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Radiotherapy

Radiotherapy's Indications and Limits in the Management of Bone Ewing's Sarcoma's Children: About 22 Cases and Review of the Literature

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Abstract **Original Research Article**

To study the indications and limits of radiotherapy in the treatment of bone Ewing's sarcoma's children, we conducted a retrospective study of 22 cases collected over a period of 10 years from January 2011 to December 2020. The study took into account various clinical, radiological, therapeutic and evolutionary aspects of this pathology. The average age of patients was 11 years, with gender equality. The diagnostic approach was identical, based on clinical, radiological and histological data. Therapeutic management was based on chemotherapy, with local treatment combining radiotherapy with or without surgical resection of the tumor. Ewing's sarcoma is a relatively rare malignant tumor that grows mainly in bone and often has a large extension into soft tissue. All the bones of the skeleton can be affected, with a clear predominance of the lower limb (60% of cases). Medical imaging is essential for diagnosis as well as for therapeutic evaluation. While the diagnosis of certainty is currently based on histological and molecular biology data. Therapeutic management combines a multimodal approach including chemotherapy, surgery and radiotherapy. Nowadays the prognosis has improved thanks to the development of therapeutic methods.

Keywords: Ewing's sarcoma - radiotherapy - children - bone.

INTRODUCTION

Ewing's sarcoma is a primary malignant bone tumor, preferentially affecting children and adolescents, and more rarely adults [1, 2]. It represents the undifferentiated form of primary peripheral neuroectodermal tumors (PNET). It's characterized by a chromosomal translocation t (11; 22) [1, 3]. Ewing's sarcoma is accompanied by extensive soft tissue extension, and all skeletal bones can be affected in different proportions. Medical imaging plays a key role in all stages of the management of bone Ewing's sarcoma. While the certainty of the diagnosis is based on histological examination. Its prognosis is classically poor because of the rapid appearance of metastases. The radio sensitivity of Ewing's sarcomas has long placed radiotherapy at the center of local treatment. However, its current therapeutic management is based on a multimodal approach combining chemotherapy, surgery and radiotherapy.

MATERIALS AND METHOD

This work is part of a descriptive retrospective study carried out over a 10-year period between January 2011 and December 2020. We collected 22 cases of bone Ewing's sarcoma in children under 16 and took in charge in the radiotherapy department at the CHU MOHAMED VI in Marrakech. The inclusion criteria used in our study are histologically confirmed bone Ewing sarcoma and age less than or equal to 16 years at the time of diagnosis. A pre-established exploitation sheet was then filled in from the available information, the purpose of which is to specify for each location: the epidemiological characteristics of the patients, the diagnostic aspects, the therapeutic methods, as well as the results of the treatment.

RESULT

The average age of the patients was 11 years, with extremes of 4 and 16 years and a sex ratio of 1.

For the background; 3 patients were from a 1st degree consanguineous marriage, 2 had trauma to the diseased limb, while one patient had exposure to tobacco (passive smoking).

The time from onset of symptoms to diagnosis ranged from 1 month to 1 year, with an average of 8 months. The delay was greater than or equal to 6 months in 72% of cases.

The general condition of the patients was assessed according to the performance index of the World Health Organization (WHO) [4]. 18% of cases had WHO scale at 0; 72% had WHO scale at 1 and 9% had WHO scale at 2. The clinical signs were dominated by pain, found in 94.5% of cases and swelling in 85.5% of cases; The topographical distribution is illustrated in figure 1. 3 patients had lymphadenopathy on initial clinical examination. Other clinical signs were present; 1 patient had fluid effusion syndrome on pleuropulmonary examination, and 4 had cauda equine syndrome on neurological examination.

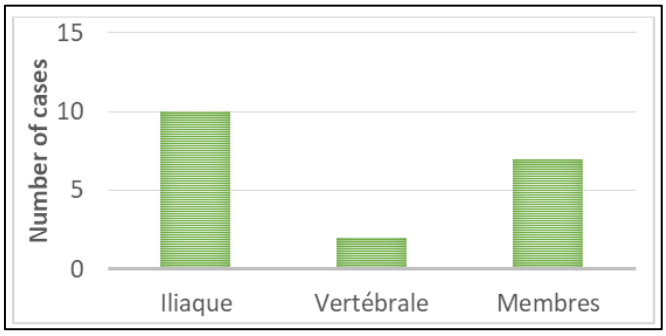

Fig 1: Topographic distribution of the 22 cases

The para clinical assessment was based essentially on radiological examinations. Standard X-ray data was available for 31.5% of patients. They were in favor of a poorly limited lacunar image associated with a periosteal reaction in the form of an onion bulb and very significant thickening of the soft tissues.

45% of cases benefited from loco regional computed tomography (CT). The results were in favor of osteolysis associated with soft tissue invasion in all patients. In addition, 30% of the examinations showed an image of osteocondensation with a rupture of the cortex in 20% of the cases.

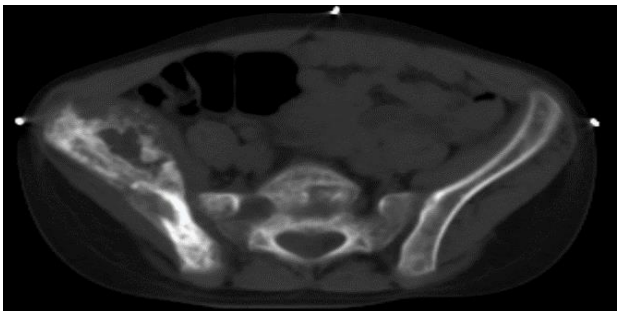

Fig 2: CT of the pelvis in axial section product in a 9-years-old boy, which illustrates osteolysis with rupture of the cortex of the right iliac wing associated with infiltration of the soft tissues

81% of cases benefited from loco regional magnetic resonance imaging (MRI). These MRIs were able to show poorly circumscribed aggressive tumors of different sizes ranging from 4 to 18cm, with an average of 11cm. 36% of cases had a tumor size greater than or equal to 10cm. None of the patients presented with invasion of the vascular axes. All the MRIs performed described a very significant infiltration of the soft tissues and 22.5% had shown skip metastases.

