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Keywords

Retinoblastoma; Inflammatory
phenomena; Metastatic retinoblastoma;
Leukocyte Antigen

Abbreviation

OCT: Optical Coherence Tomography;
NSAIDs: Non-Steroidal Anti-Inflammatory
Drugs; APL: Abductor Pollicis Longus;
EPL: Extensor Pollicis Longus; ECRB:
Extensor Carpi Radialis Brevis; DRUJ:
Distal Radioulnar Joint; PET-CT: Positron
Emission Tomography-Computed
Tomography; PA: Posterior-Anterior

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Research Article

Late and Distant Metastases of Retinoblastoma to Long Bones: A Purpose of a Case

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Abstract

Is presented a 13 year old male patient case, with a history of Bilateral Retinoblastoma since 2 years old, performing enucleation of the right eye in June 2007, and salvage of the left eye by chemotherapy and radiotherapy, the patient 11 years after of first episode, presented metastasis in the distal end of the right radius, performing neoadjuvant and subsequent wide oncological resection with healthy margins of the distal end of the radius plus reconstruction with the ipsilateral proximal end of the fibula and wrist arthrodesis.

Introduction

Retinoblastoma is the most common malignant intraocular tumor in childhood (approximately 18 months of age), and it comes from primitive cells of the sensory retina [1-4]. The origin of retinoblastoma is found in the cells of the retina [5]. It represents around 1-3% of cancers in children and approximately 1% of all cancers [3,6,7]. It is a hereditary tumor in 25 to 30% of cases characterized by a mutation in the RB1 germline gene and may be associated with bilateral lesions, however, 75% of cases are associated with mutations in the germinal development of the retina that are considered non-hereditary [8]. Its incidence worldwide is estimated at one case per 18,000 to 30,000 live births (2). In Venezuela, the presentation rate is 25 to 30 new cases per year and around 3% of all childhood cancers are usually found [9]. The most important clinical sign is leukocoria, which is seen as a white reflection in the pupil, another important sign is strabismus, which occurs when the macular area is involved. Inflammatory phenomena and glaucoma can also be observed, both secondary to the tumor that invades and collapses the lens diaphragm and the trabecular meshwork [10]. Another characteristic sign is proptosis secondary to retrobulbar extraocular expansion, orbital cellulitis, or verification of distant metastases [11,12]. Tumor invasion and metastases represent the most common causes of mortality [13,14], for which several studies have been carried out in order to determine the main risk factors for them. It is estimated that the development of metastatic disease occurs in less than 10% of affected patients [15,16]. Likewise, the local control of the disease consists of the enucleation of the affected eyeball, in a stage V of retinoblastoma, and possible metastatic disease should be considered in case of extraocular extension of the lesion, such as: invasion of the choroid, scleral or nerve involvement that extends to the cribriform plate, in these cases there is a high risk of metastatic disease [17]. And its spread worsens the patient's life prognosis. Metastatic retinoblastoma is rare in developed countries with a reported range of 4.8% in the United States to 5.8% in the United Kingdom. However, the frequency in developed countries varies from 9 to 11% at presentation. Mortality is very high due to late presentations, late diagnosis aggravated by socioeconomic factors. The management of Metastatic Retinoblastoma is evolving but remains a challenge in pediatric oncology. One of the affected areas in cases of distant metastases is the bone marrow, showing infiltration of disseminated tumor cells in the blood [18,19]. These metastases may present as bone lesions and they have to be carefully distinguished from other primary bone tumors.

Post-mortem studies have shown that the cranial and orbital bones are the most common sites of extension and metastasis [6,13]. Mackay [20] in their studies found that the patients with metastasis, 35% had only in brain and 65% had in skull and distant organs. The tumor can spread to long bones, lymph nodes, and viscera (including the liver, kidneys, pancreas, and gonads), and rarely to the lungs [6]. Generally, distant disease in patients with retinoblastoma can occur between 6 and 20% of cases, regardless of whether it is advanced unilateral, bilateral or in cases known as trilateral, and the most common metastatic spread is usually to the central nervous system (through the meninges) and bone jointly represented by 60% of metastatic cases [21]. 90% of cases affected bones are usually represented by orbital and cranial bones and only 10% in long bones [21]. As for the treatment options in extracranial Metastatic Retinoblastoma (specifically long bones), they include systemic chemotherapy followed by high-dose myeloablative chemotherapy with stem cell rescue, in combination with radiotherapy, however, extraocular disease, especially in older early is usually associated with a poor prognosis [22]. Another option regarding distant disease in long bones is local control through resection surgery, improving local healing rates, allowing the preservation and functionality of the limb, in other cases ablative surgery should be used above all in patients with late-onset metastases, after local ocular treatment [23]. Given the above, a case of Retinoblastoma Metastasis to the Distal Metaphysis of the Right Radius is presented, 12 years after Enucleation or Recession of the Primary Tumor, being managed and studied multidisciplinary.

