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RESEARCH ARTICLE

ATYPICAL PRESENTATION OF METASTATIC EWING'S SARCOMA OF PUBIC BONE-A RARE CASE

Dr. Syeda Zaineb Humaira Hussaini[1], Dr. A. Srinivasa Rao[2] and Amini Raunaq Fatima[3]

1. Pharm.D (Doctor of Pharmacy), Clinical Pharmacist, Basavatarakam Indo-American Cancer Hospital and Research Institute, Hyderabad, India.
2. Professor and Principal, Department of Pharmacy Practice, Bhaskar Pharmacy College, Moinabad(M), Hyderabad, India.
3. Pharm.D, Department of Pharmacy Practice, Bhaskar Pharmacy College, Moinabad, Hyderabad.

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Abstract

Ewing's sarcoma is a highly malignant bone tumor which usually occurs in children and young adults and is not common in adults older than 30 years. It often arises from diaphysis of long bones. Although it may develop in any bone, the most frequent sites are femur, ilium, tibia, pelvic area, ribs and scapulae. A delay in early symptoms and diagnosis is quite common, particularly of pelvic tumors in which this mass is not palpable until it is quite large. The most important and earliest symptom is pain which may radiate to the limbs and constitutional symptoms (such as malaise and fever). Majority of patients have metastasis involving the lungs and other bones. Ewing's sarcoma involving the pelvis is a great challenge in terms of local control due to the complexity of pelvic anatomy, which increases the difficulty of treating them. We report a rare case report of Ewing's sarcoma of right pubic ramus with metastasis to lungs and spine in a 19 years old male. Further multislice spiral CT pelvis, Magnetic Resonance Imaging (MRI) of dorsal and lumbar spine and nuclear medicine positron emission tomography (PET-CT scan) was done to assess the involvement of soft tissue and proven Ewing's sarcoma. He was treated by a multidisciplinary approach by surgery, chemotherapy (CT) and radiation therapy (RT) for effective response. The prognosis and survival of patients in this location (pelvis) are much less favourable than for patients with tumors of other extremities.

Introduction:-

Ewing's sarcoma is a primary malignant bone tumor that usually occurs during the first two decades of life. It is the second most common bone tumor of childhood and adolescence. It has been classified within a large group of neoplasms termed "Ewing's Sarcoma Family Of Tumors" (ESFT)[(1)]. Ewing's sarcoma can spread (metastasize) to other parts of the body, such as the lungs, bone marrow, and other soft tissues. When compared with other cancers, malignant bone tumors like Ewing's sarcoma are rare. Of these rare bone tumors, Ewing's sarcoma is the second most common in children and young adults. According to data on children younger than 15 years old, approximately 1.7 children out of a million develop the disease.[(2,3)]

Corresponding Author:- Dr. Syeda Zaineb Humaira Hussaini
Address:- Pharm.D (Doctor of Pharmacy), Clinical Pharmacist, Basavatarakam Indo-American Cancer Hospital and Research Institute, Hyderabad, India.

There are four types of cancer, referred to as the Ewing's Family of Tumor (EFT). This includes the Ewing's sarcoma of bone, the Ewing's sarcoma of soft tissue, primitive neuroectodermal tumor (PNET) which may occur in both bone and soft tissue, and Askin's tumor, a PNET that occurs in the bones of the chest.[4]

Histologically, Ewing's sarcoma may vary in its degree of neural differentiation though it most commonly consists of sheets of small, uniform cells with round nuclei, often with an infiltration of the surrounding tissue, haemorrhage and necrosis. The specific progenitor cell for ES is not clear. However it is hypothesized to be of neural crest or mesenchymal origin. Two sensitive but not specific, cytological markers for ES includes a cluster of differentiation 99 (CD99) and less commonly identified markers including keratin, Epithelial membrane antigen (EMA), carcino embryonic antigen (CEA) and Desmin.

A typical clinical presentation with Ewing's sarcoma includes localized pain and swelling in the affected bone and may have other non-specific symptoms such as fever, decreased appetite and weight loss which are usually seen in advanced disease. The lower extremity is the most common primary site for Ewing's sarcoma,accounting for approximately 40% to 45% of newly diagnosed cases. The pelvis is the second most common primary site, accounting for an additional 20% to 25% of new cases.[5,6]Diagnosis usually includes Medical Imaging, Computerized Tomography (CT scan), Magnetic Resonance Imaging (MRI), Positron emission tomography (PET-CT) scan and Biopsy.