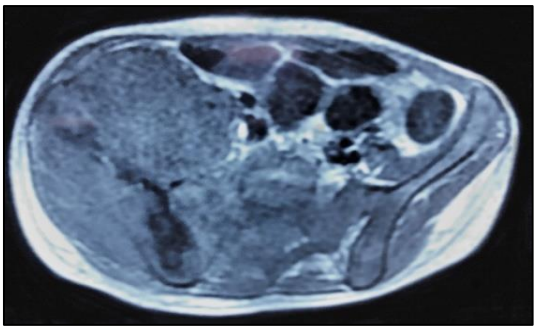

Fig 3: MRI of the pelvis in axial sections of the same patient figure 2 with injection of gadolinium and which shows the significant infiltration of the soft tissues

The definitive diagnosis is histological. All patients had a surgical biopsy. The pathological study was in favor of malignant round cell tumor proliferation in all patients, with round nuclei in 63% of cases and scanty and dense cytoplasm in 90% of cases. The mitotic index was low in 90% of cases, tumor necrosis was present in 72.7% of cases, vascular emboli were found in 9% of cases, while perineural sheaths were absent in all our patients. The immunohistochemical study objectified the CD99 transmembrane glycoprotein in all cases. None of the patients benefited from a cytogenetic or molecular biology study.

All patients had an extension assessment. Thoracic-abdominal and pelvic CT enabled the diagnosis of pulmonary metastases in 22.5% of cases, inguinal lymphadenopathy in a patient with Ewing's sarcoma of the upper end of the femur, lumbo-aortic lymphadenopathy associated with Ureterohydronephrosis (UHN) in a patient with Ewing's sarcoma of the iliac wing. Bone scintigraphy was able to show bone metastases in 45% of patients. Of which 13.5% had distant bone metastases, 18% had spinal metastases in the form of metastatic skips and 9% had both distant metastases and metastatic skips. Myelograms and BOMs didn't show any bone marrow invasion.

For the classification of our patients, we used the TNM classification of the AJCC 8th edition for bone tumors [5]. 13.5% of cases were classified as T1; 58.5% of cases were classified as T2; while 27% of patients were classified as T3. Regarding lymph node involvement, 9% of cases were classified as N1. And 22.5% of patients had pulmonary metastases classified as M1a, while 18% had distant bone metastases classified as M1b.

Therapeutic management includes systemic treatment consisting of chemotherapy, local treatment represented by surgery and radiotherapy.

All patients received primary chemotherapy according to the Saint Jude Memphis protocol which combines Cyclophosphamide and Doxorubicin.

And All patients underwent post-chemotherapy MRI evaluation; the tumor size regressed partially in 58.5% of cases and completely in 4.5% of cases. Stabilization was noted in 13.5% of patients, while 22.5% of cases showed progression.

7 patients subsequently underwent surgical treatment. A conservative treatment was performed in a patient with Ewing's sarcoma of the lower femur, a radical treatment was performed in three patients whose disarticulation was recommended in a patient with Ewing's sarcoma of the iliac wing, an amputation performed in a patient with Ewing's sarcoma of the lower extremity of the femur and a parietectomy in a patient with Ewing's sarcoma of the rib. While decompressive surgery was proposed in three patients with vertebral Ewing's sarcoma. Lymph node dissection of the inguinal region was performed in a single patient.

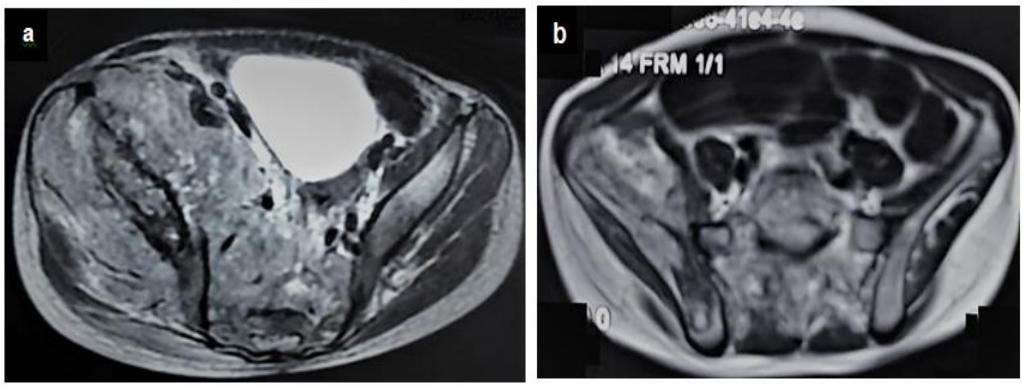

Fig 4: Ewing's sarcoma of the right iliac wing in a 10-years-old girl, before chemotherapy (a) and after neoadjuvant chemotherapy (b)

Our study focused on a series of 22 cases who all received radiotherapy. It was indicated for curative purposes in 45% of patients; Either alone for unresectable tumors in 27% of cases or postoperatively for unsound margins in 18% of cases. It was indicated for palliative or symptomatic purposes in 54% of cases, in particular for analgesic purposes in 36% of cases and for decompressive purposes in 18% of cases. 59.5% of the irradiated cases had tumors at the iliac level, 31.5% had a femoral tumor, 22.5% had a vertebral tumor while 4.5% had a humeral location. In addition, 13.5% of our series had the indication of pulmonary irradiation. All the patients obeyed a technical step. The preparation phase of which is essential in order to choose a comfortable and reproducible position for the radiotherapy sessions. The use of restraints or sedation may be necessary to reproduce the same position. Then, any patient scheduled for radiotherapy must perform a dosimetric scan which will serve as a support for virtual treatment planning. It also makes it possible to better

visualize the tumor and its extensions in the soft tissues using a fusion technique with CT or MRI images.