Case Report

A case of a Late Metastatic Retinoblastoma is presented, which affected long bones, specifically the distal end of the right radius, the following data were assessed: male patient, mix race, chronological age 13 years, native of Nueva Esparta State, Venezuela. No known family cancer history. He presented Bilateral Retinoblastoma since he was 2 years old, performing enucleation of the right eye in June 2007 and salvaging of the left eye through chemotherapy (6 cycles) + radiotherapy (21 Sessions). It should be noted that this patient attends strict controls through Optical Coherence Tomography (OCT). Cerebral Nuclear Magnetic Resonance, orbit and eye fundus by the Ophthalmology Oncology treating service. In June 2019, the patient reported increased volume in the right wrist, concomitant pain of moderate intensity and functional limitation, which was attenuated with Non-Steroidal Anti-Inflammatory Drugs (NSAIDs). He is treated by the Traumatology Service of his locality (Nueva Esparta State, Venezuela), requesting X-ray studies of the wrist in Anteroposterior and Lateral projections, the results show an alteration of the bone structure (Figure 1), with the presence of a lytic lesion with periosteal reaction, therefore, he was referred

to the Bone Tumors Service of the Padre Machado Oncology Hospital.



Figure 1: X-ray show an alteration of the bone structure.

In October 2019, the patient was evaluated at the Bone Tumors Service of the Padre Machado Oncology Hospital in Caracas, where the alteration of the aforementioned bone structure was clinically and imaging studies evidenced, it was decided to perform an incisional biopsy, observing from the histological point of view the presence of densely cellular areas made up of round blue cells with little cytoplasm and moderate cytological atypia without the presence of production of any type of osteoid or cartilaginous matrix with a mitotic activity of 2 mitosis x 10 fields of higher magnification (mitotic activity was reported in 10 fields since the change suggested by the World Health Organisation, WHO 2020, did not exist to date), no vasculolymphatic tumor embolism was seen, concluding as morphological findings compatible with malignant round cell tumor (Figure 2).

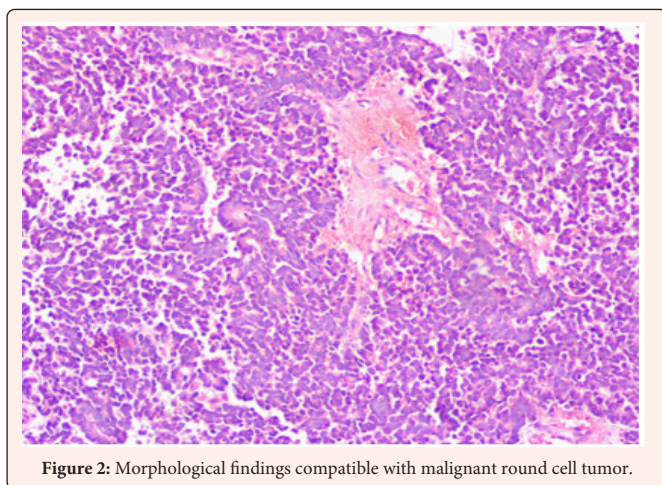


Figure 2: Morphological findings compatible with malignant round cell tumor.

For which an immunohistochemical study of the sample is indicated, showing diffuse positivity to enolase (Figure 3) and synaptophysin (Figure 4), and on the other hand vimentin, cytokeratin AE1/AE3, Common Leukocyte Antigen, CD34, CD99, Fli1 and protein S100 negative in tumor cells with a proliferative activity measured with ki67 of the 85%, taking into account the known history of the patient, considers Metastatic Retinoblastoma as the best diagnostic option. It should be noted that in developed countries retinoblastoma is diagnosed more frequently when the tumor is still intraocular in contrast to what happens in underdeveloped countries, where diagnosis is late and the tumor has the possibility of spreading to the optic nerve, orbit or even disseminating giving rise to metastasis [24], that is what we observed in the treated patient.

