IV. 研究成果の刊行に関する一覧表

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書籍

著者氏名	論文タイトル名	書籍全体の編集者名	書 籍 名	出版社名	出版地	出版年	ページ
横山良平	骨腫瘍	別所文雄、杉本徹、横森欣司(編)	新小児がんの診断と治療	診断と治療社	東京	2007	307-310

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Hosono A, Makimoto A, et al.	Utility of immunohistochemical analysis for cyclo-oxygenase 2 in the differential diagnosis of osteoblastoma and osteosarcoma.	J Clin Pathol	60	410-414	2007
Tateishi U, Makimoto A, et al.	Accuracy of 18F fluorodeoxyglucose positron emission tomography/computed tomography in staging of pediatric sarcomas.	J Pediatr Hematol Oncol	29	608-612	2007
Yonemori K, Makimoto A, et al.	Prediction of response and prognostic factors for Ewing family of tumors in a low incidence population.	J Cancer Res Clin Oncol	134	389-395	2007
Uno T, Sumi M, et al.	Postoperative radiotherapy for non-small-cell lung cancer: results of the 1999-2001 patterns of care study nationwide process survey in Japan.	Lung Cancer	56	357-362	2007
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Shimizu T, Sumi M, et al.	Concurrent Chemoradiotherapy for Limited-disease Small Cell Lung Cancer in Elderly Patients Aged 75 Years or Older.	Jpn J Clin Oncol.	37	181-185	2007

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Oda Y, Yokoyama R, et al.	Diffuse-type giant cell tumor/pigmented villonodular synovitis arising in the sacrum: Malignant form.	Pathol International	57	627-631	2007
斎藤祐介、横山良平、他.	ホジキンリンパ腫瘍の治療後に発症した二次がんの2例	日小血会誌	21	172-175	2007
Takahashi D, Yokoyama R, et al.	Primary Ewing's Sarcoma Family Tumors of the lung. A case report and review of the literature.	Jpn J Clin Oncol	37	874-877	2007
大喜多　肇	Ewing肉腫ファミリー腫瘍の分子生物学	小児外科	39巻 11号	1344-1347	2007

Ⅴ．研究成果の刊行物・別刷

10 骨腫瘍

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I はじめに

小児に発生する悪性骨腫瘍のなかでは，骨肉腫が最も多く，ついでEwing肉腫ファミリー腫瘍である．後者については，次項で述べられるので，ここでは骨肉腫について述べる．骨肉腫は，10歳代の少年・少女の膝周囲の骨に好発する高悪性の肉腫である．強力な全身化学療法が導入される1970年代初頭までは，患肢切断が唯一ともいえる治療で，5年生存率は10～15%にすぎなかった．しかし，化学療法の導入とともに予後は劇的に改善され，現在では初診時に転移がなければ60%以上の5年無病生存率が期待できるようになった．また，術前より化学療法を行うNeoadjuvant chemotherapyの導入，画像診断法の進歩，延長可能な腫瘍用人工関節の開発などの整形外科的手術手技の進歩によって，成長期の小児であっても患肢温存が可能になった．一方，初診時に転移がある場合や，初期治療終了後に転移をきたした進行期骨肉腫でも，積極的な治療により治癒する患児も増加している．

II 概念

骨肉腫は，悪性の間葉系腫瘍細胞が増殖し，これらの腫瘍細胞が類骨あるいは骨を形成するものと定義されている．発生部位，生物学的態度，病理組織学的特徴より亜分類が行われる．小児ではほとんどが通常型であり，本稿ではこれについて述べる．

III 発生機序

正確な機序は不明である．遺伝性の両側網膜芽細胞腫に続発する肉腫の一つであること，一部の骨肉腫ではp53の異常が見いだされたり，ほかにもいくつかの遺伝子異常が報告されたりしているが，いまだ確定的なものはない．

IV 症状

骨肉腫に特異的な症状はない．初発症状は隣接関節の痛みである．すなわち，大腿骨遠位や脛骨近位では膝関節痛を，上腕骨近位では肩関節の痛みを訴える．それに続いて患部の腫脹を生じる．下肢では痛みのために跛行を呈する．進行は速く，痛みを自覚して2～4週以内に腫れに気づくことが多いようである．患者の大半は発症から1か月前後で医療機関を受診．