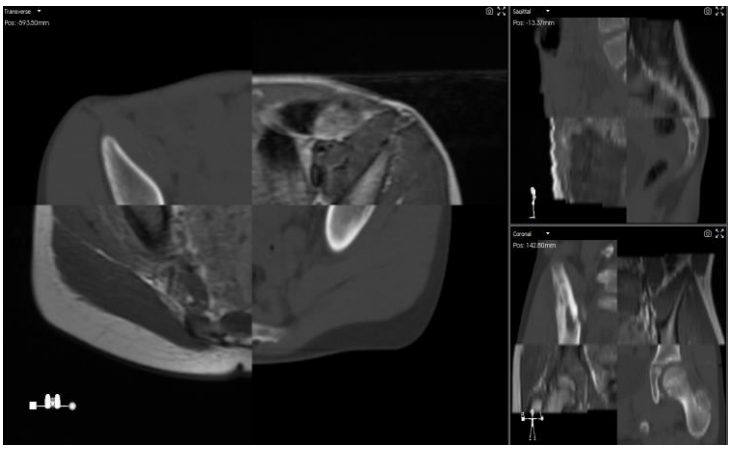

Fig 5: A fusion image in a 9-years-old child with right iliac Ewing's sarcoma

The dosimetric scanner makes it possible to define the target tumor volumes. Three types of target volumes are to be defined. Macroscopic tumor volume (GTV) visualized by clinical and imaging data. The microscopic tumor volume (CTV) corresponds to the microscopic extensions of the tumor. The predicted tumor volume (PTV) obtained by adding a margin of 10 to 15 mm around the CTV. In our series, the GTVs ranged from 40.15ml to 510.068ml with an average of 246.978ml. The CTVs ranged from 122.141ml to 1233.500ml with an average of 470.510ml. While the PTVs varied from 238.476ml to 1764.794ml with an average of 679.588ml.

The dosimetric scanner also makes it possible to define the organs at risk. They are delineated according to the irradiated area. It is all the healthy organs that surround the tumor. And this is a very important element to know in order to protect them and document the dose received by each organ.

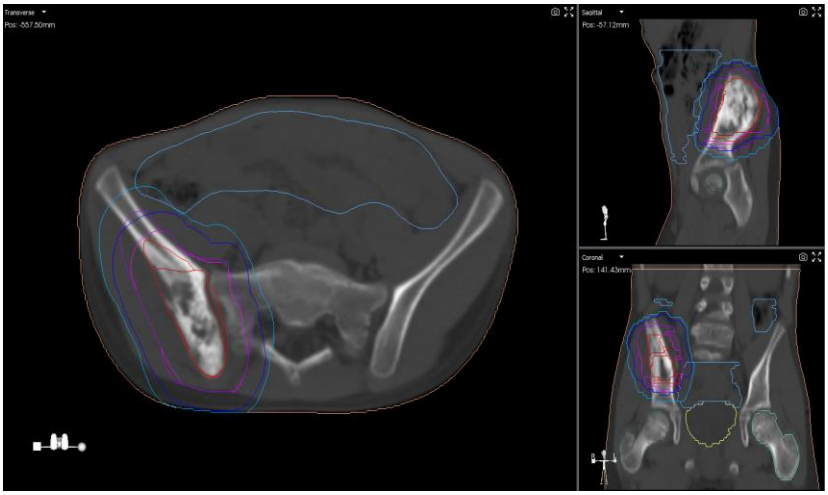

Fig 6: Contouring of a right iliac Ewing's sarcoma in a 9-years-old boy; GTV (red), CTV60 (pink), CTV45 (purple), PTV60 (blue), PTV45 (sky blue), organs at risk (bladder in yellow and intestines in sky blue)

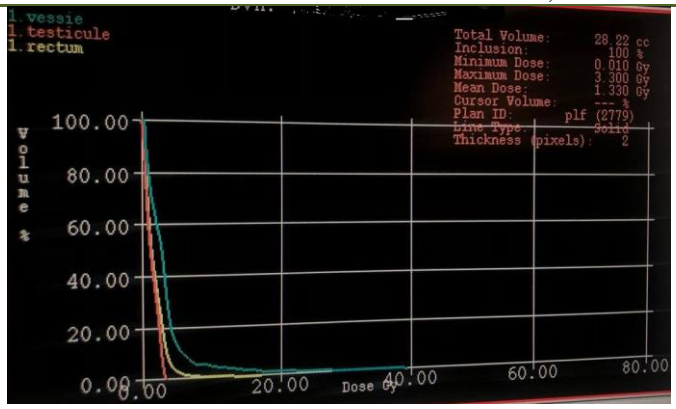

Fig 7: The dose received by the testicles of a 14-years-old boy with Ewing's sarcoma of the upper extremity of the left femur

The dose received by patients was 45Gy to 66Gy in one to two so-called curative series in 90% of patients. While 9% received a palliative dose of 30Gy. 13.5% of cases had lung metastases requiring 15Gy lung irradiation. The dose overprint or the BOOST represents the second series. In our study it is variable from 5.4Gy to 21Gy.

The dose received was divided from 1.8Gy to 2Gy per fraction in 90% of cases. While 9% received palliative irradiation at 3 Gy per fraction. Patients irradiated on pulmonary metastases received irradiation with a daily fractionation of 1.5Gy. The duration of treatment varied from 12 days to 61 days with an average duration of 38 days.

In order to correctly deliver the radiotherapy, a position control was done by portal imaging (PI) in all patients on the 1st, 2nd and 3rd day, then weekly and at each change in the treatment plan. The occurrence of acute toxicity and the proper course of the treatment were also checked during a weekly medical consultation.

