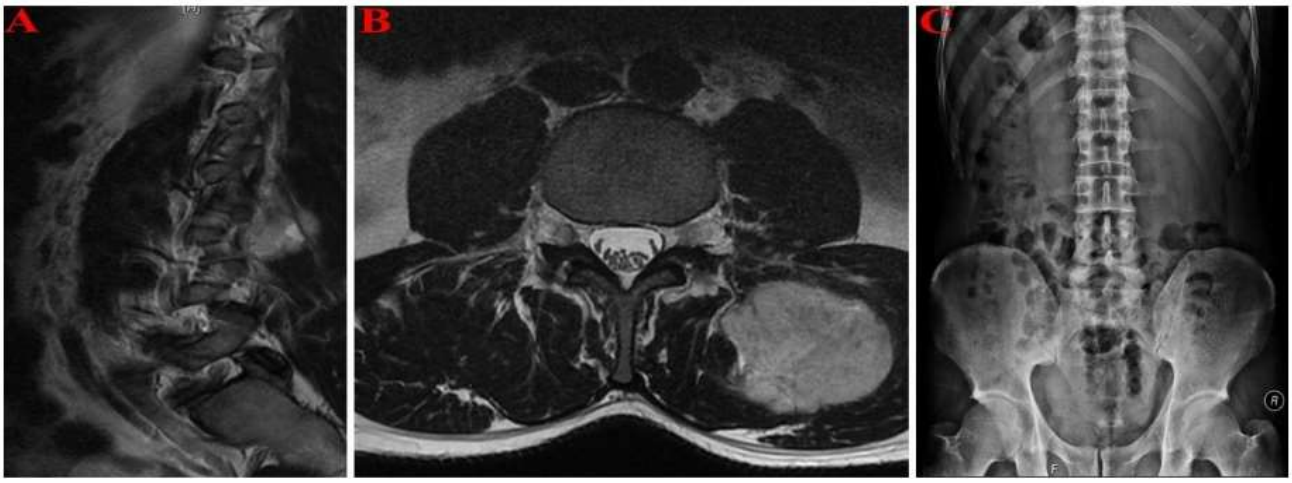

Figure 2. A; Localized mass lesion in the posterior of the L-3 vertebral corpus, in the preoperative non-contrast T2-weighted sagittal lumbar spine MRI section of the case. B; Preoperative unenhanced T2-weighted axial lumbar vertebra MRI section, showing a mass lesion at the level of L-3 vertebra. C: No pathological finding was observed in the preoperative lumbar anteroposterior direct radiograph of the case.

Figure 3. Preoperative images. A; Image taken after the dissection of the tumour tissue from the surrounding muscle tissues. B; Image the operation site after excision of the paraspinal soft tissue mass. C; Macroscopic image of the excised tumoural mass.

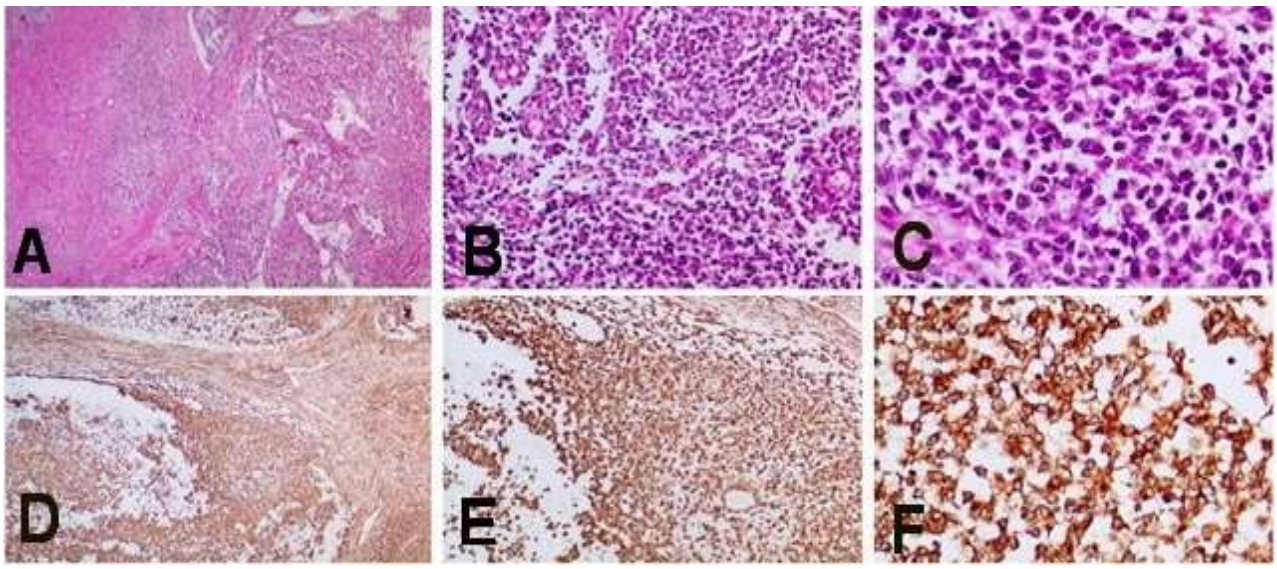

Figure 4. The images of the histopathological examination of the excised tissue, A; Tumour infiltration within muscle fiber (H&E staining, x100 magnification). B; Tumour cells with round uniform nuclei and clear cytoplasm (H&E staining, x200 magnification). C; Images of tumour cells showing slight pleomorphism at close magnification (H&E staining, x400 magnification). D; Image of vimentin positivity in the surrounding muscle and tumour tissue in the immunohistochemical examination. E; Close-up image of vimentin antibody. F; Image of CD99 positive tumour cells.

who did not receive any oncological treatment during his follow-ups in the oncology clinic showed no significant pathology. Thorax computed tomography (CT) also revealed no pathological involvement. After the MRI examination of the lumbar spine performed approximately three months following the first surgery, the patient was referred to the neurosurgery clinic. The physical examination showed an expansile palpable mass in the left paravertebral lumbar region, on the incision line of the previous operation (Figure 5).

