Diagnosis and management of relapsed osteosarcoma

Essay
submitted for fulfillment of
the master degree in orthopaedic surgery

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2010

بِسْمِ اللّٰهِ الرَّحْمٰنِ الرَّحِيْمِ

وَقُلْ رَبِّ زِدْنِي عِلْمًا

Acknowledgment

I would like to express my deepest gratitude to

Walid Atef Ebeid .dr .Prof

Cairo university for his Professor of orthopaedic surgery faculty of medicine .operation-valuable guidance, kind supervision and his patience and helpful co

And I would like to offer my sincere thanks to

Ahmed Nabil El Ghoneimy .Dr

Lecturer of orthopaedic surgery faculty of medicine Cairo university for his helpful suggestion and co-operation in this work.

Abstract

Although the regimens of chemotherapy improved, about 30 - 35% of osteosarcoma patients however still had local or systemic relapse. The lung, involved in more than 80% of all patients. Surgical remission is critical in the management of these challenging patients**.** Local control was achieved by amputation or by local excision. Treatment at disease recurrence should consist not only of local control with surgery but also systemic treatment, however, the difficulty lies in the number of effective agents of chemotherapy that remain available to these patients. Only 25% of patients are expected to survive 5 years after recurrence and 10-year survival is approximately 20%.

Keywords: osteosarcoma, relapse, treatment, chemotherapy, surgery, prognosis.

Introduction

Osteosarcoma is the most common primary malignant neoplasm of bone in children and adolescents[145]. (A total of 30%–40 %of patients with localized osteosarcoma will develop a recurrence in spite of incredibly aggressive chemotherapy and surgery[16&146]. (Recurrences usually occur as pulmonary metastases or, less frequently, metastases to distant bones or local recurrences[147].

The multidisciplinary approach is maintained in the management of recurrent disease .Complete surgical resection is still key to prolonging life and maximizing the opportunity for long-term survival .Timely surgical resection of all gross pulmonary metastasis is the mainstay of therapy .There is no consensus regarding the optimal particular agent)s (or the overall effectiveness of the chemotherapeutic approach to recurrent disease .Several studies have shown a positive correlation between "second-line" chemotherapy)alternative agents to those used during the initial treatment (and survival[16,148&149].

Radiotherapy is reserved for patients unable or unwilling to undergo surgery, based disease, patients found to have positive or close -patients with pleural margins after resection, or patients with unresectable disease[16].

Ability)and possibility (of achieving a complete resection of metastatic lesions is the most relevant prognostic factor, with)at first relapse (a 5-year survival rate of 20 %to 45 %following complete resection of metastatic pulmonary lesions, and 10 %to 15 %following complete resection of metastases in other sites.

Factors associated with better outcome in recurrent osteosarcoma include solitary pulmonary nodules, a long interval from initial diagnosis and achievement of a second complete remission[150&151].

Aim of the work

To study diagnosis and treatment of relapsed osteosarcoma, clarifying the most appropriate methods of investigation for local and systemic relapse, and the most recent and accepted methods of treatment .

Contents

List of abbreviations

.associated promoter-Basal cell lymphoma 2 **.BAD**

.Basal cell lymphoma **.BCL**

."extra large-cell lymphoma-B"Stands for **.BCLXL**

Core needle biopsy **.CNB**

surgical remission Complete **.CR**

Disease free interval **.DFI**

.DHFR Dihydrofolate reductase

macrophage colony stimulating factor-Granulocyte **.GMCSF**

Fine needle aspiration **.FNA**

Human epidermal receptor 2 **.HER2**

.like growth factor receptor-Insulin **.ILGF receptor**

. Insulin recepyor substrate**.IRS**

. Local recurrence**.LR**

. Mitogen activated kinase**.MAP**

. Mitogen activated protein kinase**.MAPK**

. Mitogen activated extracellular signal regulated kinase**.MEK**

Muramyl tripeptide phosphatidyl ethanolamine **.PE-MTP**

Mammalian target of rapamycin **.mTOR**

derived growth factor receptor-Platelet **.PDGFR**

.Positron emission tomography **.PET**

. Phosphatidyl inositol 3 kinase**.PI3K**

Receptor activator for nuclear factor κ B ligand **.RANKL**

free interval-The recurrence **.RFI**

free survival Recurrence **.RFS**

Standard uptake value **.SUV**

(sometimes referred to as tumor growth factor)Transforming growth factor **.TGF**

Vascular endothelial growth factor**.VEGF**

.Fluorodeoxyglucose **.FDG-18F**

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Introduction

Introduction

Following the introduction of adjuvant chemotherapy, in the early 1970s, the long-term outcome for patients with high-grade osteosarcoma of the extremities has dramatically improved with survival rates rising from 10-15% to 50-60%. [1,2 &3] However, in most of these patients, the surgical treatment was still amputation. In the early 1980s, adjuvant chemotherapy was substituted by neoadjuvant chemotherapy that enabled limb-sparing segmental resections instead of cross bone amputations in most patients.[6,7&8]