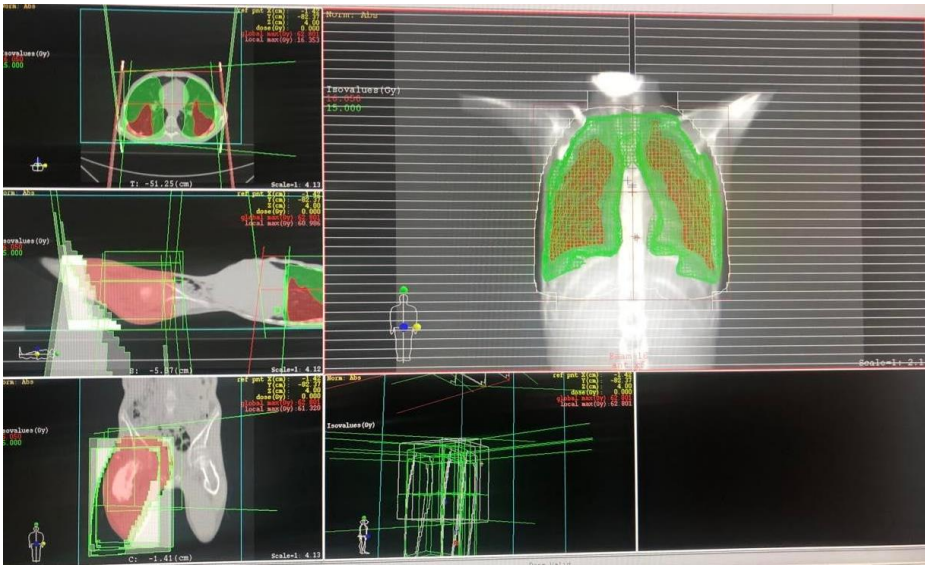

Fig 8: Dosimetry of an Ewing sarcoma of the upper extremity of the femur in an 11-years-old boy with lung metastases

All patients underwent control MRIs after radiotherapy. 23% of patients had a complete response to radiotherapy, 45% had a partial response, while 32% had stability.

In adjuvant, 40.5% of cases, having had a good response, received chemotherapy according to the Saint Jude Memphis protocol.

40.5% who had a bad response received the VIDE protocol made of Vincristine associated with Ifosfamide, Doxorubicin and Etoposide. 27% subsequently received a single cure according to the VAI protocol which consisted of Vincristine, associated with Actinomycin, Ifosfamide with mesna, and only 13.5% of cases continued with the VAC protocol which consisted of Vincristine with Actinomycin and Cyclophosphamide.

67.5% of cases received metronomic chemotherapy at the end of treatment based on Etoposide and Cyclophosphamide in combination with sodium valproate.

The evolution was marked by a complete remission in 13.5% of cases, a local recurrence in 18% of cases, within a variable period of 12 to 36 months and an average of 27 months, a progression was noted in 18% of cases 13.5% of which progressed remotely with a variable delay of 2 to 8 months and an average of 4.5 months. In addition, we deplore the death of 27% of cases with a delay of 1 month to 1 year and an average of 7 and a half months after radiotherapy. Whereas, 22.5% of cases were lost sight of.

DISCUSSION

Ewing's sarcoma is an undifferentiated malignant tumoral proliferation originating in the bone and which was first described by James Ewing in 1921 [3]. Before the age of 16, it's the second most common malignant bone tumor (30% of cases) behind osteosarcoma (60% of cases) [17]. Its incidence is estimated at 3.2 per million children under 15 years old, approximately 80 to 100 cases per year in France. In the United States, the incidence of Ewing's sarcomas hasn't changed for the past 30 years, remaining at 2.93 cases per million inhabitants [19]. Studies report frequencies of 9% in children under 5 years old, 60% are between 5 and 15 years old, 25% of cases are between 15 and 20 years old and only 6% are over 20 years old [7]. Like osteosarcoma, the majority of epidemiological studies show a slight male predominance with a sex ratio of 1.5 to 2 [8, 9]. Despite advances in molecular biology and cytogenetics, the precise cause and risk factors for Ewing's sarcoma have not been identified. The presence of a hereditary factor has been suggested given the preferential involvement of subjects of Caucasian origin (96% of cases) and the rarity of the involvement of subjects of African, Afro-American and Asian origin (1.8 %) [3].

On the clinical level, the duration of the evolution of the disease before the diagnosis and the symptomatology are variable according to the aggressiveness of the tumor, the location without forgetting the symptomatic treatments during the medical consultations, without thinking of pushing the investigations in order to have a diagnosis. Table 1 shows the different topographic aspects described by the IESS group (the intergroup Ewing's sarcoma study). Onset usually begins with localized pain and/or swelling lasting a few weeks or months. The pain may be mild at first, worsened by exercise and become permanent even at night. A swelling is often present, a source of pain sometimes associated with inflammatory signs. The notion of trauma, perhaps the initiating event that draws attention to the lesion, but also a reason for the delay in diagnosis. Certain modes of revelation may be specific to the location of the tumor, in particular spinal cord or radicular compression syndrome in spinal tumors, respiratory disorders and pleural effusion in rib tumors, or even sphincter disorders in pelvic tumors [6]. As for lymphatic invasion, it is rare and is present in only 10% of cases [10]. General signs of disease progression, such as fever, fatigue, weight loss, or anemia, are present at diagnosis in approximately 10-20% of patients and should be investigated for disseminated disease or pelvic localization [11].

Table I: The different locations of Ewing's sarcoma on the skeleton in the IESS group [12]

Primary location	Percentage %
Lower limbs	45,6
Femur	20,8
Fibula	12,2
Pelvis	20
Hipbone	12,5
Upper extremities	12,9
Humerus	10,6
Axial skeleton and ribs	12,9

The contribution of imaging is fundamental both for the diagnosis, the extension assessment, but also for the therapeutic evaluation and the detection of recurrences during follow-up. The radiological appearance of Ewing's sarcoma is variable, but usually associated with signs of osteolysis and sclerosis. The typical form (which is not the most frequent), sitting on the long bones, is that of a lytic lesion, surrounded by a fusiform periosteal reaction in thin strips parallel to the long axis of the bone, producing an image in "onion bulb". Bone lysis is poorly limited, irregular, giving a worm-eaten appearance, with cortices appearing mottled, corresponding to the so-called permeation image. The existence of a Codman spur is inconstant, encountered in less than 30% of cases [3, 13, 14].

