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RESEARCH ARTICLE

BONE CANCER- CURRENT PHARMACOTHERAPEUTIC APPROACH.

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Abstract

Bone cancer is a malignant (cancerous) tumor of the bone that destroys normal bone tissue. Malignant tumors that begin in bone tissue are called primary bone cancer. Primary bone cancer is far less common than cancer that spreads to the bones. Types of Primary bone cancer are Osteosarcoma, Chondrosarcoma. Diagnostic tests may include the following:-X-rays**,** Bone scan**, C**omputed tomography (**CT** or CAT) scan, Magnetic resonance imaging (MRI), Angiogram**.** Treatment options depend on the type, size, location, and stage of the cancer, as well as the person's age and general health. Treatment for bone cancer includes Surgery, Chemotherapy, Radiation therapy, and Cryosurgery. Surgery is one of the main treatments for primary bone cancers and is very specialized treatment. Chemotherapy works very well for some types of bone cancer, particularly Ewing's sarcoma. Radiotherapy called Intensity modulated radiotherapy (IMRT) to treat bone cancer. Cryosurgery is used to treat some types of low-grade cancerous and noncancerous tumors of the bone & is sometimes used instead of conventional surgery to destroy the tumor. Regular follow-up care ensures that changes in health are discussed and that problems are treated as soon as possible. Participation in clinical trials is an important treatment option for many people with bone cancer. NCI, a part of the National Institutes of Health, is sponsoring clinical trials in many hospitals and cancer centers around the country. Several cases of long bone giant cell tumor have been reported in the literature. We report the case of a patient with a giant cell tumor in the distal ulna. This is very unusual, with a reported incidence of 0.45 to 6%. A 17-year male presented with a painful swelling of the left wrist. After performing an instrumental examination, a diagnosis of distal ulna giant cell tumor was made. The tumor was treated with an intralesional curettage, phenol application and bone grafting. This tumor may have a good prognosis if it is diagnosed early and radically treated. It is important to be aware of atypical cancer localizations in order to perform a proper diagnosis.

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Introduction:-

BONE CANCER-Is defined as the abnormal growth that are found in the bone which is affected. The growth may be malignant or may be benign[1].

The bone tumor can be divided into two type's i.e.

- Primary bone tumor
- Secondary bone tumor

Primary bone tumor-this arises or orginates from the bone.

Secondary bone tumor-this arises from other areas of body and then also starts spreading to the bone.

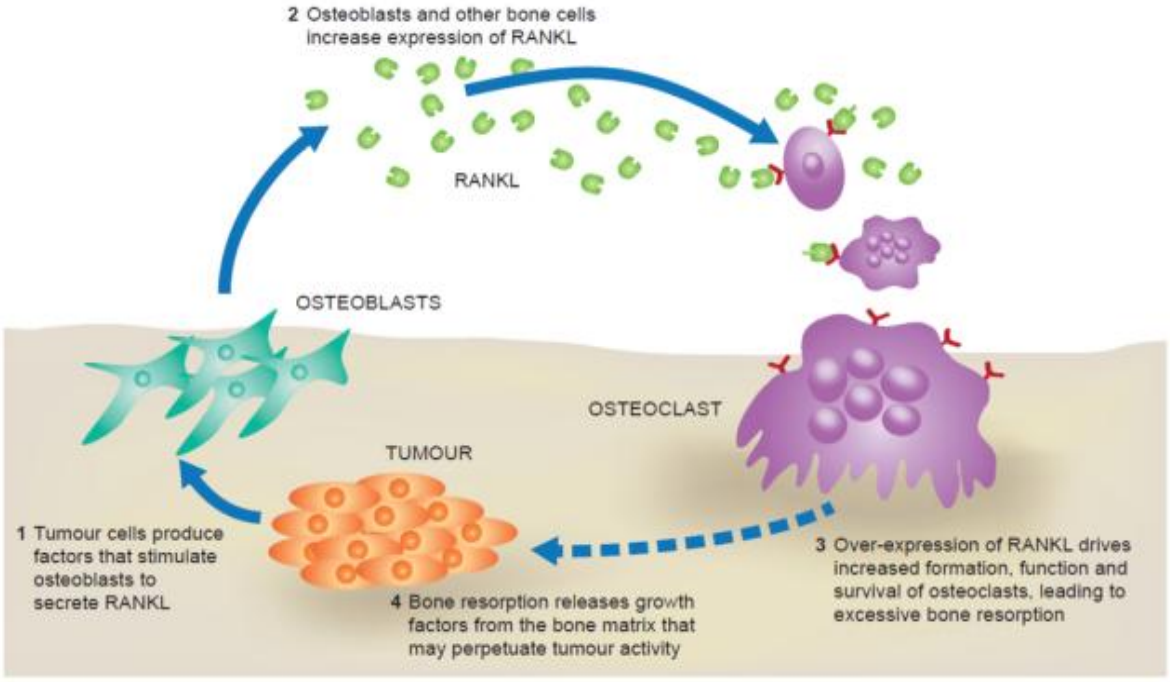


Figure 1:- Vicious cycle of bone destruction in metastatic bone.