身体所見は，患部の腫脹と熱感を認める．最近は皮膚の静脈怒張を伴うほど大きくなって医療機関を受診する患者は少ない．隣接関節の可動域は，痛みと腫脹のために制限されていることが多い．圧痛も著明である．

V 診断

骨肉腫は進行が速いので，早急に治療を開始するための迅速かつ効率的な診断手続きが重要である．Oncological emergencyの対象となる疾患であり，緊急入院，生検も含めて緊急検査の対象とする施設が多い．図1に診断と治療のフローチャートを示す．

A 単純X線所見(図2-a)

最終診断は生検による病理診断で決定されるが，臨床診断で最も有用なのは単純X線所見である．臨床症状と単純X線写真のみで大半の骨肉腫は診断可能である．

大部分の患者で，腫瘍は長管骨の骨幹端，特に大腿骨遠位，脛骨近位，上腕骨近位骨幹端にみられる．病変は溶骨性の変化と造骨性の変化が混じっていることが多い．その割合は様々である．正常骨髄との境界は不明瞭で，虫食い様，あるいは浸透状と称される小さな溶骨性の変化が認められる．骨皮質にも同様の破壊性変化がみられ，場合によっては骨皮質が消失している．骨皮質の外側には骨膜反応が認められる．しばしばみられる骨膜反応には，病巣の上下に三角形に立ち上がるCodman三角や，破壊された骨皮質に直角に棘のように立ち上がるスピクラなどがある．注意深く観察すると，骨外に浸潤増殖した軟部腫瘍陰影を認めることができる．

B MRI(図2-b)

組織のコントラスト，空間解像能に優れ，横断面だけでなく，矢状断面，冠状断面もみることができることから，病巣の広がりを正確に把握するために欠かせない検査である．特に，骨外腫瘍の広がりを評価するのに必須の検査である．術前化学療法の評価や，手術計画を立てるうえでも必要な検査である．

図1 骨肉腫に対する診断および治療の手順

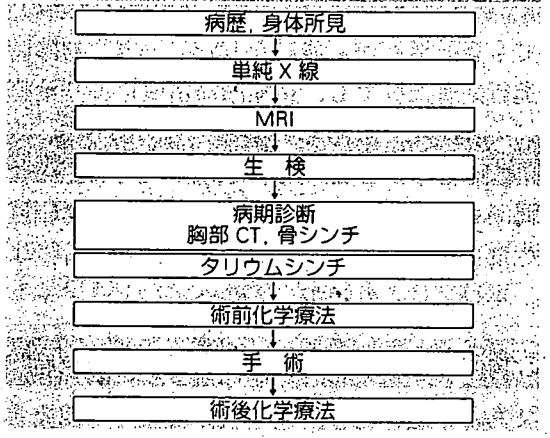
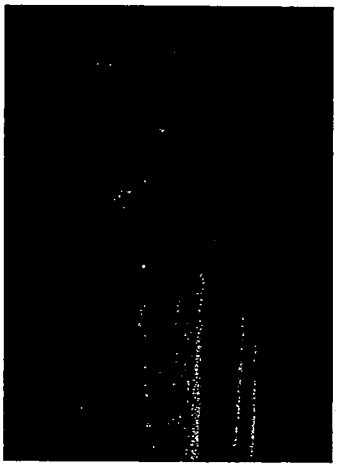
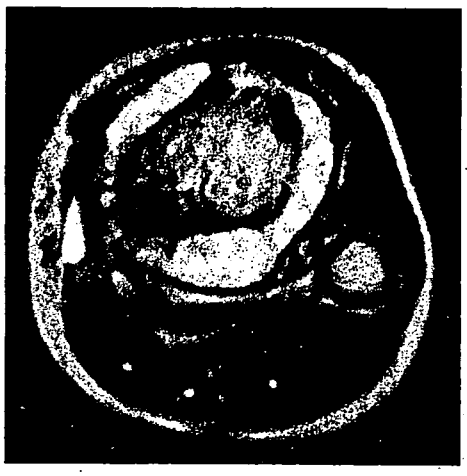