Neurological examination of the patient was normal. Contrast-enhanced lumbar spine MRI revealed a tumoral mass with a size of 135x75x73 mm located in the subcutaneous fat and muscle tissues in the lumbar left paravertebral area. Significant contrast involvement was observed in the area surrounding the mass (Figure 6).

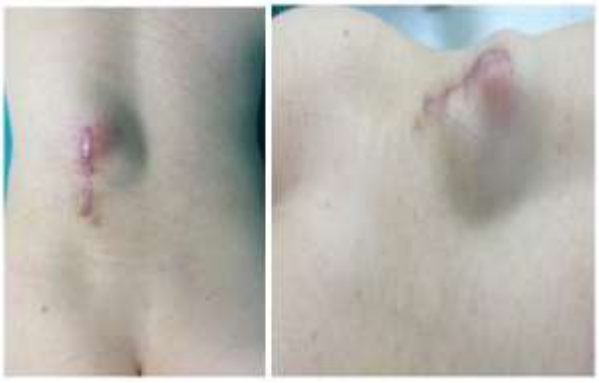

Figure 5. Macroscopic image of a palpable mass localized on the old incision line in the left paravertebral lumbar region, which was detected by inspection, approximately three months after the first operation of the case.

Therefore, the patient was operated on again. The old skin incision was used in the operation. The mass extending to the inferior was grossly excised. No problem was observed in the post-surgical follow-up, and the patient was discharged after being recommended to re-apply to the oncology clinic. In the oncology clinic, the treatment with chemotherapeutic agents was initiated and a total of 12 treatment cycles were administered. In this treatment algorithm, many pharmacological agents such as doxorubicin 85mg, vincristine 2mg, cyclophosphamide 1000/1500, etoposide

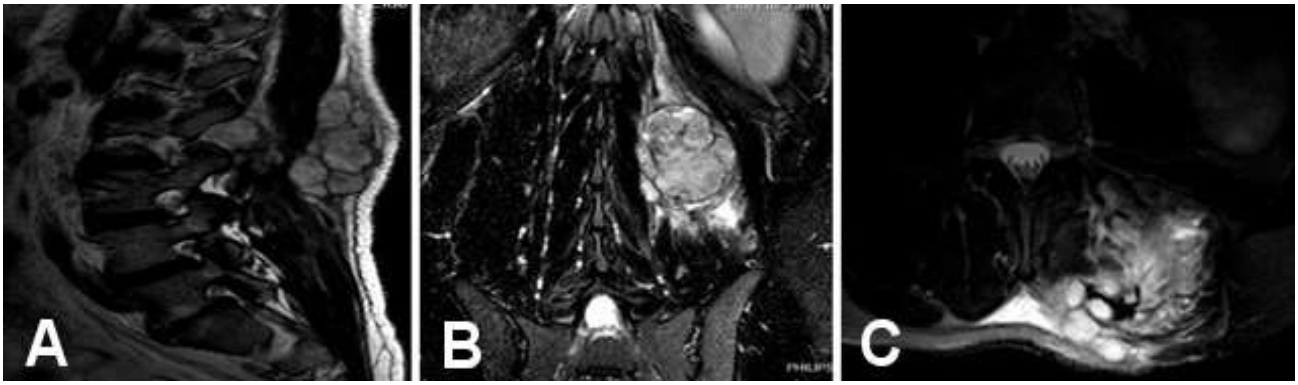

Figure 6. A; Contrast-enhanced T2-weighted sagittal lumbar vertebra MRI taken at the third month postoperatively. Recurrent mass lesion image showing multilobular heterogeneous contrast enhancement localized posterior to L2-L4 vertebral corpuscles. B; Postoperative contrast-enhanced T2 weighted coronal lumbar vertebra MRI section. The image of a recurrent mass in the left paravertebral muscle tissue. C; Postoperative contrast-enhanced T2 weighted axial lumbar vertebra MRI section showing a localized, multilobular expansile mass lesion at the previous operation site.

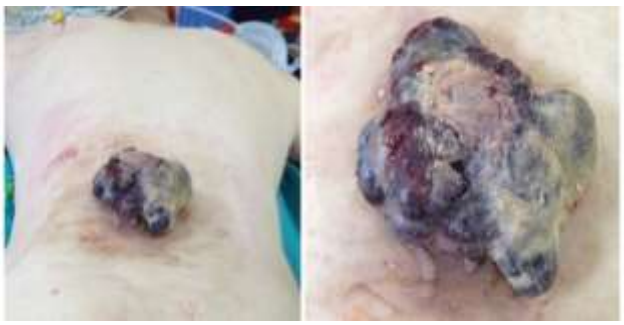

Figure 7. Intraoperative microscopic image of an exophytic, expanded, necrosed, multilobular mass located in the left paravertebral lumbar region at the surgical incision line, which was detected in the physical examination performed approximately 14 months after the second operation.

180mg, ifosfamide 3000mg, dactinomycin 2mg were administered in a variety of combinations. The abdominal and thoracic CT of the patient revealed multiple paraaortic and mediastinal adenopathies at the follow-up period. After 12 cycles of chemotherapy, the contrasted MRI of the lumbar spine was performed and the patient was referred again to the neurosurgery clinic. The physical examination of the patient showed a necrotic lobulated mass lesion with a diameter of 8x8 cm, which had extended outwards from the line of the previous surgical incision, in the left paravertebral lumbar region (Figure 7).