Epidemiology:-

he primary bone cancer involves less than 0.02 %of cancer. As per the analysis done by the Surveillance, Epidemiology and End Results Cancer Statistics Review of the National Cancer Institute[2], they have an estimation of that 2,810 men and women will be diagnosed with and 1,490 will die of cancer of bones and joints in 2011.In UNITED STATES the malignancies diagnosed accounted for 0.2%of bone sarcomas.

Variable in Cox regression model	Deaths/PYs	HR	95% CI
Bone metastasis at or subsequent to diagnosis			
None	83,133 / 132,988	1.0 (referent)	-
Yes, without SREs	11,482 / 5,382	2.4	(2.4, 2.5)
Yes, with SREs	12,099 / 5,302	2.4	(2.4, 2.5)
Age at cancer diagnosis			
65-69	19,320 / 33,628	1.0 (referent)	-
70-74	26,334 / 41,783	1.1	(1.1, 1.1)
75-79	27,519 / 37,163	1.3	(1.2, 1.3)
80-84	20,084 / 21,275	1.5	(1.5, 1.6)
85+	13,457 / 9,824	2.0	(1.9, 2.0)
Race/ethnicity			
White	90,441 / 123,502	1.0 (referent)	-
African American	8,870 / 10,262	1.1	(1.1, 1.1)
Hispanic American	3,390 / 4,112	1.0	(1.0, 1.1)
Other	4,013 / 5,797	0.9	(0.8, 0.9)
Gender			
Men	58,406 / 70,875	1.0 (referent)	-
Women	48,308 / 72,798	0.9	(0.9, 0.9)
Stage at cancer diagnosis			
Distant	56,564 / 36,078	1.0 (referent)	-
Localized	14,144 / 53,818	0.3	(0.3, 0.3)
Regional	24,092 / 44,646	0.5	(0.5, 0.5)
Unstaged	11,914 / 9,131	1.0	(1.0, 1.0)
Charlson comorbidity score			
0	85,690 / 122,151	1.0 (referent)	-
1	2,274 / 3,030	1.1	(1.0, 1.1)
2	6,594 / 7,647	1.2	(1.2, 1.2)
3+	12,156 / 10,844	1.4	(1.4, 1.5)

*HRs for each variable are adjusted for all other variables in the table

Table 1:- Epidemiology and End Results Cancer Statistics

Etiology(risk factors):-

The risk factors for the bone cancer includes as following-

- In general nobody knows the true cause of bone cancer.
- Patients with long term inflammatory diseases.
- Radiotherapy
- Paget's disease
- Heriditary renoblastoma
- Genetically heridited(close relatives)
- Li-fraumeni syndrome.

Pathophysiology:-

Normal bone remodeling maintains an appropriate balance between the action of osteoclasts (bone-resorbing cells) and osteoblasts (bone-forming cells). Skeletal malignancies, including bone metastases, disrupt the OPG-RANKL-RANK signal transduction pathway and promote enhanced osteoclast formation3, thereby accelerating bone resorption and inducing bone loss. This osteolysis in turn leads to the release of bone-derived growth factors, contributing to a “vicious cycle” in which interactions between tumor cells and osteoclasts not only lead to increased osteoclastogenesis and osteolytic activity, but also aggressive growth and behavior of the tumor cells. The osteolytic complications associated with bone metastases are caused by tumor-induced alterations of the OPG-RANKL-RANK system, which are accompanied by enhanced bone resorption and disassociated from counterbalancing bone formation by osteoblasts4.