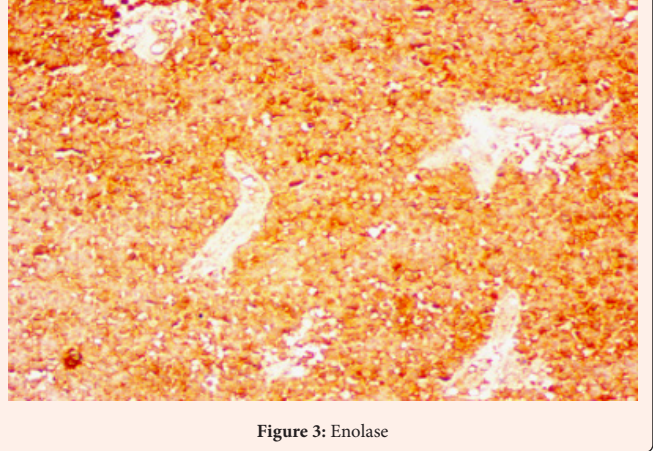


Figure 3: Enolase

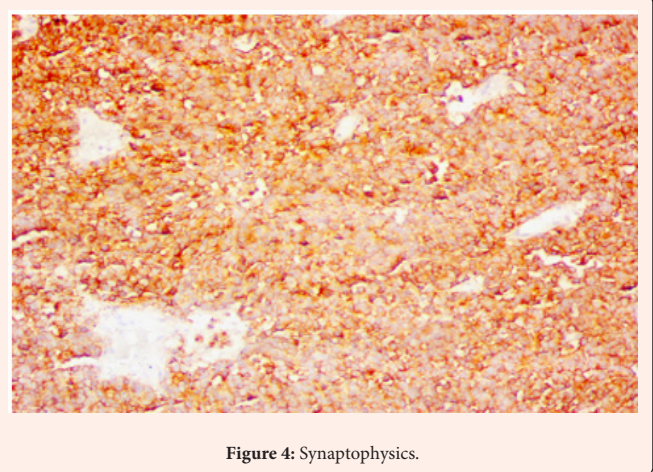


Figure 4: Synaptophysin.

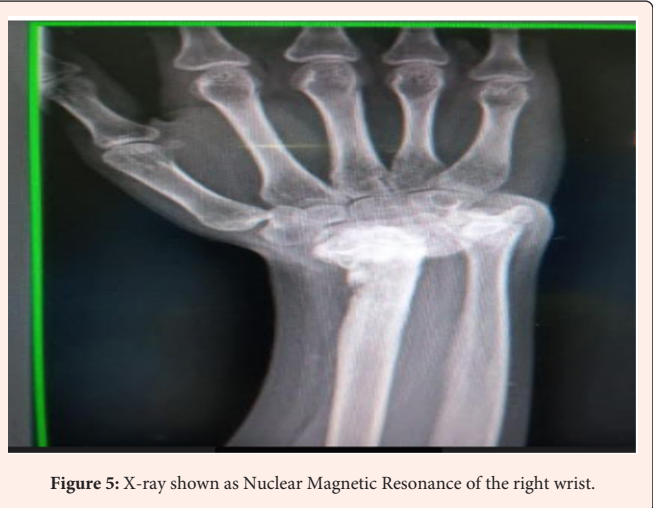


Figure 5: X-ray shown as Nuclear Magnetic Resonance of the right wrist.

The patient is referred and treated at the Pediatric Oncology Service of the Luis Razetti Oncology Hospital, Caracas-Venezuela, in conjunction with the Radiotherapy Service at the José Manuel de los Ríos Hospital, Caracas-Venezuela where a Neoadjuvant treatment was performed, through eight (08) chemotherapy cycles plus ten (10) radiotherapy sessions at a dose of 250 cGy each. Local and distant imaging studies were requested again (X-rays, Nuclear Magnetic Resonance of the right wrist, CT-PET), where a fork-back deformity and marked limitation of wrist flexion and extension were observed (Figure 5, 6). In view of presenting only this oligometastasis, the decision was made from the surgical point of view to perform an oncological en bloc resection of the right distal end of the radius (metasopiphyseal), plus the distal epiphysis of the ulna, the latter due to contamination of compartments, reconstructing with proximal fibular autograft plus wrist arthrodesis in November 2020 (Figure 7).