Treatment for Ewing's sarcoma includes chemotherapy to treat any potential metastasis (spread) to the lungs. A multimodality approach is used even when the disease only appears to be localized at diagnosis. The first set of chemotherapy drugs for Ewing sarcoma often includes vincristine, doxorubicin (Adriamycin) and cyclophosphamide (VAC). Following recovery from the first set of drugs, ifosfamide and etoposide (IE) may be given.

Following initial chemotherapy to shrink the tumor, patients receive another MRI and CT scan of the chest to restage the tumor.

If the tumor is operable, the patient will usually have a resection (surgery). Generally, if cancer can be removed, surgery is recommended as an alternative to radiation, which can cause profound side effects, especially in young children.

If the tumor is inoperable, radiation may be required. Surgery may be discouraged in the following scenarios:
1. The tumor is in a location where it's unlikely that all tumor cells can be removed (e.g., the spine)
2. The effects of surgery (e.g., living with paralysis or amputation) would significantly alter the patient's quality of life
3. There's a high risk that function in certain body parts (e.g., the pelvis or wrist) cannot be restored

Sometimes both surgery and radiation are required. After tumor resection, the pathologist will analyze the tumor and look for a negative margin on the resected tissue. A negative margin indicates that the portion of tissue around the tumor does not have any live cancer cells. If any live cells are found, radiation is required as a follow-up treatment. Ewing tumors are typically very responsive to radiation.[7]

We report a case of Ewing's sarcoma arising from the pubic bone in a 19 year old male with metastases involving lungs and spine.

Case study:
A 19 year old male patient presented with complaints of right sided hip pain followed by weakness of both lower limbs every 3 days gradually progressive, swelling, restriction of hip movements and fever over the past few months, with no history of trauma. He is a K/C/O asthma. Past history and family history was unremarkable.

Pelvic and chest radiography, computed tomography(CT), blood and histological (including PAS staining) tests as well as immunohistochemistry(IHC) and bone marrow aspiration, biopsy were performed for diagnosis and evaluation of treatment.

Biopsy revealed Malignant round cell tumor and IHC consistent with clinical diagnosis of Ewing's sarcoma. The Multislice spiral CT pelvis showed expansile mixed density lesion with wide zone of transition noted involving right pubic symphysis, superior T inferior pubic rami on right side with adjacent soft tissue component – Residual lesion. (Fig.1)

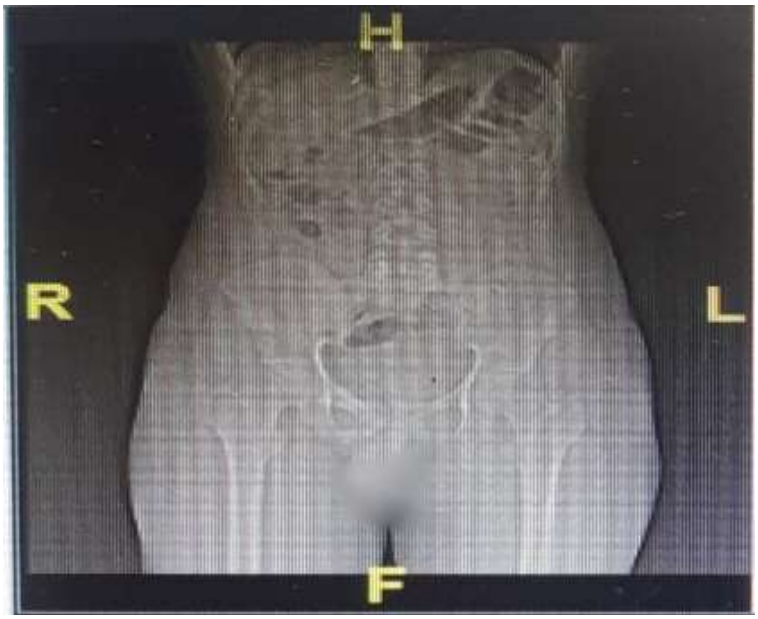

Figure 1:- Multi slice spiral CT Pelvis: Topogram0.6.