図2-a 脛骨骨肉腫の単純X線写真



脛骨近位骨幹端に不規則で広範な硬化陰影がみられ，溶骨像も混在している．両側にCodman三角とスピクラからなる骨膜反応が認められる．

図2-b 脛骨骨肉腫のMRIのT2強調横断画像



脛骨の周囲に高信号を示す骨外腫瘍の形成が認められる．

T1強調画像では，筋肉と同程度がそれより低い信号強度を示す．T2強調画像では，全体的に高信号を呈する．骨形成が豊富で，単純X線で硬化像としてみられる部分でも高信号を呈することがあり，腫瘍細胞が骨梁間に豊富にあることを示唆している．壊死や，壊死に伴って嚢包を形成している場合には極めて高い信号を示す．血管拡張型骨肉腫(Telangiectatic osteosarcoma : TOS)のような嚢包状変化が目立つ腫瘍では，液面形成が認められる．造影MRIでは壊死部を除き強く造影される．

C 胸部CT

病期決定のために必要な検査である．肺転移は骨肉腫に最も多い転移病巣であり，治療前に評価しておくことが望ましい．

D 骨シンチグラフィ

原発巣は強い集積を示す．また，骨転移や多発病巣の有無を知るために行うべき検査である．

E タリウム(Tl-201)シンチグラフィ

心臓の血流シンチグラフィとして利用されているが，1990年代に骨軟部腫瘍の領域で応用が広まった．特に骨肉腫においては術前化学療法後の集積の減弱が組織学的評価とよく相関することが示されており，効果判定として利用価値が高い．タリウム注射後数時間を置いて撮影する晩期相での集積の程度が病勢と相関するので，必ず晩期相を撮影することが必要である．最近はPETがこれにとって代わる感があるが，タリウムシンチグラフィはシンチグラフィを行える施設でできることから汎用性は高いと考えられる．ガリウムシンチグラフィは，骨肉腫では有用性が低い．

タリウムは骨シンチグラフィに用いられるテクネシウムより半減期が長いので，骨シンチグラフィを先に行うべきである．

F 血液検査

診断的に有用な項目はないが，骨形成が旺盛な腫瘍ではアルカリホスファターゼ(ALP)が高値を示すが，小児では正常でも高値を示すため解釈には注意を要する．腫瘍が大きなものや遠隔転移を有するような場合には，乳酸脱水素酵素(LDH)が高値を示すことがある．

G 生検

確定診断は，生検による病理診断で決定される．異型に富む腫瘍細胞が増殖し，腫瘍細胞の間に好酸性の類骨が認められれば診断は容易であるが，必ずしも類骨が認められるとは限らないので，画像所見を参考にして診断することが重要である．サンプリングエラーを避けるために，生検前にMRIを参考にして生検部を決定し，壊死部を避けて腫瘍組織を採取する．発育先進部が最も腫瘍細胞が多く，中心に行くほど壊死の割合が高くなるので，辺縁から採取するほうが間違いが少ない．また，生検創は後の手術の場合に切除しなければならないので，手術を念頭に置いて皮膚切開の方向と位置を決めなければならない．すなわち，生検はすでに治療の一環であり，治療しない施設で行うべきではないことを強調しておきたい．

初診から1週間以内，遅くとも2週間以内に治療が開始されるべきである．具体的な診断手順は，MRIに引き続いて生検を行い，胸部CTや骨シンチグラフィ，タリウムシンチグラフィなどは生検の病理診断が得られるまでの期間に行うことにしている．

VI 治療

術前化学療法，手術，術後化学療法が治療の骨格である．

1970年代以降，骨肉腫に対する化学療法の研究が積極的に行われ，ロイコボリン救援療法を併用したメトトレキサート大量療法(HDMTX)，アドリアマイシン(ADR)，シスプラチン(CDDP)を中心