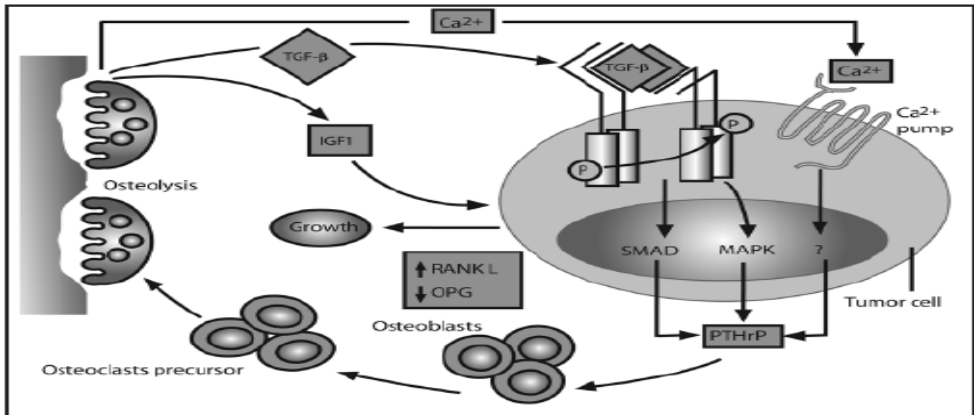
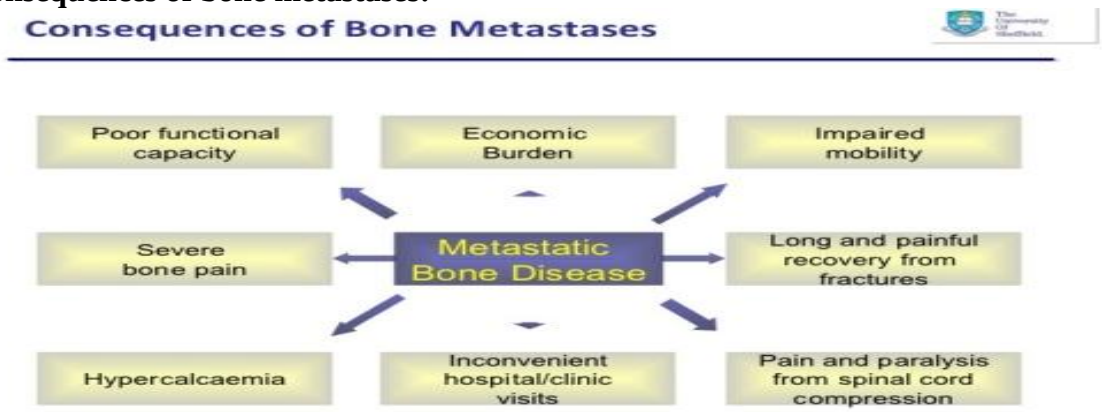


Figure2: Physiology of osteolytic metastases. Release of TGF-_) and IGF1 and increased concentrations of Ca2+ contribute to a "vicious cycle" in which interactions between tumor cells and osteoclasts not only lead to increased osteoclastogenesis and osteolytic activity, but also aggressive growth and behavior of the tumor cells.

Consequences of bone metastases:-



Lab investigations:-

Tests that may be done include:- Alkaline phosphatase blood level,Serum phosphorus, Ionized calcium, Serum calcium,Bone biopsy,Bone scan,Chest x-ray,CT scan of the chest,MRI of the bone and surrounding tissue,X-ray of bone surrounding tissue.This disease may also affect the results of the following tests:-Alkaline phosphatase isoenzyme,Blood calcium level, Parathyroid hormone(PTH),Blood phosphorus level,ESR, Glucose tolerance test, CRP,PSA, PAP, Electrophoresis and Urinary Bence Jones protein[5].

Treatment of bone cancer:-

The treatment includes as follow-

Treatment options depend on the type, size, location and stage of the cancer, as well as the person's age and general health. The treatment options for the bone cancer includes as follows-

- Surgery
- Chemotherapy
- Radiation therapy
- Cryosurgery
- Genetics
- Analgesics
- Endocrine therapy
- Biologic therapy
- Radiopharmaceuticals
- Biphosphonates
- Supportive care

Surgery:-

This is the usual treatment for bone cancer[6]. Here the procedure is carried out by removing the entire tumor with negative margins. There are different types of surgeries done. They are as follows

- Surgery for cancer that does not affect the limbs.
- Surgery for removing the cancer while sparing the limb
- Surgery for removing a limb

Surgery for cancer that does not affect the limbs -is an surgical procedure performed for removing the bone and some nearby tissue if the bone cancer takes place in the bones apart from legs and arms[7]. The bone which is removed is then replaced with a part of bone from different place of the body or can be replaced by metal prosthesis[8].

Surgery for removing the cancer while sparing the limb-here the surgical procedure is performed by sparing the limb if the bone cancer can be separated from other tissues and nerves. Then the lost bone can be replaced with other bone from the body or metal prosthesis[9].

Surgery for removing the limb-this surgery is performed when the bone cancer is large by removing a part or all part of a limb. This is also done when it is located on very complicated point on the bone.

Chemotherapy:-

It is the use of anticancer drugs to kill cancer cell. It is the treament which makes the use of chemicals for destroying cancer cells. This drugs or chemicals are given through a vein which travels in the entire body. Radiation therapy is often combined with the chemotherapy for shrinking the cancer to a manageable size so as to enable a surgeon to carry out a limb-sparing surgery. Currently chemotherapy is not being used to treat chondrosarcoma[10].