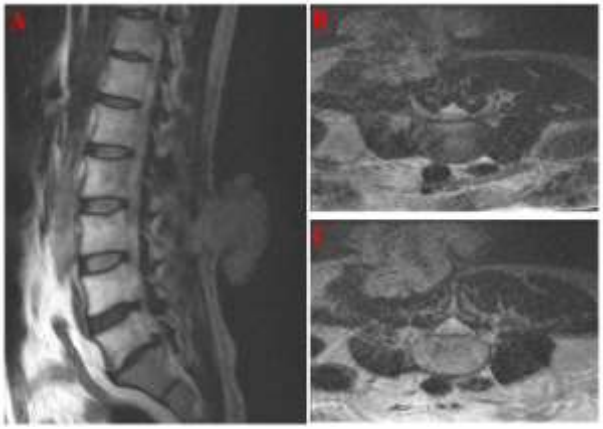

Figure 8. A; Uncontrasted T2 weighted sagittal lumbar vertebra MRI section is taken at the fourteenth month after the second surgery. A multilobular, hyperintense recurrent mass lesion localized in the posterior of the L2-L4 vertebral corpuscles, expanded outward from the skin tissue. B and C; Unenhanced T2-weighted axial lumbar vertebra MRI section of the same case showing a multilobulated, hyperintense recurrent mass lesion localized to the left lumbar paravertebral region in the previous operation area, expanding outward from the skin tissue.

Contrast-enhanced MRI of the patient with a normal neurological examination revealed a recurrent, heterogeneous, and peripherally enhanced mass lesion with a diameter of 15x11x20 mm extending outward from the skin at level L-3 (Figure 8).

Approximately 14 months after the second surgery, the patient was operated on again, and the expansile mass was grossly excised together with the invasive skin tissue. Then, the skin defects were repaired by plastic and reconstructive surgeons. Contrast-enhanced MRI did not reveal any residual mass, except for changes secondary to the operation (Figure 9).

The patient was then administered 15 more mono- and poly-therapies with different combinations and different posologies, including temozolomide 100 mg, irinotecan 40 mg, gemcitabine 1200 mg, and docetaxel 60 mg. The patient died approximately 24 months after the first operation due to multiple systemic metastases and respiratory failure.

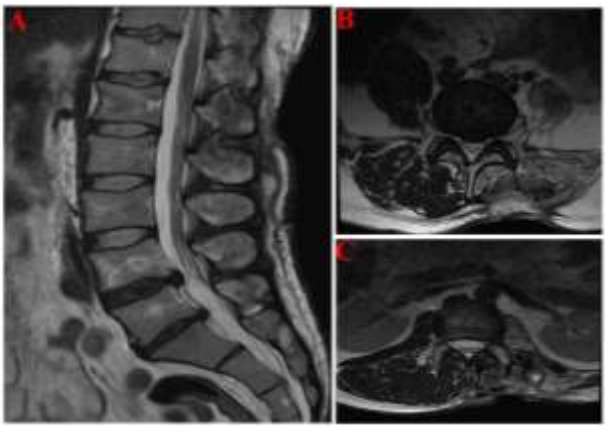

Figure 9. A; Uncontrasted T2-weighted sagittal lumbar vertebra MRI section taken after the third surgery, changes related to the previous surgery are observed in the posterior part of the L2-L4 vertebral corpuscles. No recurrence or residual mass was detected. B and C; postoperative uncontrasted T2-weighted MRI sections of the axial lumbar vertebra. Except for postoperative changes, no recurrence or residual tumour tissue is observed.

A comprehensive and systematic literature search of electronic databases, including the National Library of Medicine at the National Institutes of Health, and PubMed was performed. The full texts of the appropriate 323 studies conducted between the years 1786 to 2021 were retrieved and examined (Table 1).

Discussion

EWS constituted 7.5 percent of bone sarcomas and EWS was known to affect more than one vertebra, and the spine was a frequent site of involvement for these tumours in the years when roentgenography was used However, no comprehensive information about the incidence of such involvement was present in the literature [27].

Given the localization of the tumor, there is no difference in the overall survival of patients diagnosed with skeletal or non-skeletal EWS,

Table 1. Data obtained from studies that were used for systematic evaluation.