とした補助化学療法の有効性が確認された[1-3]．現在はこれらの3剤を用いるレジメンがほぼ世界的に共通のものとなり，さらに術前から投与するNeoadjuvant chemotherapyがほぼ標準的な方法となっている[4～6]．

現在日本で広く用いられている術前化学療法のレジメンでは，2週連続でday 1，8にHDMTXを投与した後，3週目のday 15にCDDPとADRを投与，6週目から再びday 36，43にHDMTXを，day 50にCDDPとADRを投与する．さらに11週目から2週連続でHDMTXを投与する．最後のHDMTXの投与終了後検査データなどに問題がなければ13週目に手術を行う．術後化学療法は，手術創が治癒したら速やかに開始する．術後のレジメンは，術前化学療法の効果によって変更する．化学療法の組織学的効果が良好であった場合は，術前と同じ薬剤を用いて，18週間の化学療法を行う．効果が不良であった場合は，これにイホスファミドを加えたレジメンに変更し，28週間の化学療法を行う．

手術の原則は，広範切除縁を確保して切除することである．四肢発生の骨肉腫患者の大部分は患肢温存が可能であるが，10歳以下の患児では，骨肉腫が膝周辺に発生した場合は患肢温存しても，左右の下肢長が成長とともに約10cmになるため有用な下肢とはならない．そのためこれまでは切断や回転形成術が行われてきたが，最近は延長できる腫瘍用人工関節や，脚延長術を駆使して有用な患肢温存を図る努力がなされるようになってきた[7, 8]．

脊椎など手術が困難な部位に発生した骨肉腫に対しては放射線治療が行われるが，有効性は極めて低い．近年重粒子線を用いた治療の成功例が報告されており，手術困難部位に対しては有効な方法となる可能性がある[9]．

Ⅶ 予後

四肢に発生した骨肉腫の場合，診断時に遠隔転移がなければ60～70%の5年無病生存率が期待できるようになってきた．また，遠隔転移が肺の場合には5年無再発生存率は30%以上である．重要な予後因子は術前化学療法の組織学的効果である．著効(組織学的に腫瘍細胞の残存がない)もしくは有効(残存腫瘍細胞の割合が10%未満)の場合は，それ以外の場合に比べて統計学的有意差をもって予後良好であることが多数の研究から明らかにされている[6]．

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ORIGINAL ARTICLE

Utility of immunohistochemical analysis for cyclo-oxygenase 2 in the differential diagnosis of osteoblastoma and osteosarcoma

Ako Hosono, Umio Yamaguchi, Atsushi Makimoto, Makoto Endo, Atsuko Watanabe, Tadakazu Shimoda, Mitsunori Kaya, Tadaki Matsumura, Hiroshi Sonobe, Tomomi Kusumi, Takehiko Yamaguchi, Tadashi Hasegawa

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See end of article for authors' affiliations

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Aims: To study the immunoexpression of cyclo-oxygenase (COX) 2 in osteoblastomas (OBs) and osteosarcomas (OSs), and to assess the utility of immunohistochemical analysis for COX 2 in the differential diagnosis of the two tumour forms.

Methods: The immunohistochemical features of COX 2 were studied in 11 OBs and 30 OSs, including 26 high-grade OSs (16 osteoblastic, 7 chondroblastic, and 3 fibroblastic) and 4 low-grade OSs.

Results: Tumour cells from all 11 OBs unequivocally showed diffuse, intense and cytoplasmic immunoreactivity for COX 2. Strong cytoplasmic expression of COX 2 was observed in 5 of 26 (19%) high-grade OSs, all chondroblastic. In one osteoblastic-type OS, COX 2 was expressed in the chondroblastic component, but this tumour was considered to be COX 2 negative. No COX 2 expression was noted in atypical osteoblastic cells. Staining in the four low-grade OSs was negative.

Conclusion: The results of immunohistochemical analysis of COX 2 suggest that in addition to the routine histopathological evaluation, COX 2 is a valuable diagnostic marker in the distinction between OB and OS.