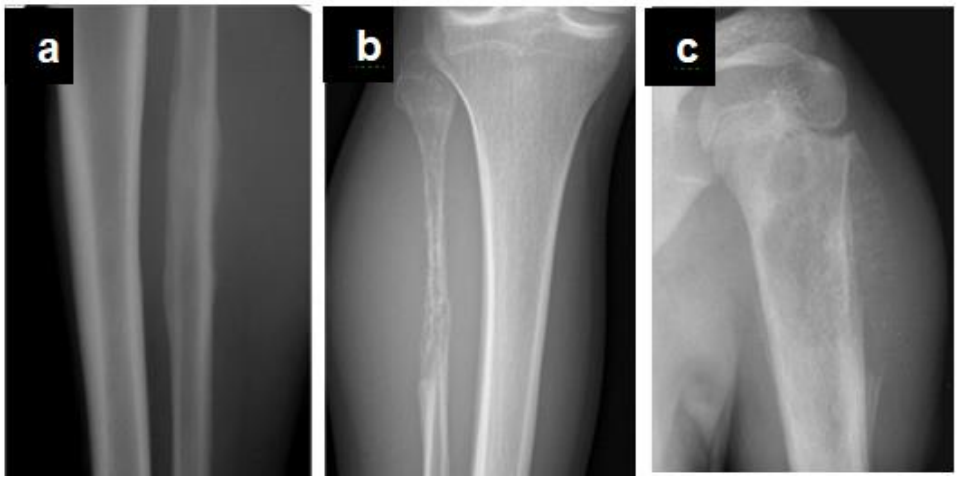

Fig 9: Radiographic presentation in three patients with Ewing's sarcoma: unilamellar periosteal apposition (a), with permeative osteolysis (b), and osteolysis with Codman's spur (c) [3]

CT allows to objectify a periosteal reaction and a rupture of the cortex whereas MRI is effective for the study of intramedullary involvement and soft tissues [14]. In the thorax, CT is more interesting in rib lesions where it clearly shows bone lysis and the extent of soft tissue invasion, which contrasts with the pulmonary parenchyma [13]. In typical diaphyseal or metaphyseal-diaphyseal forms, T1-weighted MRI shows intramedullary damage that is often more significant than conventional radiology would suggest. In T2, there is a heterogeneous reinforcement of the tumor mass signal, and a usually intense contrast uptake after injection of gadolinium. T1 images, in high contrast with fat saturation, give very precise images of soft tissue involvement. The contrast between the importance of the soft tissue mass visible on MRI and sometimes discreet radiological involvement is quite characteristic of Ewing's sarcoma [3].

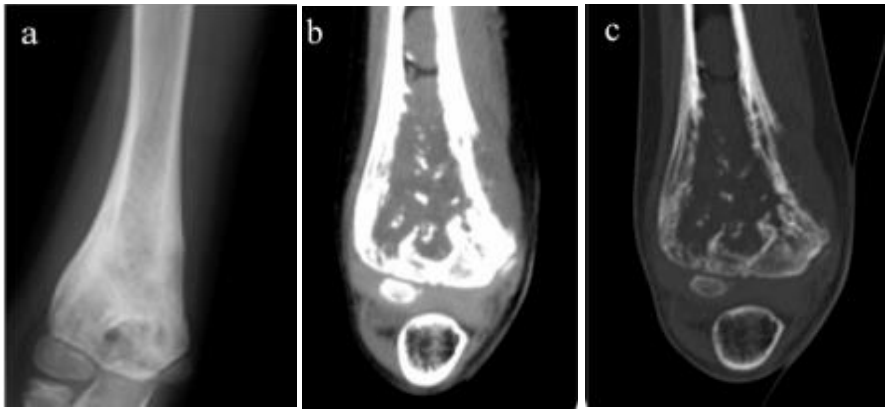

Fig 10: Ewing's sarcoma in an 8-year-old child, comparison of standard X-rays (a) and CT scans (b,c) [10]

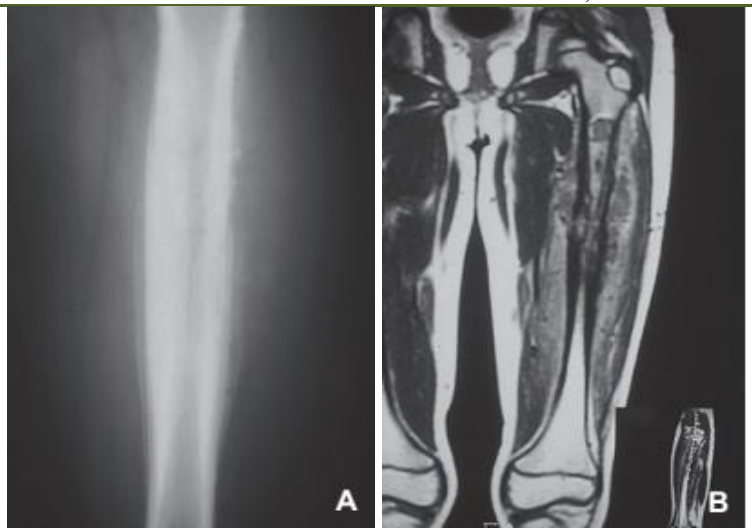

Fig 11: Ewing's sarcoma of the femur in a 9-years-old boy A. Plain X-ray appearance. B. Aspect in MRI imaging showing the importance of intramedullary invasion and extension in the soft tissues [3]

The positive diagnosis is based on the anatomo-pathological examination of a surgical biopsy or trocar micro-biopsies. It must be sent fresh to the anatomo-pathology laboratory in order to allow the molecular analyzes necessary for the diagnosis of Ewing's sarcoma [15]. Macroscopically, the tumor has irregular contours and very imprecise boundaries. It is a greyish-white, soft, shiny mass, taking on a liquid, even milky consistency in the necrotic areas. Microscopically, the cells are all identical to each other, rounded, measuring between 12 and 14µm. Their nucleus, oval or rounded, is provided with a dense but dispersed chromatin and is delimited by a thin nuclear membrane. Mitotic activity is highly variable, often weak. The cytoplasms are pale and very sparse, with fuzzy borders [3, 16]. Reorganizations are extremely frequent, linked to the fragility of the cells, associating hemorrhage and necrosis. Immunohistochemistry allows positive diagnosis by demonstrating positive staining for the CD99 glycoprotein (encoded by the MIC2 gene) overexpressed by cells of the Ewing tumor family [17]. Its expression is not specific to Ewing sarcomas, it is also observed in a large number of normal cells in the body, such as fibroblasts, as well as in various tumors such as certain carcinomas [20]. Demonstration of EWS gene rearrangements in cytogenetics has become one of the essential elements in the diagnosis of Ewing tumours. The t(11;22) (q24;q12) translocation, first described, is present in 85 to 90% of cases, constituting a true cytogenetic marker as well as the variant translocation t(21;22)(q22;q12) present in 5 to 10% of cases. There are other variants less frequently found [1, 11].