The main chemotherapy drugs used in treatment of bone cancer are

DOXORUBICIN
CISPLATIN
CARBOPLATIN
ETOPOSIDE
IFOSFAMIDE
CYCLOPHOSPHAMIDE
METHOTREXATE
VINCRISTINE

Usually, several drugs (2 or 3) are given together. For example, common combination is cisplatin and doxorubicin.

Side effects of chemotherapy:-

Chemo kills cancer but it will also damage some normal cells. The side effects of chemo depend on the type of drugs, the amount taken, and the length of time they are taken.

Some common temporary side effects include -

- Nausea and vomiting
- Loss of appetite
- Hair loss
- Mouth sores

Drugs used in chemotherapy and their side effects:-

Doxorubicin:-

- Cardiomyopathy [11] leading to congestive heart failure
- Thyphlitis[12]
- Some may develop PPE characterized by skin eruptions on the palms of the hand or soles of the feet, swelling, pain and erythema.
- Dyspigmentation[13]

Cisplatin:-

- Nephrotoxicity
- Neurotoxicity(common neurological side effects include visual perception and hearing disorder)
- Nausea and vomiting
- Ototoxicity

- Electrolyte disturbance
- Haemolytic anemia

Carboplatin:-

- Relative to the cisplatin, the greatest benefit of carboplatin is that its reduced side effects, particularly the elimination of nephrotoxic effects.
- Nausea and vomiting are less severe and more easily controlled.
- Its main drawback is myelosuppressive[14] effect.(usually occurs 21-28 days after the first treatment, after which the blood cell and platelet levels in the blood begin to stabilize ,often coming close to its pre-carboplatin levels.

Etoposide:-

Common side effects-

- Low blood pressure
- Hair loss
- Pain and burning at the IV side
- Constipation and diarrhea
- Metallic food taste
- Bone marrow suppression leading to -

i. decreased white blood cells
ii. low red blood cell counts
iii. low platelet counts

Less common side effects include-

- Nausea and vomiting
- Rash
- Allergic type reactions
- Fever(occuring due to IV administration and not due to infection)
- Mouth sores
- Acute myeloid leukaemia
- When given with warfarin it may cause bleeding.

Ifosfamide:-

- Encephalopathy[15]
- Normal anion gap acidosis specifically renal tubular acidosis.

Cyclophosphamide:-

- Nausea and vomiting
- Bone marrow suppression
- Stomach ache
- Haemorrhagic cystitis
- Diarrhea
- Alopecia
- Lethargy
- Cyclophosphamide is itself carcinogenic and may increase the risk of developing
- lymphomas
- leukaemia
- skin cancer
- transitional cell carcinoma of bladder or other malignancies
- Cardiotoxicity is major problem with oncology patients treated with higher dose regimens.
- High dose IV can cause syndrome of inappropriate antidiuretic hormone secretion and a potentially fatal hyponatremia when compounded by IV fluids administered to prevent drug-induced cystitis[16].

Methotrexate:-

- Common include-
- Black tarry stools
- Blood in urine or stools
- Bloody vomit
- Diarrhea
- Joint pain
- Reddening of the skin
- Sores in the mouth or lips
- Stomach pain
- Swelling of the feet or lower legs

Vincristine:-

- Blurred or double vision
- Constipation
- Difficulty in walking
- Drooping eyelids
- Headache
- Jaw pain
- Joint pain
- Lower back or side pain
- Numbness or tingling in fingers and toes
- Pain in fingers and toes
- Pain in testicles
- Stomach cramps
- Swelling of feet or lower legs
- Weakness

Radiotherapy:-

It is also known as radiation therapy which involves the use of high energy x-rays to kill cancer cells. This treatment may be used in combination with surgery. It is often used to treat chondrosarcoma[17,18,19], which cannot be treated with chemotherapy, as well as EFTs. It is also considered in patients who refuse surgery. The high power beam of energy are targeted at precise points in the body. Radiation may also be used after surgery if cancer cells were present in the edges of removed tissue[20].

Types-

- **Intensity modulated radiation therapy**[21]
- **Proton beam radiation**[22]

Side effects of radiation therapy:-

Common side effects include-

- Fatigue
- loss of appetite
- skin changes in the area being treated, ranging from redness and hair loss to blistering and peeling
- low blood counts
- nausea, vomiting and diarrhea(these are more common if radiation is given to the belly)

Cryosurgery:-

It is the use of liquid nitrogen to freeze and kill cancer cells. This technique is used sometimes in place of conventional surgery to destroy the tumor[23].