Figure 6: Fork-back deformity and marked limitation of wrist flexion and extension.

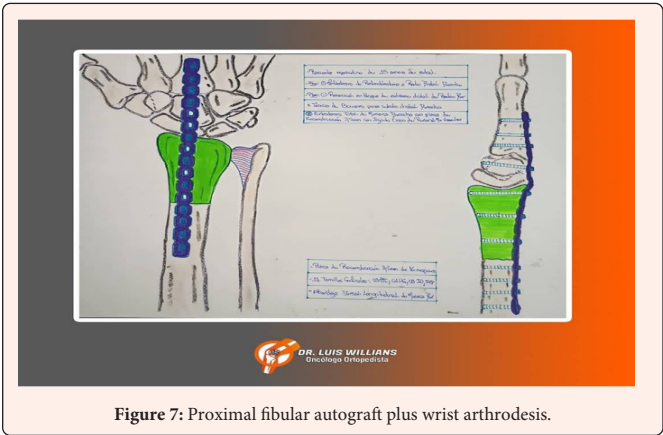


Figure 7: Proximal fibular autograft plus wrist arthrodesis.



Figure 8: Post-Neoadjuvant Piece.

From the macroscopic point of view of the piece, the distal radius segment was received, it measured 8 cm. in length with variable diameters between 1.3 and 3 cm. (Figure 8). Articular surface of the radial dome without significant macroscopic lesions was identified. The cortex was intact with areas of irregular appearance. In the sagittal section of the piece, medullary bone increased in consistency with calcified areas was identified. The rest of the cancellous bone looks normal. Samples of the entire bone surface were included with post-neoadjuvant piece protocol for definitive histological study and response evaluation. In the microscopic study of the piece, there is no evidence of residual tumor with reparative changes typical of neoadjuvant therapy.

Materials and Methods

Total wrist arthrodesis

Total wrist arthrodesis is a basic operation, whose objective is stable and painless radiocarpal and intercarpal fusion with proper alignment and preservation of pronosupination mobility. Numerous methods of wrist arthrodesis have been described over the years (Figure 9, 10). The surgical procedure that was carried out after surgical planning in this case was:

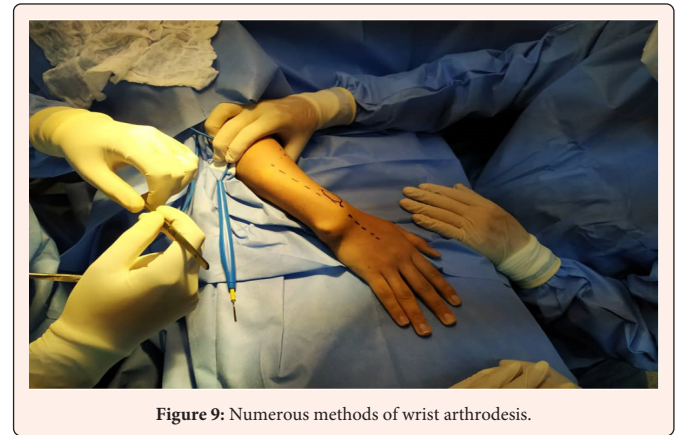


Figure 9: Numerous methods of wrist arthrodesis.

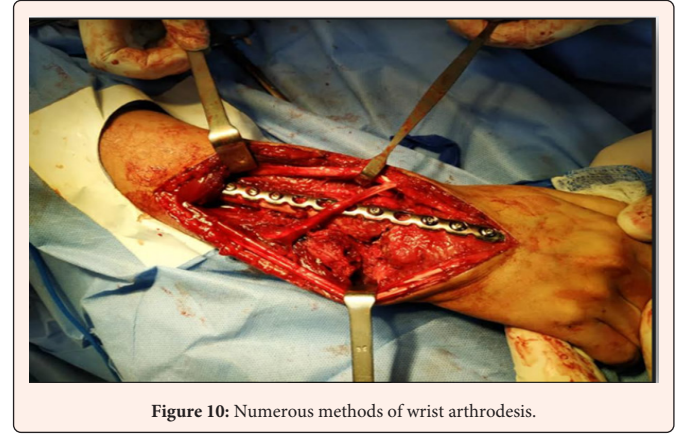


Figure 10: Numerous methods of wrist arthrodesis.