The aim of the extension assessment is to show the local extent of the tumour, its extension into the bone and into the surrounding soft tissues, as well as the involvement of the vasculo-nervous structures located nearby. It should also make it possible to judge the unifocal or multifocal nature of the lesions and their remote dissemination, particularly in the bone and lung. The local therapeutic strategy depends on this locoregional evaluation. MRI is the examination of choice to analyze the local extension of a bone tumour. The signal from the normal (fatty) medullary spaces differs from that of the tumor so that it is possible to assess the extent of the tumor, to detect possible “skip metastases” and to evaluate a possible extension to the tumor adjacent joint [6]. SAIFUDDIN reported, in his study of 26 cases, the presence of skip metastases in 25% of cases [11]. According to the Euro Ewing 99 protocol, in the event of a rib tumour, it’s essential to look for the existence of a pleural effusion, the nature of which (tumor or reaction) will be sought by cytological puncture. The presence of pleural effusion (even positive) does not cause the patient to be considered as metastatic but as a carrier of a locoregional disease. The remote extension assessment must systematically include a thoracic-abdominal and pelvic CT scan, a bone scintigraphy and myelograms associated with an osteo-medullary biopsy. Metastases are common. They are present in 20 to 30% of cases at the time of diagnosis. These are mainly lung (38%) and bone (48%) metastases. Other metastatic locations are rare such as lymph node, brain and liver metastases 9% [3, 11, 21, 22]. The search for the 11-22 or 21-22 fusion transcript by reverse transcription polymerase chain reaction (RTPCR) on a pool of spinal taps confirms the existence of micro metastatic diffusion, the prognostic value of which is now accepted [23]. The usefulness of positron emission tomography (PET) or PET-CT in the initial staging workup is unclear [24]. At least three series note a better sensitivity of PET compared to bone scintigraphy for the detection of bone metastases [25-27]. However, since CT scans are generally limited to the neck above and the femurs below, not all bones are visualized as they would be with a bone scan knowing the limitations of OS for osteolytic versus bone lesions. sclerotic nature. Moreover, PET can be more useful for monitoring the response to chemotherapy and/or

radiotherapy (in particular neoadjuvant chemotherapy), in the postoperative evaluation of a possible recurrence, but also to guide the radiotherapist in defining his target volumes to determine the dose needed to be administered. Currently, PET or PET/CT is increasingly used for the initial staging of patients with Ewing's sarcoma. National Comprehensive Cancer Network (NCCN) consensus guidelines recommend PET and/or bone scan for initial workup and baseline PET is recommended at COG (The Children's Oncology Group) referral if the primary bone tumor doesn't fix on bone scintigraphy [28].

The management of Ewing's sarcoma is multimodal involving surgery, radiotherapy and chemotherapy. A common European protocol for the treatment of Ewing's sarcomas and related tumors has existed since 1999, but is still under evaluation. This protocol, called Euro-EWING 99 for European Ewing tumor Working Initiative of National Groups 1999, includes general treatment, chemotherapy and local treatment, surgery and radiotherapy [3]. All the decisions around the therapeutic strategy can only be taken within the framework of a multidisciplinary consultation in a specialized center. The Euro-Ewing 93 protocol includes, for localized forms, induction chemotherapy consisting of three to five initial courses, called "Memphis", combining cyclophosphamide and doxorubicin, and sometimes a combination of etoposide and fosfamide. Maintenance chemotherapy after surgery includes, depending on the response of the tumour, first six courses of vincristine associated with actinomycin D, then in a second phase, six courses of "Memphis" [4]. The Euro-Ewing 99 protocol includes induction with six courses of vincristine, ifosfamide, doxorubicin and etoposide (VIDE). After surgery or radiotherapy in non-surgical forms, chemotherapy then uses different drugs, either vincristine with actinomycin and ifosfamide (VAI), or vincristine, actinomycin and cyclophosphamide (VAC) [4]. In the forms of poor prognosis, the two protocols call for an intensification of chemotherapy associating busulfan and melphalan inducing complete bone marrow aplasia [4]. The cure is followed by an autologous bone marrow transplant taken by cytapheresis and frozen.

Surgery is both a diagnostic and a therapeutic act. Its final goal is to carry out a carcinologically satisfactory intervention passing in all respects into healthy tissue without forgetting the possibility of conservation and construction. In the absence of contraindications, surgery can reduce the risk of local recurrence, reduce radiation doses and analyze the histological response to chemotherapy. Historically, surgery provides better loco regional control compared to radiotherapy, but with advances in systemic treatments and irradiation techniques in the context of multimodal treatment, local relapse rates have decreased and the difference between the two means of local control has become almost insignificant [29, 30].