Genetics:-

In addition to clinical trials, researchers are making progress in learning about the causes of bone tumors. For example, changes to a certain part of chromosome 6 have been found in chordomas. Changes the *COL2A1* gene, which codes for a major form of collagen found in cartilage, have been found in many chondrosarcomas[24]. Further, more information about the DNA changes that cause bone cancers will eventually lead to treatments aimed at these gene defects[25].

ENDOCRINE THERAPY:-

Tamoxifen, aromatase inhibitors, ovarian suppression.

***Biologic therapies*:**-Herceptin**,T**ykerb, Avastin

***Analgesics*:**-Pain control medications

- Tylenol, NSAIDs (ibuprofen), narcotics, steroids
- Success can be limited by side effects.

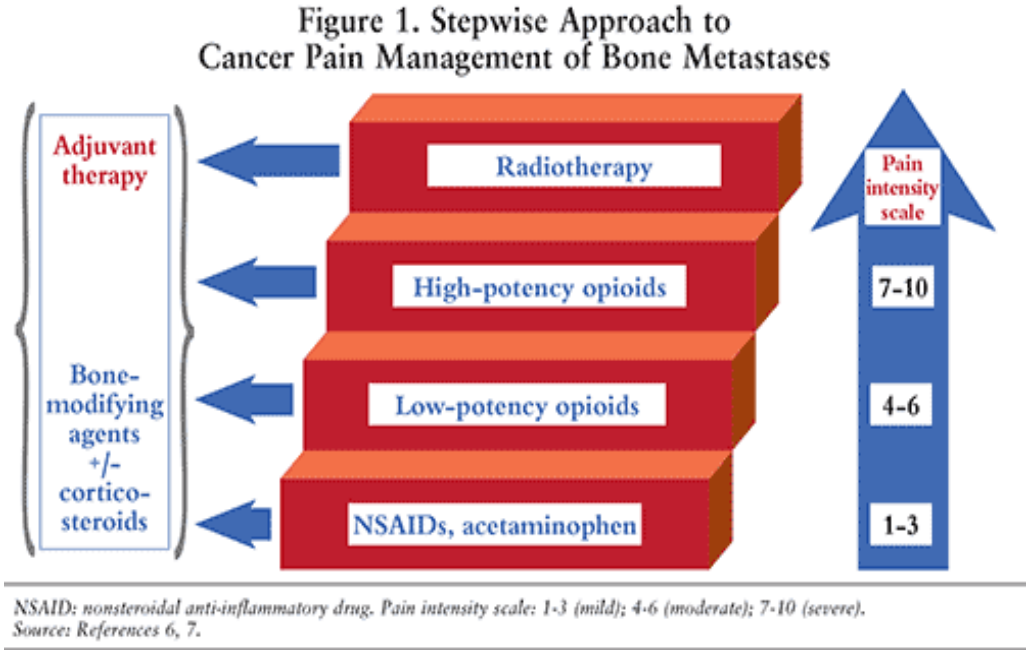


Figure 1:- Stepwise approach to cancer pain management of Bone Metastases

Radiopharmaceuticals:-

Strontium-89 and samarium-153 are radioactive particles travel directly to tumor in bone, & Can reduce pain refractory to other measures, but they are infrequently used[26].

Biphosphonates:-

Bind to and inhibit osteoclast action

– Inhibit bone breakdown
– Prevent bone damage
– Improve bone density and strength