Keywords	Case Report	Randomized Controlled Trial	Systematic Review	Meta-Analysis	Total (amount)	Range of Date
Lumbar	21,821	5,576	1,411	983	132,652	1786- 2021 Feb
Lumbar Pain	9,656	4,516	1,847	831	62,175	1925 Aug-202 Mar
Lumbar Radiculopathy	993	172	66	29	3,794	1949 Jun-2021 Jan
Ewing's Sarcoma (EWS)	2,650	67	46	30	10,360	1898 Feb-2021 Jan
Lumbar EWS	72	0	1	0	119	1953 Aug-2020 Oct
Lumbar paravertebral EWS	4	0	0	0	5	1995 Sep-2016 Jul
Lumbar paraspinal EWS	3	0	0	0	5	1999 Nov-2017 Mar
Surgery	808,084	131,252	45,068	33,270	4,891,341	1786-2021 Mar
Surgery+EWS	1,241	34	27	10	3,730	1939 Mar-2020 Oct
Cabozantinib	59	34	27	27	963	2006-2021 Jan
Cabozantinib+EWS	1	0	0	0	6	2013 Jul-2020 Jul
Checkpoint kinase 1 inhibitors	1	3	0	1	1,129	1993 May-2020 Oct
Checkpoint kinase 1 inhibitors+EWS	0	0	0	0	4	2017 Jun-2020 Jan
Ciclopirox	56	51	13	8	619	1976 Jul-2020 Oct
Ciclopirox+EWS	0	0	0	0	2	2016 Sep-2018 Mar
Cyclin-dependent kinase pathway	32	8	6	11	13,551	1989 Jun-2021 Jun
Cyclin-dependent kinase pathway+EWS	0	0	0	0	17	1995 Feb-2020 Jan
Cyclophosphamide	14,863	4,534	362	341	74,857	1946 May-2021 Feb
Cyclophosphamide+EWS	140	37	2	3	622	1962 Oct-2020 Oct
Dactinomycin	4	160	16	11	19,241	1946 May-2020 Nov
Dactinomycin+EWS	29	26	0	1	233	1967 Feb-2020 May
Docetaxel (DTX/DXL)	1,650	1,335	207	211	17,073	1993 Sep-2021 Feb
Docetaxel (DTX/DXL) + EWS	3	0	0	0	22	1995 Aug-2020 Jul
Doxorubicin	7,597	3,792	173	237	74,642	1946 Mar-2021 Feb
Doxorubicin + EWS	118	33	1	2	573	1972 Oct-2020 Oct
Etoposide	4,344	1,385	64	79	25,848	1946 Aug-2021 Jan
Etoposide+EWS	76	19	0	1	327	1979 Nov-2020 Oct
Gemcitabine	1,913	1,009	172	191	17,590	1988 Jul-2021 Jan
Gemcitabine+ EWS	3	0	0	0	27	2004 May-2020 Jul
Ifosfamide	1,494	436	33	37	7,284	1953 Dec- 2021 Jan
Ifosfamide+EWS	93	24	1	3	369	1981-2020 Oct
Irinotecan	1,073	594	110	153	11,274	1987 Mar-2021 Mar
Irinotecan+EWS	5	0	1	0	63	2000 Jul-2020 Dec
Ribonucleotid reductase inhibitors	22	22	2	3	1,750	1968 Sep-2020 Dec
Ribonucleotid reductase inhibitors+EWS	0	0	0	0	5	2016 Sep-2020 Nov
Cytostatic drugs	336	106	13	14	8,996	1949 Sep-2021 Jan
Cytostatic drugs+EWS	1	0	0	0	23	1976 Sep-2018 Mar
Temozolomide	790	190	80	57	8,134	1985 Nov-2021 Jan
Temozolomide+EWS	3	0	0	0	39	2004 Feb-2020 Dec
Tyrosine kinase	9,511	2,477	733	1,085	258,998	1959 Sep-2021 Jun
Tyrosine kinase+EWS	12	0	1	0	283	1986 Nov-2020 Dec
Vincristine	7,482	2,075	86	104	31,929	1946 Mar-2021 Jan
Vincristine+EWS	117	32	1	1	520	1964 Apr-2020 Oct

and the outcome does not change when patients in both groups are grouped according to the presence of systemic metastases [28]. It is also reported that oncological outcomes of EWS are related to tumor characteristics and patient age and are not determined by whether they occur in bone or soft tissue [28].

Metastatic EWS is frequently seen in the spine. Primary sacrum and spine involvement are less common, especially in adult patients. Because of the low incidence of these tumors, there are no clinical guidelines outlining their management and numerous therapeutic strategies are employed. The current treatment algorithm of EWS or spinal sarcoma includes a combination of three main modalities. These are aggressive surgery, radiotherapy, and combined chemotherapy. En bloc spondylectomy or extralesional resection is a preferable procedure that can provide a better oncological outcome with longer survival and better preservation of spine biomechanics in adult patients with non-metastatic, primary lumbar spine EWS [29].

Imaging methods are critical in the diagnosis, staging, and follow-up of EWS [30]. Thoracic CT scan for lung, MRI for the spine, bone scintigraphy, or PET scan for evaluation of osseous metastases is recommended. Although lytic lesions are frequently seen in the bone tissue, different radiological findings can be observed from osteolytic lesions to sclerotic changes. Lamellar periosteal new bone formation, permeative/moth-eaten destruction can be seen radiologically; however, there is less frequent reactive bone formation [30].

Onion-skin periosteal reaction or Codman's triangle is not specific to EWS. This is more indicative of tumour aggressiveness. On X-ray, cortical destruction of the affected bone tissue can be seen as a result of the extrinsic compression of the large soft tissue mass and the destruction of the periosteal surface of the osseous tissue. In many patients, tumoral cell infiltration is detected in the soft tissues adjacent to the tumor tissue at the time of diagnosis. However, calcification, which is common in osteosarcoma, may not be seen in these tumors. Therefore, differential diagnosis with radiography can be very difficult [31].

MRI is the most sensitive imaging modality for evaluating EWS. Intra- and extraosseous extension and the relationship with adjacent anatomical structures can be configured through MRI. It is also a useful imaging technique to assess the response of tumor tissue to treatment after chemotherapy. The appearance of EWS is usually heterogeneous, being hypointense on T1-weighted sequences and often hyperintense or heterogeneous on T2-weighted sequences.

The use of any pharmaceutical preparation containing gadolinium improves imaging performance [30]. Skipped metastases within the same bone tissue may be present in 10% to 20% of patients. To assess this, it is important to include all bones involved seen in MRI [30]. A bone marrow biopsy is performed to examine possible micrometastases and the data obtained is evaluated through molecular research.

Most of the discussion in the literature regarding the staging of EWS takes place within the context of the role and accuracy of PET scans [32]. The increase in PET uptake used in diagnosis is expected to decrease due to tumor necrosis after treatment. For this reason, increased PET involvement is interpreted to be associated with poor prognosis.[32] PET scans are preferred more than bone scintigraphy for accurate diagnosis [33]. Bone scans are even reported to be more sensitive [34]. In the present study, up-to-date imaging techniques were used per the literature, and the outcomes were consistent with paraspinal lumbar EWS.

There is no EWS -specific staging system. The musculoskeletal tumour surgical staging system, which was defined in 1980, can be used for EWS, [35] or the system created by the American Cancer Committee can be also used. The staging systems are used to evaluate the size of the tumor, its grade, and the presence of metastases. In both systems, low-grade tumors are defined as stage I and high-grade tumors as at least stage II. EWS is a high-grade tumor in nature, and it is described as stage II.