Surgical technique

- a) Under general anesthesia, after placement of a tourniquet with emptying by gravity, asepsis and antisepsis of the right upper limb, a straight, longitudinal incision is made in the midmetacarpal area, centering between the second and third metacarpals. The incision passes through Lister's tubercle and ends on the dorsum of the distal radius just proximal to the muscle belly of the Abductor Pollicis Longus (APL).
- b) The radial side of the incision is raised as a flap directly off the dorsal surface of the retinaculum and contains the superficial branch of the radial nerve. The back of the retinaculum is opened by incising directly on the third compartment of the Extensor Pollicis Longus (EPL).

- c) The EPL of the compartment is mobilized and transposed radially. Full transposition requires release of the sheath distal to the retinaculum.
- d) The distal radius is exposed subperiosteally and the incision is extended longitudinally in the periosteum distally through the capsule to the radial base of the third metacarpal. The Extensor Carpi Radialis Brevis (ECRB) attachment is elevated subperiosteally by scalpel dissection and reflected radially.
- e) An incision is made in the interosseous fascia on the radial side of the third metacarpal, exposing the dorsal surface of the third metacarpal on both sides.
- f) A scalpel blade is used to elevate the two capsule flaps from the carpus. And the second dorsal compartment is elevated subperiosteally from the radius and reflected radially from its underlying capsule.
- g) The fourth extensor compartment of the radius is elevated subperiosteal and reflected from its underlying capsule ulnarly over the Distal Radioulnar Joint (DRUJ). Note that the second and fourth dorsal tendon compartments are not entered.
- h) Resection of the distal radio-ulnar joint is performed in a block of approximately 7 cm. and the dorsal cortices at the base of the third metacarpal and carpal bones are removed to provide excellent visual access to all joints to be included in the fusion. However, because he was a child, resection of the first proximal row of the carpus was not performed.
- i) The articular cartilage of the first proximal row is removed and non-vascularized fibular bone graft is placed.
- j) It is fixed with a 3.5 mm. 16 holes reconstruction plate and the plate is centered directly on the dorsal aspect of the third metacarpal so that three screws are placed in the metacarpal (one metaphyseal and two diaphyseal).
- k) A 2.0 mm. drill hole is made in the dorsal to volar direction under direct vision precisely in the midline of the metacarpal. This is the most critical screw hole because the metacarpal is narrow at this point. If the hole does not pass in a direct dorsal to volar direction, the plate will be somewhat oblique to the frontal plane and will potentially rotate the metacarpal when it is attached posteriorly to the radius.
- l) The distal hole is then measured for depth with the plate repositioned and a 2.7 mm. self-tapping cortical screw of the appropriate length is applied and with the plate so aligned over the third metacarpal, the most proximal of the three is drilled screws into the metacarpal in neutral mode with a 2.0 mm. drill bit, depth is measured, and a 2.7 mm. screw is inserted.
- m) The position of this second screw is also fundamental because it determines the angle at which the plate will overlap the distal radius, then the central one of the three metacarpal screws is inserted to then place a 2.7mm cancellous bone screw in the bone great.
- n) Finally, the hand is aligned with the forearm and the capitate is manually compressed against the nonvascularized distal fibula.
- o) With the plate aligned on the fibula and the hand properly oriented the second most distal screw is drilled into the fibula with a 2.5 mm. drill bit in compression mode and a 3.5 mm. cortical screw is inserted and the remaining fibular holes are fixed with cortical screws.
- p) If the plate is in direct contact with the dorsal aspect of the capitate, choose the screw length as measured.
- q) Retained radial and ulnar blades from the previously opened third compartment (EPL) are used to close the capsule over the plate.
- r) The transposed EPL is left radially out of Lister's canal by slightly elevating the tendon away from the fibula so that it is separated by the second closed compartment. The EPL tendon does not touch the plate except sometimes at its proximal origin.

Resection and Interposition Arthroplasty

Bowers technique

- a) The articular surface of the ulna is resected because it is continuous with the tumor of the excised radius, and a segment of soft tissue is inserted inside the radioulnar joint preserving the triangular fibrocartilage.

- b) Resection of the dorsal and articular portion is performed preserving the ulnar styloid with capsular plasty that surrounds the distal end of the ulna, and is later reinforced with the extensor retinaculum.
- c) With this technique, the stability of the Distal Radioulnar Joint (DRUJ) is better achieved and pronosupination improves maintaining the length of the ulna.