Osteosarcoma may metastasize regionally (within the same extremity) or systemically (to other organs, such as the lung). Tumor nodules growing outside the reactive rim but within the same bone or across a neighboring joint are termed "skip lesions" and represent regional intraosseous or transarticular metastases, respectively.[Fig1] Systemic metastases have a predilection for the lungs. The bones are the second most common site of metastasis and usually become involved after pulmonary metastases have occurred. Distant bone metastases represent the latest stage of disease and are associated with the poorest prognosis.[12, 13&14] After primary treatment of osteosarcoma patients should undergo a physical examination and radiographic (chest X-ray or CT scan) evaluation at 3-month intervals for 3 years, 6-month intervals through 5 years, and 8–12 month intervals through 10 years .[15] Because of the risk of long-term toxicity and possibility of late relapses,[16,17&18] follow-up should continue into the second decade of disease-free survival.[33] Although the regimens of

chemotherapy improved, about 30 - 35% of these patients however still had local or systemic relapse.[19]

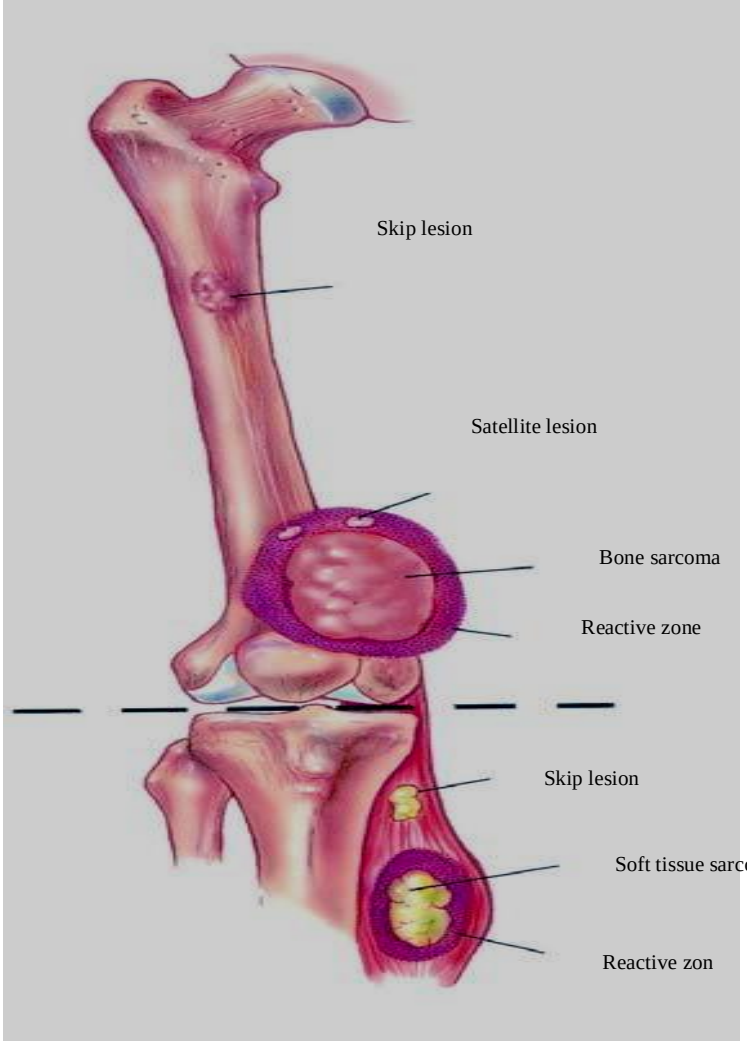

Figure 1. Biologic growth pattern of osteosarcomas. Locally, an-osteosarcoma grows radially and compresses the surrounding soft tissues, forming a pseudocapsular layer referred to as the "reactive zone." The reactive zone contains microscopic extensions of the main tumor mass, termed "satellites." Regional metastases within the same bone (transarticular) are referred to as "skip metastases." An osteosarcoma can also metastasize to distant sites, most commonly the lungs and other bones.[25]

The patterns of relapse in osteosarcoma:

The lung, involved in more than 80% of all patients, and as the only site in nearly two thirds of all patients, only 20% of patients with lung metastases had additional disease, 50% of patients with bone metastases had additional disease.[16] More of the pulmonary recurrences occurred slightly unilaterally, the presence of multiple nodules was more common than single nodules .[21]

The sites of local recurrence:

- 20% arose in bone
- 80% in soft tissue[22]

The patterns of relapse in second and subsequent recurrences:

- The proportion of patients with bilateral involvement decreased with increasing numbers of recurrence.
- Increase in the proportion of patients with metastases outside the lungs or skeleton[32]

The time of relapse depends on :

- Serum alkaline phosphatase value.
  (The median interval from initial diagnosis until first recurrence was 25 month for normal value versus 18 month for high valye)
- The type of chemotherapy.
  (The median interval from initial diagnosis until first recurrence was 24 month for neoadjuvant chemotherapy versus 16 month for adjuvant chemotherapy)
- Histological response to preoperative treatment.