The medical record of the patient examined in the present study revealed no information about whether any staging system was used or the evaluation of the tumour typical signs visible on X-ray can usually reinforce the suspicion of a malignant bone tumour. Additional findings of the tumour can be obtained using various imaging methods such as MRI and/or CT. However, for the definitive diagnosis of the disease, a tissue sample must be extracted from the tumoural lesion by performing a biopsy or surgical resection and specialists must examine the said lesion.

Round cell lesions are undifferentiated round cell tumours that grow without matrix production. Histologically, neuroectodermal differentiation is dominant. Immunohistochemical studies are useful to configure the diagnosis with CD99, CAV-1, nerve, and neuroendocrine markers. It has been reported that EWS originates from mesenchymal stem cells, is affected by neuroectodermal gene fusions such as EWSR1/ETS, may resemble pus, and the definitive diagnosis can be made by tissue biopsy [36]. The nuclear cytoplasm ratio is high. The stroma may be limited, fibrotic, or lace-like with sclerosis. Geographic necrosis is common, and apoptosis or mitosis develops depending on the situation. The cytoplasm typically has few or many organelles and abundant glycogen [37].

Tumor cells show abundant PAS-positive glycogen, but sometimes there may be variability. Immunohistochemically, MIC2 is specific for the diagnosis of EWS. Most EWS cells show strong staining for CD99, a cell surface glycoprotein encoded by the MIC2 gene [38]. However, CD99 dye is very sensitive for EWS, but not specific [38]. Therefore, cytogenetic, and molecular findings are used to confirm the diagnosis. Genetic studies have shown common translocations of the EWS gene on chromosome 22. The most common is FLI1 on chromosome 11 [39]. Among other translocations and cytogenetic abnormalities, much rarer translocations such as EWS-ETV1, EWS-FEV, and EWS-EIAF have been reported [40].

Today, these translocations are determined using fluorescent in situ hybridization (FISH) and reverse transcriptase real-time polymerase chain reaction (RT-qPCR). Both of these methods are used to detect the presence of micro metastases in bone marrow biopsies obtained for staging purposes [41]. Although the FISH method is more sensitive and specific than RT-qPCR, these two techniques are complementary to each other [42].

In the present study, the patient was not tested for gene translocations and cytogenetic abnormalities. Vimentin antibodies together with Haematoxylin & Eosin (H&E) staining were used for immunohistochemically analysis in the tissue specimens obtained from the patient. In addition, CD99 dye, which is very sensitive but non-specific for EWS, was also used.

A variety of treatment modalities including multi-agent systemic chemotherapy, surgical excision, and/or radiotherapy are used in the treatment of EWS. Vincristine, doxorubicin and cyclophosphamide, ifosfamide, and etoposide

(vdc/ie) are the most commonly used chemotherapy regimens. Targeted therapeutics and IGF-1r inhibitors have presented good clinical responses. Chemotherapy has been first used in the treatment of EWS in the early 1960s and cyclophosphamide has been used as a chemotherapeutic agent [43].

Currently, the standard treatment for EWS bone sarcoma is surgery and/or radiotherapy after neoadjuvant chemotherapy, depending on tumor characteristics such as size, proximity to critical structures, and resectability. This modality is followed by adjuvant chemotherapy. European treatment protocol for the multiagent chemotherapeutic treatment of EWS consists of vincristine, doxorubicin, and etoposide [44]. In the United States, vincristine, doxorubicin, cyclophosphamide, ifosfamide, and etoposide are generally used as treatment protocols [45]. Subsequent studies have examined the benefit of using additional drugs, including ifosfamide and etoposide, and reported that the drug used has improved the average survival. Dactinomycin is not used in the United States but is used in *Euro Ewing* studies. Currently, protocols combining VAC + Adr with IFX + VP-16 are used for chemotherapy treatment of non-metastatic EWS.

In the present study, the patient was treated with many different pharmacological agents such as dactinomycin, docetaxel, doxorubicin, etoposide, gemcitabine, ifosfamide/cyclophosphamide, irinotecan, vincristine, and temozolomide. Paraspinal/paravertebral lumbar surgeries were performed for recurrent EWS to obtain better oncological results. However, since the tumoral tissue did not metastasize to the bone tissue, total tissue resection was performed instead of en bloc spondylectomy or extralesional resection. EWS is a rare condition that presents with local pain, neurologic deficit, and a palpable mass. Current treatment of primary spine-derived EWS includes maximum surgical resection, radiotherapy, and combination chemotherapy. Some studies have reported that decompressive surgery may be performed with an appropriate approach in the presence of acute neural tissue compression [46]. Initial chemotherapy can be administered without surgical resection in the neurologically stable patient since EWS is sensitive to chemotherapy and the treatment is planned considering the patient's medical response [47].

EWS is aggressive cancer characterized by chromosomal translocations that form fusions of ETS transcription factors and EWSR1-gene [47]. EWSR1-FLI1 induces gene expression by binding to enhancer-like GGAA microsatellites whose activity correlates with the number of consecutive GGAA repeats [47]. In a study by Dallamer et al. [48] the role of the secretory neuropeptide CALCB (calcitonin-related polypeptide β) in EWS, which signals via the CGRP (calcitonin gene-related peptide) receptor complex, containing RAMP1 (receptor activity modifying protein 1) as a vital part for receptor specificity was investigated. The authors suggested that CALCB is a direct target of EWSR1-FLI1 and that targeting the CALCB/RAMP1 axis may offer a new therapeutic strategy for inhibition of EWS growth. The approach to silencing certain repetitive elements using epigenome editing has been reported to affect EWS tumor growth. Further research may provide insight into the applicability of these findings and approaches to additional types of cancer [48].