Osteoblastoma (OB) is an uncommon benign bone-forming tumour, most frequently occurring in the vertebral column of patients aged <30 years. OBs have a wide spectrum of clinicoradiological and histopathological features. Besides the classic OB, borderline tumours with radiological and histopathological features between OB and osteosarcoma (OS), such as pseudomalignant OB,[1 2] aggressive OB or malignant OB,[3 4] exist. Moreover, a fraction of OBs may undergo malignant transformation.[5 6] It is often difficult to distinguish an OB from an OS by routine histopathological procedures alone.[7] Although clinicoradiological findings are sometimes helpful, appropriate immunohistochemical markers are still not available for the differential diagnosis of the two tumour forms.

Cyclo-oxygenase (COX) is a key biosynthetic enzyme in prostaglandin synthesis and two forms have been identified: COX 1 and COX 2. COX 1 constitutively occurs in normal tissue, whereas COX 2 may be induced in inflammatory tissue.[8] Recent studies showed that the expression of COX 2 is increased in various human tumours[9]; the enzyme seems to play an important role in carcinogenesis, since it can inhibit apoptosis,[10] stimulate angiogenesis[11] and increase invasion and metastatic potential.[12 13] COX 2 expression has been reported in benign bone tumours such as osteoid osteoma, suggesting that the activation of eicosanoid synthesis by COX 2 has biological importance in such tumours.[14–16] However, there is little information about COX 2 expression in OB, a tumour form that closely resembles osteoid osteoma histologically. Although the expression of COX 2 in OS has been reported in a small series of tumour samples[17 18] and some cell lines,[19] the distribution of COX 2 has not been fully elucidated. In this study, we investigated the expression profile of COX 2 in OB and OS, and we assessed the utility of immunohistochemical analysis for COX 2 in the differential diagnosis of the two tumour forms.

MATERIALS AND METHODS

Tumour samples and histological evaluation

A total of 41 primary tumour specimens were retrieved from the pathological files of the National Cancer Centre Hospital, Tokyo, Japan, and Sapporo Medical University Hospital, Sapporo, Japan. Tumours included 11 OBs and 30 OSs. Of the 30 OSs, 26 were high grade (16 osteoblastic, 7 chondroblastic and 3 fibroblastic) and 4 were low grade.

The histopathological diagnosis of each tumour was re-evaluated by TH. The histological criteria of the diagnosis and the determination of the histological grading of OS were based on textbook descriptions.[20] An OB in this study was defined as a bone-forming neoplasm showing woven bone spicules, which are bordered by prominent osteoblasts without atypia (fig 1A,C). Conventional OS is a high-grade (grade 3, 4) malignant tumour characterised by the presence of osteoids (fig 2A,C). This high-grade OS is subdivided into three major groups: osteoblastic OS (bone and/or osteoids are the predominant matrix), chondroblastic OS (chondroids are the predominant matrix) and fibroblastic OS (mainly composed of spindle cells with only minimal amounts of osseous matrix). Low-grade (grade 1, 2) OS is classified primarily on the basis of a hypocellular to moderately cellular fibroblastic stroma with osteoids. For light microscopic studies, all specimens were fixed in 10% buffered formalin, decalcified in Plank and Rychlo solution (Wako Pure Chemical Industries, Osaka, Japan) and processed routinely for embedding in paraffin wax. Sections of 4 μm thickness were stained with H&E.

Immunohistochemical studies

Immunohistochemical analysis was performed on tissue sections from paraffin wax blocks by the labelled streptavidin–biotin