The Whole body Positron emission tomography (PET-CT) scan showed lesion in right pubic bone superior and inferior pubic rami with few small nodules in bilateral lung parenchyma in sub pleural locations. The definitive diagnosis was confirmed as "Ewing's sarcoma of right pubic ramus – stage 4."

He was planned for chemotherapy with VAC/IE Regimen. VAC (Vincristine, total dose of 2mg, Adriamycin 110mg and Cyclophosphamide 1800mg) was given intravenous bolus infusion on day 1, followed after 21 days by IE (Ifosfamide 3gm infused over 1 hour, daily for 5 consecutive days, with mesna as uroprotective, plus Etoposide170mg infused over 2 hours on the first day). Courses were repeated every 3 weeks. Myelosuppression was the major dose limiting toxicity.

Post 2 cycles of VAC/IE Regimen, response to treatment was accessed by (PET-CT) scan which showed:
Metabolically active lytic sclerotic lesion in the right pubic bone, right superior and inferior pubic ramus with adjacent mild soft tissue component- Residual lesion. *Metabolically active bilateral lung lesions –likely metastasis.

No other evidence of metabolically active disease.

Based on the PET-CT scan, post 2 cycles of VAC/IE, re-evaluation shows progressive disease and he was planned for second line chemotherapy with 3 cycles of Irinotecan and Temozolamide. (Inj. Irinotecan 60 mg IV in 500ml 5% dextrose over 2 ½ hours for 5 days and Cap. Temozolamide120mg PO OD for 5 days). Palliative pelvic RT was in continuation with chemotherapy cycles. A follow up imaging for further characterization included Magnetic resonance imaging (MRI) of dorsal spine with contrast and MRI of lumbar spine with contrast.

MRI of dorsal spine with contrast demonstrated: a) Diffuse altered marrow signal intensities are seen involving cervico- dorso- lumbo- sacral vertebrae and their appendages. After contrast administration vertebral body marrow shows heterogeneous enhancement suggestive of marrow infiltrative disease- metastases. (Fig.2a)

Anterior epidural soft tissue mass is seen from D6 to D8 producing gross compression over the spinal cord(Fig.2b). After contrast administration epidural soft tissue mass shows moderate heterogeneous enhancement and also

enhancement of the left D9 nerve root – suggestive metastatic epidural soft tissue mass with gross compression over the spinal cord.

Focal hyperintense signals on T2W/T/STIR are seen in the spinal cord from D6 to D8 due to gross compression over the spinal cord by anterior epidural soft tissue mass–compressive myelopathy.(Fig.2c)