Using high-dose chemotherapy along with hematopoietic stem cell transplantation may be effective for patients at high risk of relapse [49]. Given that EWS has common genetic translocations and abnormalities, it is an

appropriate disease for molecular therapies [50]. In the present study, no biopharmaceutical was used in the treatment of the patient.

In a study seeking new treatment methods [51], the use of TRAIL (TNF-dependent apoptosis-inducing ligand), which binds with DR4 and DR5 cellular death receptors, is recommended as an anti-tumoural agent. Zhou et al. [52] suggested that overexpression of the HER2/neu oncogene may be associated with drug resistance in many human tumours. It is also reported in the literature that overexpression of the HER2/neu gene in three different human EWS commercial cell lines can be reduced by transduction with the gene E1A using an adenoviral vector [52].

Some studies have reported tumour-specific mutations in the cancer genome and the potential of pharmacological treatment methods. However, many oncoproteins are not detected by conventional molecular screening methods [24]. Even if tumour-specific somatic mutations are revealed, most cancer treatments are performed with non-specific cytotoxic drugs. The EWS treatment is one of those methods. Although the EWS/FLI oncoprotein has been identified in many EWS for 10 years, it has not been among the treatment targets. Therefore, interest in gene-based approaches in sarcoma treatments has begun to increase [24].

The application of local therapy is followed by chemotherapy which is called consolidated chemotherapy. The intensity of this therapy depends on the tumour's response to preoperative chemotherapy, its size, and its spread at the time of diagnosis. Patients with small tumours who respond to therapy or whose tumour volume is less than 200 ml are given several cytostatic, like the initial course of chemotherapy. Today, especially vincristine, actinomycin-D, and cyclophosphamide or combinations of vincristine, actinomycin-D, and ifosfamide are applied.

High-dose chemotherapy including autologous stem cell transplantation or standard chemotherapy is applied to patients with large tumors who respond poorly to induction chemotherapy or whose tumour volume is 200 ml and larger. The appropriate treatment method is applied for both patients with and without metastases. In some cases, radiotherapy can be applied to the patient after normal-dose chemotherapy or high-dose chemotherapy.

In a study where five primary spinal column sarcoma cases were presented [53], sarcomas originating from paravertebral soft tissues were excluded. EWS was diagnosed in two of the five cases, and tumor localization was reported to originate from the L5-S1 and L4-5 pedicles, respectively [53]. All cases presented with complaints of pain and progressive weakness in the extremities. The time from onset of symptoms to diagnosis ranged from one to five months. The patients were treated with subtotal tumour resection, chemotherapy, radiotherapy, and spinal canal decompression [53]. Posterior spinal fusion surgery was performed in two cases. Three patients were reported to have survived 10 to 98 months after diagnosis, while only the case with EWS of the L5-S1 pedicles was in complete remission and discontinued treatment at 98 months postoperatively.[53] Researchers underlined that the surgical decompression and stabilization procedures are preferred, especially in neurological symptomatic patients, even in the presence of high-grade diffuse tumours. They emphasized that they do not intend to cure the disease with spinal canal decompression and stabilization, but they aim to provide neurological recovery, spine stabilization, improved quality of life, early mobilization, and cytoreduction of the

patient with surgical tumor ablation, which can make chemotherapy more effective [53].

The data obtained from different studies in the literature should be converted to the same effect size, and the same effect size of the research results to be included in the analysis should be calculated. In addition, it should be tested whether the effect sizes are homogeneously distributed. If the effect sizes show homogeneous distribution, the fixed-effect model should be used, and if it does not show a homogeneous distribution, the random-effects model should be used. In the present study, no randomized controlled clinical study that met the inclusion criteria was found. Therefore, effect size or homogeneity tests were not performed statistically. This seems to be a limitation of the research. However, no studies have yet examined the effects of repetitive surgical interventions and medical treatment modalities on the medical management of patients with EWS.

Conclusion

Surgical interventions performed in both paraspinal tumours and malignant tumours of the spine reduce the tumour cell load and increase the effectiveness of chemotherapeutic treatment administered after surgery. Adjuvant local treatments or systemic chemotherapy can be applied to eliminate known and occult metastases to increase the potential success of treatment. There is a significant need in cancer therapeutics that may improve outcomes and reduce toxicities compared to conventional, cytotoxic chemotherapy. Therefore, every patient with a spinal tumour, not just lumbar paraspinal EWS, should be treated with a multidisciplinary approach. The approach should not consist of radiological diagnosis and a surgical procedure. The multidisciplinary working group should include spinal surgeons, radiologists, pathologists, medical oncologists, radiation oncologists, and pharmacologists.

Abbreviations: *Cav-1: Caveolin-1; CDK: Cyclin-dependent kinase; DTX: Docetaxel; EWS: Ewing's sarcoma;*
IFX: Ifosfamide; MIC2 (CD99): Cluster of differentiation 99; RET: The receptor tyrosine kinase rearranged during transfection; siRNA: Small interfering RNA; VP-16: Etoposide.

Funding: *The author(s) received no financial support for the research, authorship, and/or publication of this article.*

Conflict of Interest: *The authors declare that they have no conflict of interest.*

Ethical Statement: *Written consent of the hospital management and the patient was obtained for the use of patient data (Date and number: 2022.03.15/3). In addition, ethics committee approval was not required as this study was a review article.*

Open Access Statement

References

[1]Mavrogenis AF, Vottis CT, Megaloikonomos PD, et al. Neovascularization in Ewing's sarcoma. Neoplasma. 2018; 65(3): 317-25.

[2]Italiano A, Mir O, Mathoulin-Pelissier S, et al. Cabozantinib in patients with advanced Ewing sarcoma or osteosarcoma (CABONE): a multicentre, single-arm, phase 2 trial. Lancet Oncol. 2020; 21(3): 446-55.