Abbreviations: COX, cyclo-oxygenase; OB, osteoblastomas; OS, osteosarcomas

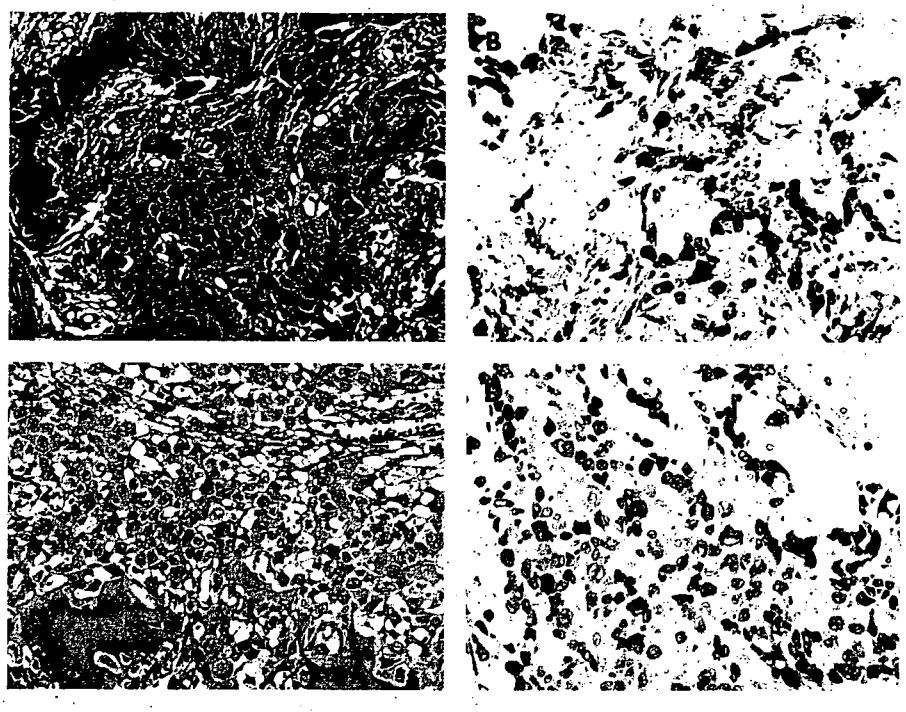

Figure 1 (A) A classic osteoblastoma (OB) showing partially calcified osteoid and immature bone formation associated with osteoblastic activity in a fibrovascular stroma. (B) The osteoblasts are diffusely positive for cyclo-oxygenase 2 (COX 2). (C) Another case of OB, showing a sheet-like arrangement of epithelioid osteoblasts between osteoid trabeculae. Although there are no hyperchromatic osteoid-producing stromal cells and large nucleoli, there still remains a possibility of misdiagnosing this tumour as an osteosarcoma. (D) The epithelioid osteoblasts are diffusely positive for COX 2.

method. The sections were dewaxed, rehydrated and moistened with phosphate-buffered saline (pH 7.4). They were pretreated in an autoclave at 121°C for 10 min in target retrieval solution (pH 9; Dako, Glostrup, Denmark), before being incubated with a mouse monoclonal anti-COX 2 antibody (clone CX-294; 1:100; Dako) in an automated immunostaining system (i6000; BioGenex, San