Recommended for almost everyone with breast cancer bone metastases

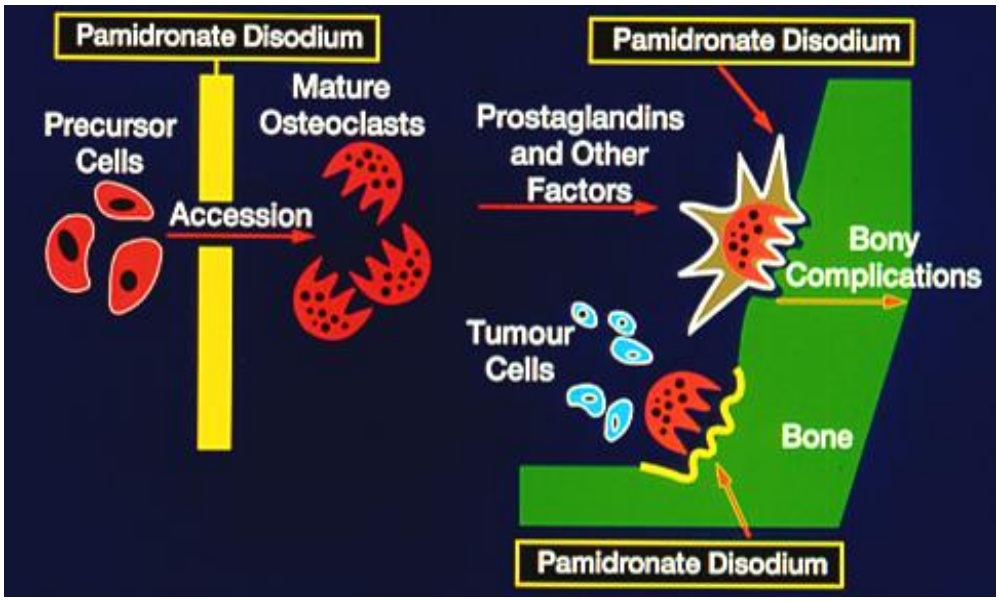


Figure 5:-Biphosphonate pharmacology: Mode of action

Supportive care:-

Supportive care is critical.It includes managing the bone diseases, anaemia, infections, kidney failure, and pain associated with multiple myeloma[27].

- Biphosphonates(medication)can prevent destructive bone lesions and spine fractures.
- Erythropoietin or occasional blood transfusions can manage anaemia.
- Antibody infusions and vaccination scan help patients with recurrent infections.
- Corticosteroids and hydration can be used to treat high blood calcium concentrations(from bone loss) and dehydration[28].
- Narcotics can decrease the pain associated with bone lesions.
- Operative intervention may be required to stabilize and control the pain associated with bone fractures29.

What happens after treatment for bone cancer?

Bone cancer treatment may remove or destroy the cancer. Completing treatment can be both stressful and exciting. The patient may have fear of cancer recurrence after the treatment. This is a very common concern in people who have had cancer. Many cancer survivors have learned to live with this uncertainty and are leading full lives. For some people, the cancer may never go away completely. These people may get regular treatments with chemotherapy, radiation, or other therapies to try to help keep the cancer in check. Learning to live with cancer that does not go away can be difficult and very stressful. It has its own type of uncertainty[30].

Follow-up care:-

When treatment ends, the doctors will keep a watch on patient. It is very important to follow –up because doctors will look for signs of cancer recurrence and treatment side effects. Almost any cancer treatment can have side effects. Some may last for a few weeks to months, but others can last for rest of the life. Following extensive bone surgery, a program of rehabilitation and physical therapy will be an important part of helping patients regain as much of the mobility and independence as possible.

Can I get another cancer after having bone cancer?

Survivors of bone and joint cancers can get any type of second cancer, but they have an increased risk of getting another bone or joint cancer (this is different than the first cancer coming back). Sometimes this is the same kind of cancer as the original tumor, but it can be a different type. For example, someone who had a chondrosarcoma[32] can get an osteosarcoma. Sarcoma of the soft tissues is also seen more often than expected after a cancer or the bone or joints. Survivors of bone and joint cancer also have an increased risk of:

• Lung cancer
• Esophagus cancer
• Stomach cancer
• Colorectal cancer
• Liver cancer
• Pancreas cancer
• Acute myeloid leukemia (AML)
The risk of leukemia is linked to treatment with chemotherapy.

Follow-up after treatment:-

After completing treatment for bone cancer, the patient should visit the doctor regularly. The patient should undergo the tests to find out whether the cancer has recurred if they have any symptoms. Survivors of bone cancer should follow the guidelines as per American Cancer Society for the early detection of secondary cancer. The Children's Oncology Group has guidelines for the follow-up of patients treated for cancer as a child, teen, or young adult, including screening for second cancers. All patients should stay away from tobacco products. Smoking increases the risk of many cancers and might further increase the risk of some of the second cancers seen after bone cancer. To help maintain good health, survivors should also:
• Achieve and maintain a healthy weight
• Adopt a physically active lifestyle
• Consume a healthy diet, with an emphasis on plant foods
• Limit consumption of alcohol to no more than 1 drink per day for women or 2 per day for men These steps may also lower the risk of some cancers**.**

Lifestyle changes after treatment for bone cancer:-

Doctors cannot change the fact that the patient have cancer but, can make their life better. Patient should make healthier choices by the following ways:

- Eating better
- Exercise can improve both the physical and emotional health.
- It improves your cardiovascular (heart and circulation) fitness. .
- It makes the muscles stronger.
- It reduces fatigue and helps in increasing the energy levels
- It can help lower anxiety and depression.
- It can make the patient feel happier.
- In long term, regular physical activity plays a role in helping to lower the risk of some cancers, as well as having other health benefits**.**

If treatment for bone cancer stops working:-

If treatment is not successful, the disease may be called advanced or terminal cancer. If cancer keeps growing or comes back after one kind of treatment, it is possible that another treatment plan might still cure the cancer, or at least shrink it enough to help you live longer and feel better. If it does not respond to any treatment the cancer tends to become resistant. Then, the doctors will compare the advantages and disadvantages of the new treatments. When the doctor opt for new treatment, it is not likely to improve the health or change the outcome or survival of patients. The doctor can estimate how likely it is the cancer will respond to the treatment patients are considering. It is important to think about and understand the reasons for choosing the plan. The patient should receive treatment for symptoms such as nausea or pain. This type of treatment is called palliative care.