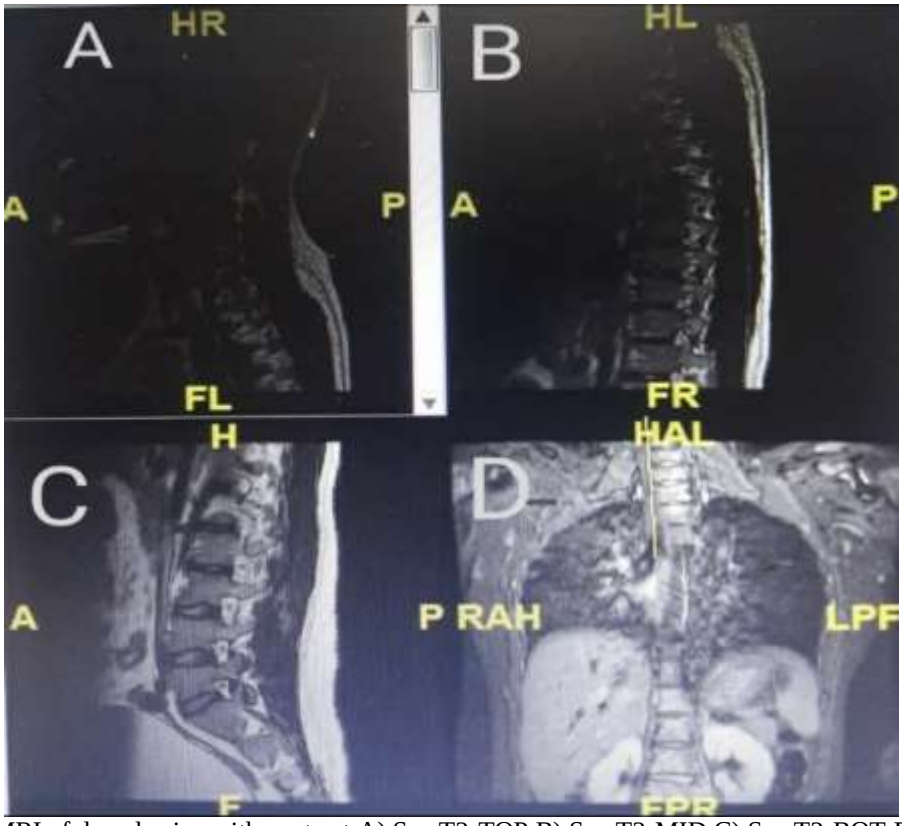

Figure.2(a):- MRI of dorsal spine with contrast:A) Sag T2-TOP;B) Sag T2-MID;C) Sag T2-BOT;D) COR-STIR.

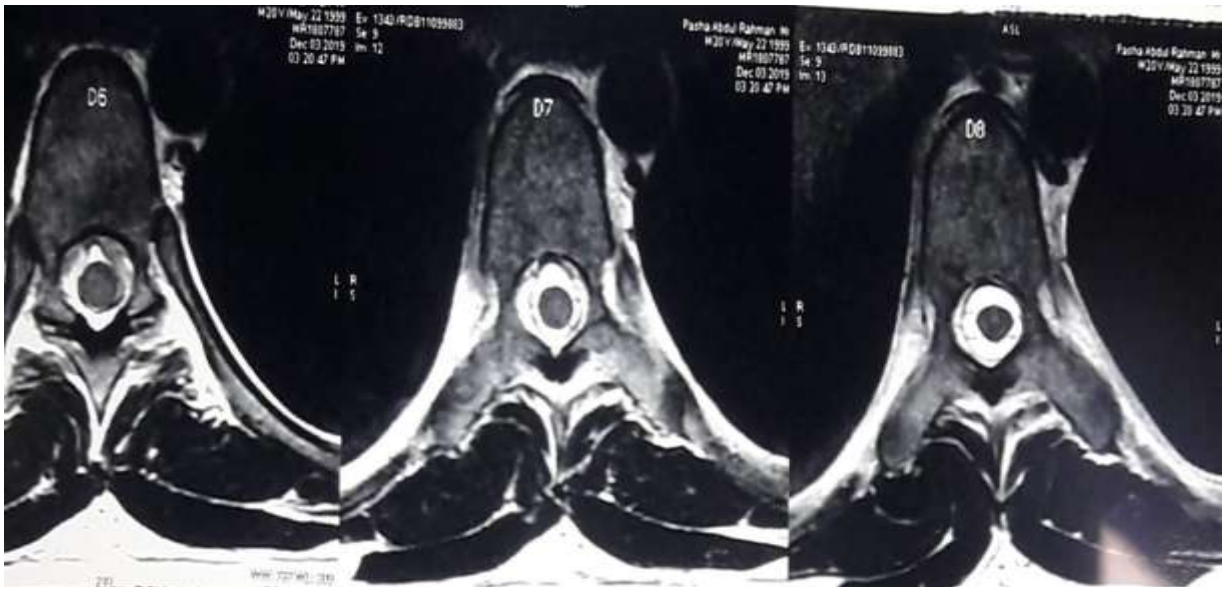

Figure.2(b):- MRI of dorsal spine with contrast showing soft tissue mass from D6 to D8 producing gross compression over the spinal cord.

Figure.2(c):- T2W/T/STIR epidural soft tissue mass is seen from D6 to D8 producing gross compression over the spinal cord.

MRI of lumbar spine with contrast revealed: a)Diffuse altered marrow signal intensities involving lumbo-sacral vertebrae and their appendages and pelvic bones. Partial central wedging of L2, L3 vertebrae(Fig.3a). After contrast administration lumbo-sacral vertebral body marrow shows heterogeneous enhancement- suggestive of metastatic lesions.

Anterior epidural soft tissue mass is seen in the spinal canal at L3 level producing moderate compression over the transiting spinal nerve roots. Paravertebral soft tissue mass is also seen at the level of L3 with infiltration of PSO as muscle on left side. After contrast administration the epidural soft tissue mass shows moderate heterogeneous enhancement- suggestive of metastatic lesions.