Radiotherapy can be delivered pre or postoperatively depending on the indications. However, the curative irradiation of a tumor requires high doses and poses the problem of late toxicities in children. Radiotherapy will be considered depending on the stage of the disease such as metastatic Ewing's sarcomas, seat of the tumor for certain inoperable tumor locations either by their seats (spine and pelvis) or by their volumes or non-oncological surgery judged R1- R2 to increase local control is to decrease the risk of recurrence [31-33]. Patients must follow several steps before starting treatment, including choosing a comfortable and reproducible position using restraints and sedation, then performing a dosimetric scan or simulation. The fusion technique remains a crucial element for the planning of "dosimetry and quality control" radiotherapy. Advances in medical imaging and radiotherapy planning systems have greatly helped the radiotherapy oncologist thanks to techniques such as the fusion of morphological images such as MRI, or functional images such as PET scan performed before systemic treatment (pre-chemotherapy tumor volume), or after (post-chemotherapy tumor volume) reflecting the degree of response. The work of the radiotherapist oncologist consists in defining the tumor volume to be irradiated which corresponds to the initial or residual tumor volume, called the macroscopic tumor volume (GTV), to which a margin is added taking into account the possible microscopic extensions in different dimensions (CTV) taking into consideration the natural history of the cancer, the areas of vulnerability to tumor extension and anatomical barriers creating areas of resistance. A second margin is added to the CTV to correct any inaccuracies in the "setup margin" positioning and the internal movements of the "ITV" organs to obtain the final volume to be treated or forecast volume (PTV) [34]. He must also outline organs in anatomical relationship with the target volumes to protect them from an excess of doses which can compromise their function and consequently permanent sequelae. The choice of organs at risk mainly depends on the tumor location and largely determines the dose to be delivered, the ballistics and the configuration of the beams. In the case of pelvic involvement, it is essential to delineate the bladder, rectum, small intestine and femoral heads, which can cause long-term disabling toxicity. Among the rules to follow when irradiating Ewing's sarcoma in a child: avoid irradiating even partially the epiphyseal growth plates in order to minimize the risk of member inequality. Circular radiation therapy should also be avoided to reduce the risk of edema and compartment syndrome. The gonads must be excluded from the irradiation fields with additional protection (lead shells for the testicles) to maintain fertility. Pay particular attention to the dose received by the soft tissues of the soles of the feet so as not to compromise the functional result because walking imposes permanent constraints on this area. Achilles tendon radiation and nail roots

should be excluded from the fields when possible. For pelvic tumors, a full bladder can reduce the volume of irradiated small intestine while paying attention to the volume of the irradiated bladder because it is already weakened by Ifosfamide-based chemotherapy with the risk of hemorrhagic cystitis. According to the Euro-Ewing 99 protocol, the recommended dose is 44 to 54 Gy for operated patients. For non-operated patients, the recommended dose is 54 Gy, with overprinting up to 60 or 64 Gy depending on age and location [1]. According to the MEMPHIS Protocol, the dose of irradiation depends on the location of the tumour, and any prior excision of the tumour. If the resection was microscopically complete, the dose is 40 Grays. In the absence of surgery or in the case of incomplete resection, it is 60 grays for the limbs and depends on the neighboring organs for tumors located on the trunk [11]. In the presence of risk factors for recurrence, an additional dose may be administered at the level of the tumor bed, ie in the region where the tumor was removed for operated patients. This additional irradiation is called BOOST or overdose. It is facilitated by the placement by the surgeon of small radiopaque clips at the level of doubtful areas of tumor residue [35]. Radiation therapy is given 2 to 4 weeks after surgery in case of conventional chemotherapy and 8 to 10 weeks in case of high dose chemotherapy. Spreading and fractionation are generally standard, with a dose per fraction between 1.8 and 2 Gy, for 5 fractions per week. In principle, patients receive 5 sessions per week from Monday to Friday [1]. Other fractionations are possible in the case of palliative radiotherapy 30Gy in 10 fractions, i.e. 3 Gy per fraction, or 5 fractions of 4Gy. For pulmonary radiotherapy, fractions of 1.5 Gy are recommended to prevent radiation pneumonitis [35, 36]. Three-dimensional conformal radiotherapy remains the standard. However, intensity-modulated radiotherapy (IMRT) often offers a ballistic advantage due to the complexity of the sites affected and the high doses to be delivered. Proton therapy should be discussed especially for head and neck tumors, especially in very young children. Intraoperative brachytherapy can be a good technique for irradiating certain locations [35]. If all the steps leading to the treatment are based on the availability of three-dimensional images of the anatomical data and the target volumes, the verification of the positioning in the absence of a "cone beam CT" in the treatment room, rested until now on the portal imagery "orthogonal images" thanks to the visualization of the bony structures. The correct positioning of the patient, of the Iso center of the beams and the limits of the fields are checked and controlled by carrying out control imaging on the 1st, 2nd and 3rd day, then on a weekly basis, and each time the plan is modified of the treatment. The most frequent acute complications of radiotherapy mainly affect the skin (erythema, desquamation, phlyctenes), the intestine and especially the rectum (radiation proctitis with pain, rectal bleeding, diarrhea), the urinary tract (radiation cystitis), the marrow spinal (myelitis, favored by local surgical or toxic trauma). Irradiation must also preserve the epiphyses in order to reduce the impact on growth in children, as well as the femoral head, given the risk of epiphysiolysis of the femoral head [6]. In the long term, the incidence of radiation-induced sarcomas is approximately 5 to 35%, 20 years after treatment for Ewing's sarcoma. These radiation-induced secondary lesions can occur very late and their high incidence in Ewing's sarcoma appears to be partly related to associated chemotherapy (alkylating agents) [37].

Several studies have assessed the response to radiation therapy compared to surgery. According to the study by SUDANESE–Institut RIZZOLI involved 196 patients with no metastases at diagnosis. The age of the patients varies from 0 to 50 years old, of which 55% between 11 and 20 years old and 2% between 31 and 40 years old. The results show an advantage to the use of surgery associated with radiotherapy [30].