Postoperative treatment

- a) Brachiopalmar splint was placed for 06 weeks,
- b) At 10 weeks, full use of the hand was allowed,
- c) Bone consolidation was observed at 08 to 10 weeks.

Discussion

Children with retinoblastoma are at risk for three pathologic conditions: metastasis, intracranial neuroblastic tumor, and secondary cancer. This metastasis develops within the first year of diagnosis [25]. Around 60% of cancer patients receive radiotherapy during the course of their disease [26] years after treatment, the development of a second neoplasm is possible (70% in the irradiated area and 30% outside the area). In their study, Antillon and Esponda published two cases of sarcoma secondary to radiation in retinoblastoma survivors [27], while Moll and Col. evaluated the occurrence of second tumors in a series of 263 patients with Hereditary Retinoblastoma, finding that Hereditary Retinoblastoma conferred a higher risk of developing second tumors, particularly in patients whose neoplasms appeared outside the radiation field or were not treated with it [28].

Conclusion

Given the limitations of the knowledge of the genetics of retinoblastoma metastasis to long bones, not all alterations are currently known. It is considered that a genetic study should be done in patients diagnosed on time. Not all mutations have been identified, new studies and new analysis models must be investigated in order to have a better understanding of the disease, both in clinical and epidemiological aspects as well as in prognoses. The patient under study has undergone an exhaustive follow-up for 19 months (from November 2020 to June 2022) in conjunction with the Pediatric Oncology and Oncological Ophthalmology service of the Luis Razetti Hospital, Caracas- Venezuela performing hand x-rays and forearm in Posterior-Anterior (PA) and lateral projections, Chest Tomography and Positron Emission Tomography - Computed Tomography (PET-CT). In the evaluations, osseointegration of the fibular autograft was observed using the arthrodesis technique, with the patient's wrist being functional (Figure 11-13). It should be noted that our patient continues in a physical medicine and rehabilitation plan to improve fine movements that help him with daily activities. From the oncological point of view, the patient does not present secondary implantation or metastatic lesion in the lung or other region of the body, he must continue with controls every 4 months for the first 2 years, observing his evolution. If there is a favorable improvement, the controls will be distanced every 6 months.



Figure 11: X-Ray.

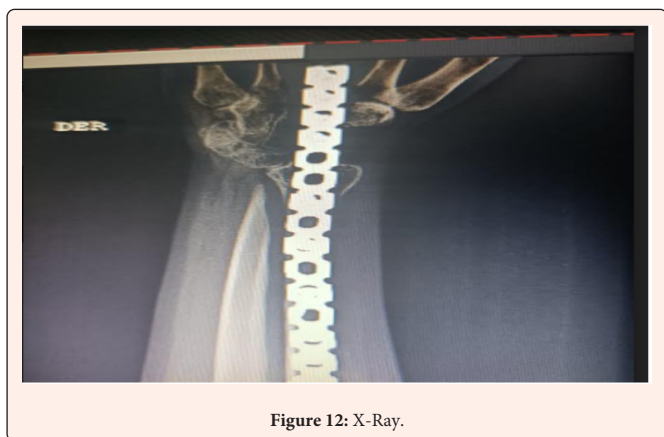


Figure 12: X-Ray.

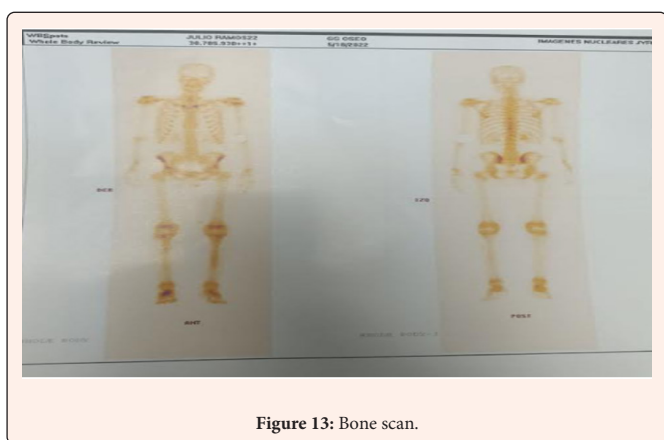


Figure 13: Bone scan.

It should be taken into account that Retinoblastoma is a curable disease if an early diagnosis and appropriate therapy are performed, since late consultation is correlated with a poor prognosis for the patient.

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