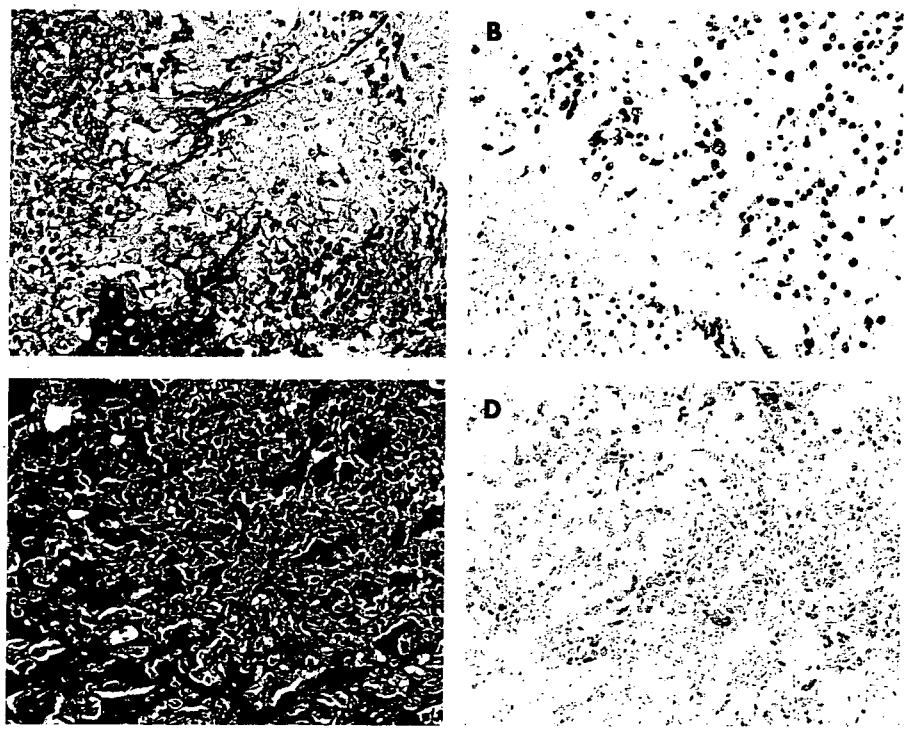

Figure 2 (A) A chondroblastic osteosarcoma. (B) Many of the chondroblastic cells are diffusely positive for cyclo-oxygenase 2 (COX 2). (C) An osteoblastic osteosarcoma showing unmineralised bone matrix. (D) None of the tumour cells shows COX 2 immunoreactivity.

Ramon, California, USA) for 30 min. For positive controls, osteoid osteoma tissues known to be positive for COX 2 were used. For negative controls, sections of normal mouse serum were used. The results of COX 2 expression were evaluated by AH and TH. A described consensus judgement[21] was adopted as the proper immunohistochemical score of the tumour based on the number of positive cells: 0, negative staining (0–9%); 1+, weak staining (10–29%); 2+, moderate staining (30–49%); 3+, strong staining (50%–).

RESULTS

We studied 11 OBs and 30 OSs (tables 1 and 2). In patients with OB, eight tumours were localised in the vertebral column and one tumour each was localised in the femur, scapula and radius. Patients with OB were aged 14–31 years (mean 20 years). Clinical details were available for 8 of 11 patients and these 8 patients were treated with local surgical resection or simple curettage of the tumour. Of the eight patients, seven had no local recurrence or metastatic disease; however, one developed a local recurring tumour 14 years after the initial surgical treatment, which showed malignant transformation pathologically. In patients with OS, 26 tumours were localised in the extremities (18 in the femur, 5 in the tibia and 1 each in the ulna, metatarsal bone and metacarpal bone). Four tumours were localised in other anatomical locations (two in the pelvis and one each in the mandible and rib). The patients with OS were aged 8–67 years (mean 29 years). Histologically, 4 were low-grade OS and 26 were high-grade OS, in which 16 were osteoblastic, 7 were chondroblastic and 3 were fibroblastic. Follow-up information was obtained for 26 of 30 OSs; 6 patients died because of their disease.

Immunohistochemically, proliferating osteoblasts of all the 11 OBs unequivocally showed diffuse, intense and cytoplasmic immunoreactivity for COX 2, and these were classified as strong staining tumours (3+) (fig 1B,D). Peritumoral inflammatory cells were also COX 2-positive, but the extent of staining was weak to moderate. Expression of COX 2 was observed in 5 of 26 (19%) high-grade OSs and they were all of the chondroblastic type. Unlike OB, however, staining for COX 2 in OS was equivocal and only observed in chondroblastic cells with a cytoplasmic pattern; the staining in these areas was generally strong (3+; fig 2B). In one OS of the osteoblastic type, <9% of the tumour cells showed COX 2 positivity, but they were all chondroblastic cells. In some cases of OS, osteoclast-like giant cells and macrophages were also weakly positive. No COX 2 expression was noted in atypical osteoblastic cells (fig 2D). Peritumoral inflammatory cells and inflammatory cells adjacent to necrotic tissue showed weak to moderate COX 2 staining. Staining in all four low-grade OSs was negative.