[3]Meshram GG, Kaur N and Hura KS. Ewing's sarcoma with distant metastasis: A brief note on management and emerging therapies. Clin Pract. 2019; 9(3): 1111.

[4]Morrison BA. Soft tissue sarcomas of the extremities. Proc (Bayl Univ Med Cent) 2003; 16(3): 285-90.

[5]Narayana Kurup JK, Kamble VC, Acharya AM, et al. Massive Embryonal Rhabdomyosarcoma of the Hand in an Infant With Metastasis at Birth: Management Dilemma. Hand (N Y). 2017; 12(5): 109-12.

[6]Hatina J, Kripnerova M, Houfkova K, et al. Sarcoma Stem Cell Heterogeneity. Adv Exp Med Biol. 2019; 1123: 95-18.

[7]Tsokos M, Alaggio RD, Dehner LP, et al. Ewing sarcoma/peripheral primitive neuroectodermal tumor and related tumors. Pediatr Dev Pathol. 2012; 15(1): 108-26.

[8]Biermann JS, Chow W, Reed DR, et al. NCCN Guidelines Insights: Bone Cancer, Version 2.2017. J Natl Compr Canc Netw. 2017; 15(2): 155-67.

[9]Lu VM, Goyal A, Alvi MA, et al. Primary intradural Ewing's sarcoma of the spine: a systematic review of the literature. Clin Neurol Neurosurg. 2019; 177: 12-19.

[10]Reed DR, Hayashi M, Wagner L, et al. Treatment pathway of bone sarcoma in children, adolescents, and young adults. Cancer. 2017; 123(12): 2206-18.

[11]Anne S, Malempati AR and Palanki G. Primary Ewing's sarcoma of the lung: a rare case report. Indian J Thorac Cardiovasc Surg. 2020; 36(4): 409-11.

[12]Kharod SM, Spiguel AR, Lagmay JP, et al. Radiation Treatment for Ewing Sarcoma Family of Tumors in Adult Patients: A Single Institution's Experience Over 40 Years. Am J Clin Oncol. 2019; 42(5): 421-25.

[13]Van Mater D and Wagner L. Management of recurrent Ewing sarcoma: challenges and approaches. Onco Targets Ther. 2019; 12: 2279-88.

[14]Goss KL, Koppenhafer SL, Harmoney KM, et al. Inhibition of CHK1 sensitizes Ewing sarcoma cells to the ribonucleotide reductase inhibitor gemcitabine. Oncotarget. 2017; 8(50): 87016-87032.

[15]Goss KL and Gordon DJ. Gene expression signature based screening identifies ribonucleotide reductase as a candidate therapeutic target in Ewing sarcoma. Oncotarget. 2016; 7(39): 63003-63019.

[16]Yuan B, Ji W, Xia H, et al. Combined analysis of gene expression and genome binding profiles identified potential therapeutic targets of ciclopirox in Ewing sarcoma. Mol Med Rep. 2018; 17(3): 4291-98.

[17]Guenther LM, Dharia NV, Ross L, et al. A Combination CDK4/6 and IGF1R Inhibitor Strategy for Ewing Sarcoma. Clin Cancer Res. 2019; 25(4): 1343-57.

[18]Jain S and Kapoor G. Chemotherapy in Ewing's sarcoma. Indian J Orthop. 2010; 44(4): 369-77.

[19]Ferrari S, Palmerini E, Alberghini M, et al. Vincristine, doxorubicin, cyclophosfamide, actinomycin D, ifosfamide, and etoposide in adult and pediatric patients with nonmetastatic Ewing sarcoma. Final results of a monoinstitutional study. Tumori. 2010; 96(2): 213-18.

[20]Wagner MJ, Gopalakrishnan V, Ravi V, et al. Vincristine, Ifosfamide, and Doxorubicin

for Initial Treatment of Ewing Sarcoma in Adults. Oncologist. 2017; 22(10): 1271-77.

[21] Whelan J, Le Deley MC, Dirksen U, et al. High-Dose Chemotherapy and Blood Autologous Stem-Cell Rescue Compared With Standard Chemotherapy in Localized High-Risk Ewing Sarcoma: Results of Euro-E.W.I.N.G.99 and Ewing-2008. J Clin Oncol. 2018; 36(31): JCO2018782516.

[22] den Hollander D, Van der Graaf WTA, Fiore M, et al. Unravelling the heterogeneity of soft tissue and bone sarcoma patients' health-related quality of life: a systematic literature review with focus on tumour location. ESMO Open. 2020; 5(5): e000914.

[23] Radiation Therapy for Ewing Tumors. https://www.cancer.org/cancer/ewing-tumor/treating/radiation-therapy.html (Accessed April 24, 2022).

[24] Ali Gumustas S, Isyar M, Topuk S, et al. Systematic Evaluation of Drug-Loaded Hydrogels for Application in Osteosarcoma Treatment. Curr Pharm Biotechnol. 2016; 17(10): 866-72.

[25] Topuk S, Akyuva Y, Karaaslan N, et al. Is it Possible to Treat Osteosarcoma Using Oligonucleotides Confined into Controlled Release Drug Delivery Systems? Curr Pharm Biotechnol. 2017; 18(6): 516-22.

[26] Karaarslan N, Yilmaz I, Ozbek H, et al. Systematic Evaluation of Promising Clinical Trials-Gene Silencing for the Treatment of Glioblastoma. Turk Neurosurg. 2019; 29(3): 328-34.

[27] Imler AE, Meilstrup DB and Bogart FB. Primary Ewing's sarcoma of the spine. Radiology. 1946; 46: 597-600.

[28] Pradhan A, Grimer RJ, Spooner D, et al. Oncological outcomes of patients with Ewing's sarcoma: is there a difference between skeletal and extra-skeletal Ewing's sarcoma? J Bone Joint Surg Br. 2011; 93(4): 531-536.