Epidural soft tissue mass also seen at the left lateral aspect spinal canal at the level of L1 and mass is extending through the left L1-L2 neural foraminae(Fig.3b). Enhancing soft tissue mass also seen in the posterior spinalis muscle at L1 level on left side. After contrast administration epidural soft tissue mass at L1 level shows moderate heterogeneous enhancement and producing moderate compression over the conusmedullaris on the left side – suggestive of metastatic lesions.

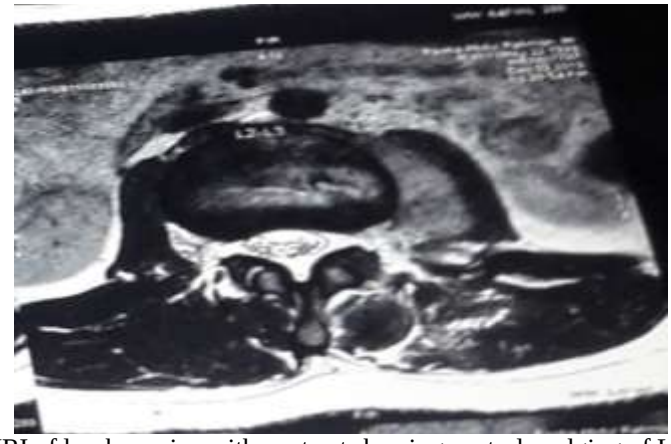

Figure3(a):- MRI of lumbar spine with contrast showing central wedging of L2, L3 vertebrae.

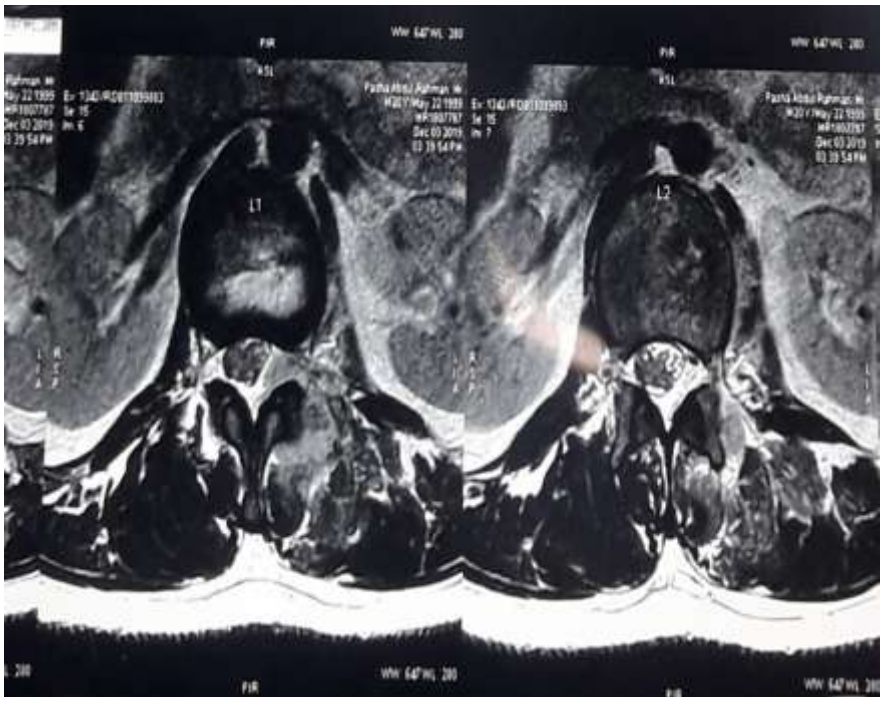

Figure 3(b):- MRI of lumbar spine with contrast showing epidural soft tissue mass extending through the left L1-L2 neural foraminae.

Based on the MRI reports which showed D6-L1 extradural mass with cord compression, a surgical intervention (D6-L1 laminectomy and surgical decompression) was offered to the patient and the family. However after a full consideration of surgical vs non surgical treatment options, the decision was made to persue chemotherapy and radiation. Now, he was planned for Third line chemotherapy with Gemcitabine + Docetaxel cycles (Inj. Gemcitabine 1200mg IV on day 1 and 8, and Inj.Docetaxel35mg on day 8, repeated at 21 days intervals until any evidence of treatment failure, followed by subsequent administration of Granulocyte colony stimulating factor (G-CSF) which help the immune system recover from side effects of chemotherapy.

