Clinical Oncology 25 (2013) 19–26

Contents lists available at SciVerse ScienceDirect

Clinical Oncology

journal homepage: www.clinicaloncologyonline.net

Overview

Management of Bone Tumours in Paediatric Oncology

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Received 10 November 2009; received in revised form 7 March 2012; accepted 17 May 2012

Abstract

The management of bone tumours in paediatric oncology requires careful multidisciplinary planning due to the need for multimodal therapy approaches. The non-specific symptoms often lead to a delayed definitive diagnosis of a bone tumour. Imaging procedures are of major importance for an individualised and optimised treatment planning. They have to be carried out before any surgery, including biopsies. The introduction of multi-agent chemotherapy has led to a significant improvement in survival rates in patients suffering from Ewing's sarcomas and osteosarcomas. However, local therapy still remains indispensable in order to achieve long-term survival. For osteosarcoma, surgery remains the only adequate local therapy modality. Radiotherapy may be considered if surgery is not feasible. In these cases, high radiation doses need to be applied. The choice for local therapy modality is not as clear in patients with Ewing's sarcoma. Today, surgery is often preferred if a wide or at least marginal resection can be carried out. Additional radiotherapy is advised in patients with marginal/intralesional resection or poor histological response to induction chemotherapy. Definitive radiotherapy is recommended for inoperable lesions. In the future, new radiotherapy approaches, such as intensity-modulated radiotherapy or proton therapy, may yield better results with minor risks of late effects.

Key words: Bone sarcoma; chemotherapy; Ewing's sarcoma; osteosarcoma; radiation; surgery

Statement of Search Strategies Used and Sources of Information

Published trials, studies and series were identified using the PubMed® database. The key words 'bone sarcoma, Ewing's sarcoma, Ewing's tumo(u)r, osteosarcoma, chemotherapy, radiation, radiotherapy and surgery' were used. Cross-referencing, using the references of all identified studies, helped complement the computer-aided searches. This overview summarises reports that illustrate important principles or philosophies. Due to the large number of reports it was not possible to include all publications related to this extensive subject.

Introduction

Primary malignant bone (associated) tumours are relatively uncommon, representing about 6% of all childhood malignancies [1]. Of these, osteosarcoma and Ewing's sarcoma are the most common and comprise 90% of paediatric malignant bone tumours. Significant improvements in overall survival have been achieved with the use of multi-agent chemotherapy in addition to local therapy approaches, namely surgery and radiotherapy in these patients. This overview comprehensively summarises the available information on the management of bone tumours in childhood and adolescence.

Methods

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0936-6555/$36.00
http://dx.doi.org/10.1016/j.clon.2012.07.010

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Results

Presentation at Diagnosis

Primary malignant bone tumours are rare. The two most common types, osteosarcoma and Ewing's sarcoma, have a peak incidence in the second decade of life and an annual incidence of 2 and 0.8 per million population, respectively [2]. Regional pain, alone or in combination with a palpable mass, is the main reason for patients to consult a medical doctor. Due to non-specific symptoms the definitive diagnosis of a bone tumour may be delayed by months, especially in pelvic, abdominal or thoracic sites. Most patients present with localised and variable intensive pain, which may be mistaken for the effects of minor injuries, e.g. after sports, which occur quite commonly in the paediatric and adolescent population. Pain as the initial symptom may be followed by the finding of a palpable mass. Systemic signs, such as malaise, fever, and indicators of a chronic inflammatory disease may arise when diagnosed at a later stage or in patients with metastatic disease [2]. Occasionally, the clinical picture may be similar to that of acute or chronic osteomyelitis and include intermittent fever, mild anaemia, leukocytosis and an elevated erythrocyte sedimentation rate. Increased serum lactic dehydrogenase levels and weight loss may also be observed and are more common in patients with primary disseminated disease.

Imaging

Imaging procedures are of major importance for individualised and optimised treatment planning. They have to be carried out before any surgery, including biopsies. In 2008, Meyer *et al.* [3] published imaging guidelines developed by a multidisciplinary group from the Children's Oncology Group Bone Tumor Committee for children with Ewing's sarcoma and osteosarcoma. The recommendations were based on the available literature and, in case of a lack of literature, consensus of the expert group. For the evaluation of bones (primary tumour and/or metastases), magnetic resonance imaging of the whole compartment with gadolinium was recommended. For the primary tumour, additional anterior–posterior and lateral radiographs were advised. In special (e.g. axial) sites or in case of further uncertainties, computed tomography (CT) scans may be necessary. CT was recommended as the method of first choice for the evaluation of the chest. Bone scintigraphy and positron emission tomography (FDG-PET) may provide further information. The combination of PET with CT in an integrated PET/CT scanner helps to overcome the limited spatial resolution of PET that hampers the precise anatomic localisation of identified lesions [3]. Gerth *et al.* [4] described inherent advantages of PET/CT over PET alone in lesion detection, the determination of malignancy, accurate localisation, and overall staging for patients with Ewing's sarcomas. The value of PET in sarcoma patients has not been evaluated systematically. In Ewing's sarcoma this issue has been addressed in the currently active protocol EWING 2008. A hybrid scanning system may be beneficial. All the different imaging procedures are used to evaluate tumour response during the multimodal therapy, to plan surgical procedures and to evaluate remission during follow-up.

Biopsy

A biopsy is the initial surgical procedure for any bone tumour. Magnetic resonance imaging before a biopsy helps to determine the optimal site for the procedure and to avoid distortion of the imaging findings by post-biopsy changes [5]. The location of the biopsy site is determined by a thorough pre-biopsy assessment of the extent of local disease and its relationship to critical structures such as the neurovascular bundle. Open biopsies are preferred as they guarantee the collection of sufficient material for histological and molecular–pathological characterisation, which becomes more important on the way towards a more personalised medicine. The procedure should be carried out by an orthopaedic surgeon who is familiar with appropriate techniques to prevent jeopardising or complicating future limb salvage surgery or radiation.

Ewing's Sarcoma

Ewing's sarcoma represents the second most common primary bone-associated malignancy in childhood, adolescence and young adults. The annual incidence is estimated at 1–3 per million population. Ewing's sarcoma occurs predominantly in Caucasians and, to a lesser extent, in Asians. This condition is rare in black and Chinese children. Males are affected more frequently than females, with a ratio of approximately 1.5:1. Staging procedures identify about 25% of patients as having metastases at diagnosis. Typically Ewing's sarcomas arise in bony sites. The most common primary bony sites include the pelvis (26%), long bones (47%), chest wall (16%) and spine (6%), but may also arise in soft tissue. In long bones, Ewing's sarcoma predominantly occurs at the diaphysis. The osseous mass may coexist with a soft tissue component resulting in a 'Codman triangle' (from elevation of the periosteum) or a so-called 'onion skin pattern' multi-layered periosteal reaction. Before the era of combination chemotherapy, the prognosis of patients with Ewing's sarcoma was poor, with more than 90% of patients dying from secondary metastases [6]. Therefore, Ewing's sarcoma must be regarded as a systemic disease.

Ewing's sarcomas are characterised as tumours consisting of small, blue, round malignant cells that may exhibit varying degrees of neural differentiation. Ewing's sarcoma,