[29] Iacoangeli M, Dobran M, Di Rienzo A, et al. Nonmetastatic Ewing's Sarcoma of the Lumbar Spine in an Adult Patient. Case Rep Oncol Med. 2012; 2012: 165289.

[30] Peersman B, Vanhoenacker FM, Heyman S, et al. Ewing's sarcoma: imaging features. JBR-BTR. 2007; 90(5): 368-76.

[31] Kuleta-Bosak E, Kluczewska E, Machnik-Broncel J, et al. Suitability of imaging methods (X-ray, CT, MRI) in the diagnostics of Ewing's sarcoma in children - analysis of own material. Pol J Radiol. 2010; 75(1): 18-28.

[32] Sharma P, Khangembam BC, Suman KC, et al. Diagnostic accuracy of 18F-FDG PET/CT for detecting recurrence in patients with primary skeletal Ewing sarcoma. Eur J Nucl Med Mol Imaging. 2013; 40(7): 1036-43.

[33] Newman EN, Jones RL and Hawkins DS. An evaluation of [F-18]-fluorodeoxy-D-glucose positron emission tomography, bone scan, and bone marrow aspiration/biopsy as staging investigations in Ewing sarcoma. Pediatr Blood Cancer. 2013; 60(7): 1113-17.

[34] Hugenholtz EA, Piers DA, Kamps WA, et al. Bone scintigraphy in nonsurgically treated Ewing's sarcoma at diagnosis and follow-up: prognostic information of the primary tumor site. Med Pediatr Oncol. 1994; 22(4): 236-39.

[35] Enneking WF, Spanier SS and Goodman MA. A system for the surgical staging of musculoskeletal sarcoma. Clin Orthop Relat Res. 1980; (153): 106-120.

[36] Biermann JS, Adkins DR, Agulnik M, et al. Bone cancer. J Natl Compr Canc Netw. 2013; 11(6): 688-723.

[37] Suh CH, Ordonez NG, Hicks J, et al. Ultrastructure of the Ewing's sarcoma family

of tumors. Ultrastruct Pathol. 2002; 26(2): 67-76.

[38] Folpe AL, Goldblum JR, Rubin BP, et al. Morphologic and immunophenotypic diversity in Ewing family tumors: a study of 66 genetically confirmed cases. Am J Surg Pathol. 2005; 29(8): 1025-33.

[39] Delattre O, Zucman J, Plougastel B, et al. Gene fusion with an ETS DNA-binding domain caused by chromosome translocation in human tumours. Nature. 1992; 359(6391): 162-65.

[40] Shulman SC, Katzenstein H, Bridge J, et al. Ewing sarcoma with 7;22 translocation: three new cases and clinicopathological characterization. Fetal Pediatr Pathol. 2012; 31(6): 341-48.

[41] Wagner LM, Smolarek TA, Sumegi J, et al. Assessment of minimal residual disease in ewing sarcoma. Sarcoma. 2012; 2012: 780129.

[42] Bridge RS, Rajaram V, Dehner LP, et al. Molecular diagnosis of Ewing sarcoma/primitive neuroectodermal tumor in routinely processed tissue: a comparison of two FISH strategies and RT-PCR in malignant round cell tumors. Mod Pathol. 2006; 19(1): 1-8.

[43] Pinkel D. Cyclophosphamide in children with cancer. Cancer 1962; 15: 42-49.

[44] Womer RB, West DC, Krailo MD, et al. Randomized controlled trial of interval compressed chemotherapy for the treatment of localized Ewing sarcoma: a report from the Children's Oncology Group. J Clin Oncol. 2012; 30(33): 4148-54.

[45] Juergens C, Weston C, Lewis I, et al. Safety assessment of intensive induction with vincristine, ifosfamide, doxorubicin, and etoposide (VIDE) in the treatment of Ewing tumors in the EURO-E.W.I.N.G. 99 clinical trial. Pediatr Blood Cancer. 2006; 47(1): 22-29.

[46] Sharafuddin MJ, Haddad FS, Hitchon PW, et al. Treatment options in primary Ewing's sarcoma of the spine: report of seven cases and review of the literature. Neurosurgery. 1992; 30(4): 610-8; discussion 618-619.

[47] Kaeding KE and Zaret KS. Microsatellite enhancers can be targeted to impair tumorigenesis. Genes Dev. 2018; 32(15-16)s: 991-92.

[48] Dallmayer M, Li J, Ohmura S, et al. Targeting the CALCB/RAMP1 axis inhibits growth of Ewing sarcoma. Cell Death Dis. 2019; 10(2): 116.

[49] Tap WD, Demetri G, Barnette P, et al. Phase II study of ganitumab, a fully human anti-type-1 insulin-like growth factor receptor antibody, in patients with metastatic Ewing family tumors or desmoplastic small round cell tumors. J Clin Oncol. 2012; 30(15): 1849-56.

[50] Lissat A, Chao MM and Kontny U. Targeted therapy in Ewing sarcoma. ISRN Oncol 2012; 2012: 609439.

[51] Mitsiades N, Poulaki V, Mitsiades C, et al. Ewing's sarcoma family tumors are sensitive to tumor necrosis factor-related apoptosis-inducing ligand and express death receptor 4 and death receptor 5. Cancer Res. 2001; 61(6): 2704-12.

[52] Zhou H, Randall RL, Brothman AR, et al. Her-2/neu expression in osteosarcoma increases risk of lung metastasis and can be associated with gene amplification. J Pediatr Hematol Oncol. 2003; 25(1): 27-32.

[53] 53. Tasdemiroglu E, Bagatur E, Ayan I, et al. Primary spinal column sarcomas. Acta Neurochir (Wien). 1996; 138(11): 1261-66.