Due to progressive residual disease, prognosis of this patient with metastases is poor. combination of chemotherapy is mainly used, however the efficacy is still uncertain. The patient was advised to continue the follow-up visits after every chemotherapy, moreover good supportive care and radiation therapy was planned further.

Discussion:-

Ewing's sarcoma is the second most common malignant bone tumor in young age group.[8,9] In the pelvic bones, it is the most common primary malignant tumor. The cell of origin is unknown, but is thought to arise from a stem cell precursor.[10]Clinically, there is a well known delay in diagnosis. When the pelvic bones are involved, poorly localisedpain and a progressive limp are common. 20% of patients have metastases at the time of diagnosis, generally involving the lungs and other bones.

A review of published literature revealed multiple cases of patients presenting with benign appearing long bones lesions with a subsequent pathology diagnostic for Ewing's sarcoma. A delay in early symptoms and diagnosis is quite common, particularly of pelvic tumors in which this mass is not palpable until it is quite large.[11,12]

This patient presented with lower abdominal pain, swelling, weakness of both lower limbs every 3 days, weight loss, restricted hip movements, neurological signs such as cord compression as seen in the MRI of spine and fever. Laboratory investigations in this case revealed increase Erythrocyte sedimentation rate (ESR), WBC's show mild leukocytosis, elevated serum procalcitonin(0.30 ng/ml), Tumor markers CA-125 and LDH were raised. Chest X-ray, ECG and 2D-Echo were normal. CNS spread is rare. In pelvic lesions CT and MRI were more informable which were useful in planning treatment.

Treatment protocols for this patient was based on size, site, stage of tumor and histopathologic response to chemotherapy. Radical resections or removing the entire epidural space may not be feasible. The role of surgery in pelvic Ewing's sarcoma is contraversial, because local control is difficult to achieve and mortality is high and Ewing's sarcoma in the pelvis are more prone to recur than in other sites.
In two intergroup studies, surgery resulted in a better prognosis and lower recurrence rate in patients with primary pelvic tumor. In our study, patient was planned to undergo D6-L1 laminectomy due to severe cord compression but owing to poor prognosis the decision was made to continue chemotherapy and radiotherapy. With the advent of modern chemotherapy, control of disease have become more essential with increased long term survival rates. The best results are achieved when chemotherapy is used both (before and after) radiotherapy and surgical treatment.

Ifosfamide has emerged as a very effective chemotherapeutic agent especially in patients resistant to other drugs. In one study of 144 patients, it was considered to be effective for Ewing's sarcoma occuring inside, rather than outside the pelvis. Moreover previously chemotherapy comprised varying regimens of induction and maintenance therapy including Vincristine, Adriamycin, Cyclophosphamide and Actinomycin-D. Currently, Ifosfamide replaced cyclophosphamide with the addition of Etoposide to the cycles of maintenance chemotherapy. Nonetheless, maximum tolerable doses of chemotherapy with supportive agents like G-CSF (Granulocyte colony stimulating factor) commonly known as Filgrastim should be used with effective radiotherapy planning.

Radiation therapy alone results in local control rate of 65-75%. If chemotherapy is added to adequate radiation, this figure raises to 90-95%.[13]The prognosis and survival of patients in this location (pelvis) are much less favourable than for patients with tumors of the extremities. Adult patients with metastatic ewing's sarcoma have a 5 year overall survival of less than 25%.[14]Another retrospective study of 300 patients, showed a 65.2% five-year survival rate overall. It also showed a 78.6% five-year survival rate for those with localized disease and a 28.1% five-year survival rate for patients with extra- pulmonary metastasis [15]. Unfortunately, this patient presented with primary lesions in the spinal cord, as well as widespread lung metastasis.

Conclusion:-

Tumors of pelvis have a poorer prognosis when compared with other sites. Whether this is related to the challenge of achieving local control or the proximity to critical deep structures remains to be elucidated. The role of surgery in treating Ewing's sarcoma is controversial. However, the use of chemotherapy in conjunction with surgery or radiation therapy to treat metastatic disease has substantially improved survivals. Tumors of the pelvic bones have the lowest survival rates. The treatment plan should be individualized for each patient, which should be based on age, location, stage, size of the tumor and response to therapy. A multidisciplinary tumor board is absolutely essential and weekly meetings mandatory to individualize the treatment scenario.

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