Palliative care helps relieve symptoms, but is not expected to cure the disease. It can be given along with cancer treatment, or can even be cancer treatment. The difference is its purpose - the main purpose of palliative care is to improve the quality of patient's life, or help them feel as good as possible. This may also requires use of drugs.

Case report on bone cancer:-

Introduction:

A 17-year male presented with a painful swelling of the left wrist. After performing an instrumental examination, a diagnosis of distal ulna giant cell tumor(GCT) was made. The tumor was treated with an intralesional curettage, phenol application and bone grafting.

Case presentation:-

A radiographic examination of the left wrist was performed in a 17-year male as a result of a direct incidental trauma. No fracture was seen, but an osteolytic area was found in the ulnar meta-epiphysis. The initial diagnosis was 'juvenile bone cyst'. The patient presented with a painful swelling at the wrist dorsal ulnar side, about 2.5 cm, in the absence of any epidermal dyschromias. The skin was elastic and smooth. Wrist examination showed a range of motion (ROM) of 45 ° of extension, 70 ° of flexion, 15 ° of radial deviation and 10 ° of ulnar deviation; pronation, supination and circumduction were painful. Contralateral wrist ROM was normal. The diagnosis of 'juvenile bone cyst' did not seem right and a second radiographic examination was performed. At this time, a multilocular osteolytic area inducing an expansion of the distal ulna was seen. A cortical bone interruption was also visible. Although the patient had been the victim of a trauma, this was a poor prognostic sign. Therefore an Magnetic resonance imaging examination was performed. It showed a hypointense signal in the T1 sequences and a hyperintense signal in the short TI inversion recovery (STIR) sequences, characterized by enhancement after contrast administration, due to the presence of newly formed tissue.