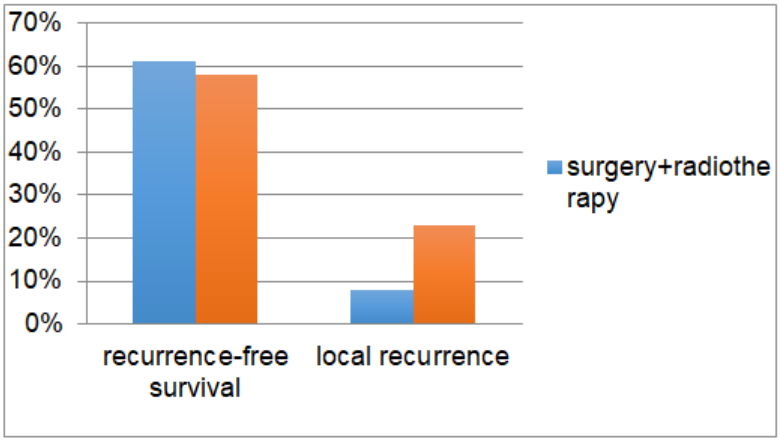

Fig 12: The retrospective role of surgery and radiotherapy according to the SUDANESE-Institut RIZZOLI study [30]

According to the CESS study, the use of surgery associated with radiotherapy with an absence of recurrence shows an advantage in 69% of cases at 3 years compared to 43% with the use of radiotherapy alone.

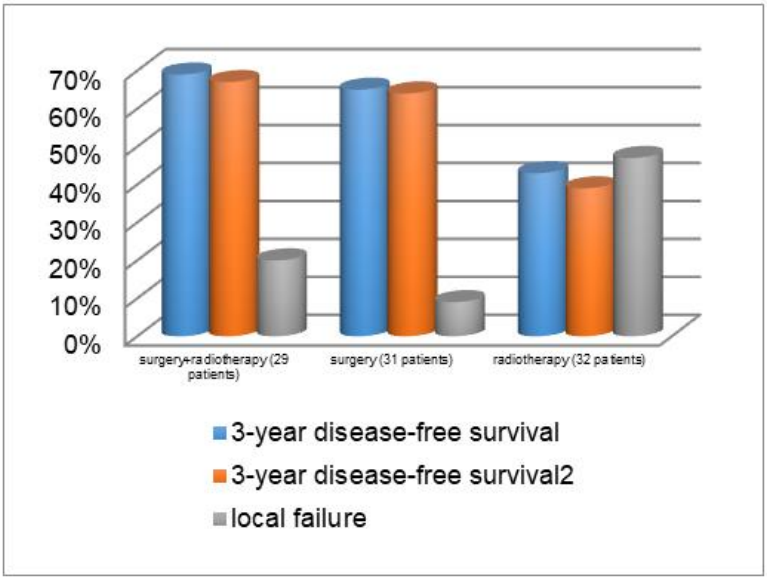

Fig 13: Recurrence-free survival rate and failure according to local treatment [29]

Ewing's sarcoma is usually a rapidly growing lesion. Locally it tends to invade the soft tissues, sometimes very significantly, and it can also extend to the entire medullary cavity of the affected bone. This invasion takes place through the Havers canals of the bone, then by a real infiltration of the surrounding healthy tissues, contrary to what happens with osteosarcoma where the tumor pushes back the healthy soft parts by developing outside the limits of the initially affected bone. There are some cases when the tumor has, on the contrary, a rather slow evolution, remaining confined in the bone for a long time and not quickly giving metastases. This probably explains why the delay in diagnosis is not regularly found as a factor of poor prognosis in clinical studies. The forms diagnosed late being perhaps the least aggressive.

The most important prognostic factor is the presence of metastases at diagnosis. The prognosis of patients with isolated lung metastases is better than that of patients with bone or bone marrow metastases. In localized forms, the size of the tumor is found to be prognostic in many studies, however since the increasingly frequent use of a surgical approach to these tumours, the response to initial chemotherapy is found to be very linked to the prognosis in the vast majority of cases. studies and eliminates the prognostic significance of size for operated tumors [18]. The current European protocol (Euro-Ewing 99) has stratified localized tumors into several groups [19]: the standard risk group represented by tumors operated on after chemotherapy alone with <10% residual perennial cells. Tumors operated on from the outset of small volume (<200ml). Tumors operated after chemo and radiotherapy and of small volume with < 10% of residual cells. As well as inoperable tumors of small volume (<200ml) at least in clinical and radiological partial response after initial chemotherapy. The high-risk group includes tumors operated on after chemotherapy alone with ≥ 10% residual cells. Large inoperable tumors (≥200ml). Inoperable tumors of small volume (<200ml) and for which the initial chemotherapy only resulted in tumor stability (response <50%). Tumors operated from the outset large volume (> 200ml). But also tumors operated after chemo and radiotherapy and small volume < 200ml with > 10% perennial cells. The hypothesis of an infra-clinical dissemination of tumor cells explaining the appearance of metastases despite complete initial local control. Using the RT-PCR technique, West *et al*., detected occult tumor cells in peripheral blood and bone marrow. It is currently accepted that 20 to 40% of localized forms of Ewing's sarcoma have detectable tumor cells in the circulating blood by this method. Schleiermarcher *et al*., further showed that a positive RT-PCR in the bone marrow was strongly correlated with the existence of clinical metastases ($p = 0.0018$). In this study, a positive RT-PCR in the marrow of patients with apparently localized Ewing's sarcoma is a factor of poor prognosis. It will most likely be necessary to include the detection of the fusion transcript in the bone marrow in future prospective studies [6].

CONCLUSION

Ewing's sarcoma remains a relatively rare disease. It is a malignant tumor that frequently develops in bone tissue and rarely in soft tissue. It is a pathology of the child in its osseous localization and of the young adult in its extra osseous localization. Its diagnosis is

currently based on histology and molecular biology data. It is necessary to make an early diagnosis before the metastatic stage and to institute an adequate treatment in order to improve the prognosis of the disease. Its prognosis has been significantly improved thanks to modern therapies. The management of Ewing's sarcoma is multidisciplinary based on the combination of surgery, radiotherapy and chemotherapy. Radiotherapy still has very specific indications despite the development of surgical techniques and chemotherapy protocols. The aim of current treatments is to reduce the sequelae directly linked to therapies in the so-called good prognosis forms and to improve the results of the treatment of the so-called poor prognosis forms, whose survival rates currently remain disappointing. Many patients, however, still die from the progression of their tumor.

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