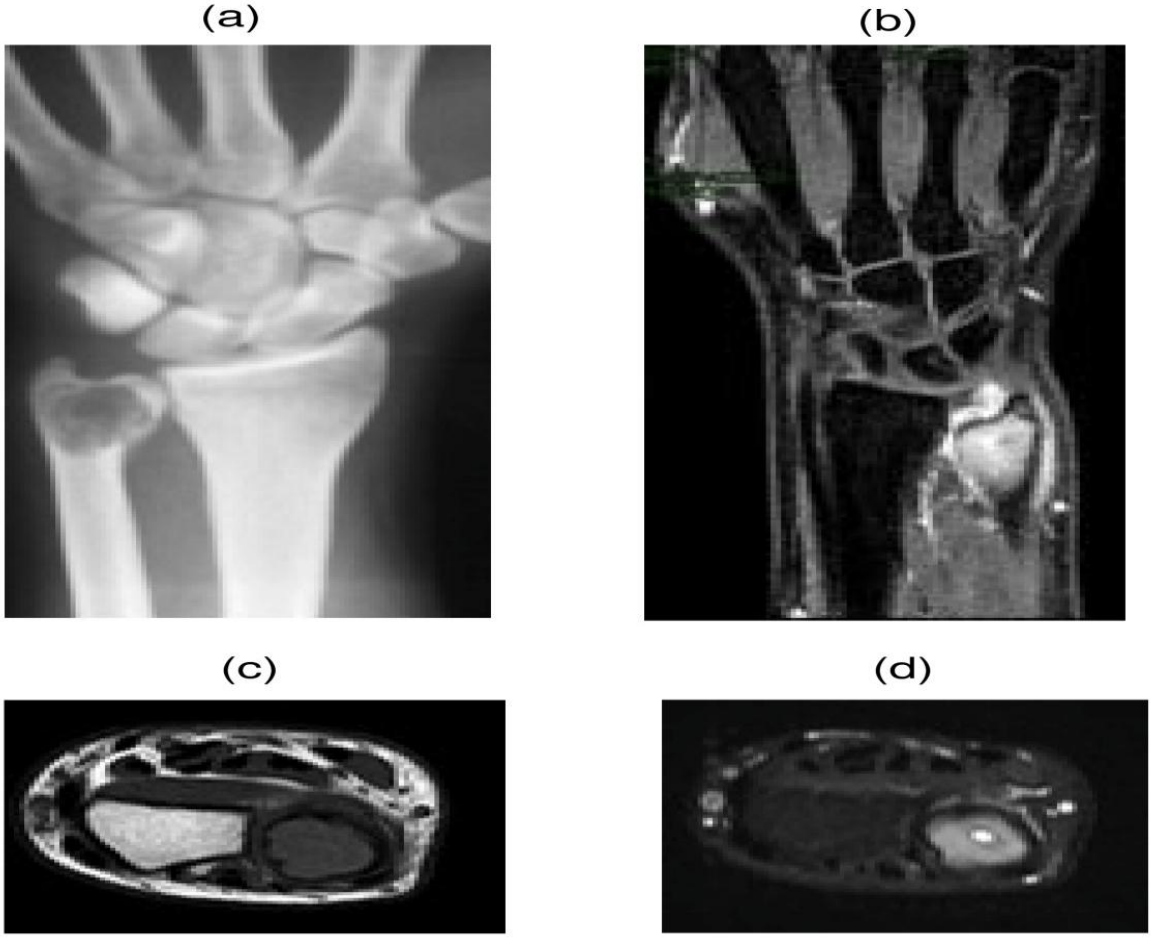


Figure 6:-
X-rays and magnetic resonance imaging with and without contrast.

Discussion:-

- It is a rare tumor, essentially benign, but it may behave unexpectedly, regardless of the results of radiological or histological examinations.
- It is usually located in the long bone meta-epiphysis and it frequently involves the subchondral bone without involvement of the articular surface; however, larger tumors may extend into the metaphysis and, more rarely, into the diaphysis. Proximal tibia, humerus, distal femur and radius are typical sites.
- GCT(Giant Cell Tumor) represents about 3% to 5% of all bone tumors and 21% of benign bone tumors[34,35].

- In 70% of cases, it involves women in the third to fourth decade of life.
- The distal epiphysis of the ulna is an unusual place for a primary bone GCT; in fact, this occurs in only 0.45% to 3.2% of all primary bone GCT's[36,37].
- In the past, these tumors were treated with amputation or large resections and ulterior reconstructions. Currently, surgical treatments are:
    - Intralesional curettage
    - Curettage and bone grafting
    - Cryotherapy of the cavity after curettage
    - Application of phenol after curettage
    - Radiation
    - Insertion of methyl methacrylate cement in the cavity after curettage
    - Resection followed by allograft
    - En-bloc resection with or without reconstruction or stabilization of the ulna and prosthetic reconstruction
    - Embolization of the feeding vessels
- The variables related to the tumor, such as size, location, biological activity, cortical bone destruction or pathologic fracture evidence, determine the treatment [37].
- Although an en-bloc resection radically assaults the tumor, significantly reducing the risk of recurrence, functional outcome is very bad. A simple curettage provides an excellent functional outcome, but with a higher recurrence rate of approximately 40% [34,35,36,37] if compared with the patients who received adjuvant therapy (45% versus 18%).
- Therefore, various adjuvant therapies have been associated with the curettage: phenol, cryotherapy , cement [39,40,41]or polymethyl methacrylate (PMMA) used intraoperatively.
- The recurrence rate ranges from 5% to 8% when cement is used, and approximately 2.3% after cryosurgery [39,40].
- However, it needs to be mentioned that a multicenter study of the Sarcoma Group[43] reported an overall recurrence rate of 17% and claimed that the filling material or the type of adjuvant would not have an absolute impact on recurrence.
- Furthermore, some studies show that the use of an adjuvant would not be necessary in some cases, such as intraosseous GCT [44].
- According to Schajowicz [44], curettage alone is an inadequate oncological procedure, but when it is combined with an adjuvant therapy, it globally provides a better result with respect to one-block excision, especially in terms of functionality.
- Therefore, the correct treatment must achieve a balance between oncological radicality and the restoration of skeletal segment functionality[43,44,45,46].
- Curettage associated with bone grafting has been shown to be effective in many cases[47] In this study it is used with phenol as an adjuvant, because it is capable of causing protein and DNA coagulation, inducing cell necrosis.
- In the present case intralesional curettage was possible because the tumor was a grade II and the reconstruction was carried out with synthetic cancellous bone, due to the young age of the patient[48].

Conclusion:-

Bone metastases are common in advanced breast cancer, and can cause significant symptoms.Multiple systemic and local therapies are available; standard therapy includes monthly zoledronic acid. Better understanding of toxicities can improve the safety of treatment.New agents take advantage of increased understanding of the biology of bone turnover.Women with advanced breast cancer may live with bone metastases for many years, therefore optimizing therapy is crucial. Neoformation bone diagnosis is difficult and requires a great deal of experience, especially in young patients. Osteolytic lesions incidentally found at a long bone epiphysis, can be misinterpreted. The tumor may have a good prognosis if treated early and radically. It is important to know atypical cancer locations in order to perform a proper diagnosis.

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