DISCUSSION

To differentiate an OB from an OS accurately is of clinical importance because the prognosis and the treatment of the two tumour forms differ. Osteoblastoma has an excellent prognosis and the treatment varies from curettage to local excision. Osteosarcoma, however, is highly malignant with an unfavourable clinical course and the treatment needs a multimodality approach including systemic chemotherapy, radiotherapy and local wide resection to sometimes mutilating en bloc resection of the tumour. Generally, the diagnosis of OB or OS is based on a combination of clinical, radiological and morphological findings. Although OB shows a predilection for the vertebral column and OS frequently affects the metaphysis of the long bone, both forms of tumour can occur in any bone. The age of occurrence and the radiological features of the two forms of tumours often overlap; both tumours occur mainly in the younger age group and cause expansion and destruction of the cortex as well as periosteal bone formation. As described above, histopathologically, OB generally shows an active osteoblastic proliferation with alternating formation of osteoids and woven bone spicules or trabeculae. Scattered foci of osteoclastic bone resorption may appear, but no destructive permeation of pre-existing bone tissues is noted. In some cases of OB, large and plump osteoblasts with a hyperchromatic nucleus and nucleoli, and occasionally mitoses, may be observed. Owing to the wide spectrum of histopathological findings of OB and the morphological overlapping with OS, some borderline tumours exist, which make the differential diagnosis between OB and OS problematic.[1–7] Unlike OB, OS generally has intense cellular pleomorphism and atypism, extensive areas of necrosis and atypical mitoses, and, in some cases, tumoural cartilage may also be present. The presence of destructive permeation is the most helpful finding in distinguishing OB from OS.[7] Nevertheless, the differential diagnosis is sometimes impossible with insufficient material—for example, from a needle biopsy—and may be impossible even with adequate tissue samples.

The absence of reproducible evidence of specific findings minimises the use of immunohistochemistry in the differential diagnosis of the two tumour forms. The literature contains little data regarding COX 2 expression in OBs. Studies on COX 2 expression in osteoid osteoma[14–16] and chondroblastoma[10] suggested that COX 2 expression in these tumours is an important factor for inducing tissue inflammatory reactions. The immunohistochemical feature of COX 2 in the OBs we studied was strikingly similar to that in osteoid osteoma. Whether the relative contribution of COX 2 expression in OB is a factor in inducing inflammatory reaction such as that in osteoid osteoma and chondroblastoma or has another role in tumour development remains to be clarified. Previous authors

Table 1 Clinical profiles and immunohistochemical cyclo-oxygenase 2 expression of 11 osteoblastomas

Case number	Age (years)	Sex	Site	Size (cm)	Treatment	Recurrence	Outcome (month)	COX 2 expression
1	22	M	LV	2	MEBR	No	NED (58)	3+
2	14	M	LV	1.1	Curettage	No	NED (33)	3+
3	19	M	LV	2.5	Curettage	No	NED (32)	3+
4	20	M	LV					3+
5	20	F	Femur					3+
6	17	M	Radius	1.4	MEBR	No	NED (30)	3+
7	14	M	TV	1.5	Curettage	No	NED (48)	3+
8	18	M	LV		MEBR	Yes*		3+
9	25	F	CV					3+
10	20	F	CV	3	MEBR	No	NED (147)	3+
11	31	M	Scapula		MEBR	No	NED (5)	3+

COX 2, cyclo-oxygenase 2; CV, cervical vertebra; F, female; LV, lumbar vertebra; M, male; MEBR, marginal en bloc resection; NED, no evidence of disease; 3+, strong staining.
*Malignant transformation.

Table 2 Clinical profiles and immunohistochemical cyclo-oxygenase 2 expression of 30 osteosarcomas

Case number	Age (years)	Sex	Tumour site	Size (cm)	Subtype	Grade	Treatment	Outcome (month)	COX 2 expression
1	63	M	Femur	5.0	FB	High	OP	NED (30)	0
2	63	F	Metatarsal bone		OB	High			0
3	32	F	Femur	6.0	OB	High	OP/CT	DOD (10)	0
4	15	M	Metacarpal bone	2.5	OB	High	OP/CT	NED (41)	0
5	23	F	Femur		OB	High			0
6	28	M	Mandible		CB	High	OP/CT	AWD (32)	0
7	37	M	Pubis	4.5	OB	High	OP/CT	NED (16)	0
8	35	M	Femur	9.0	OB	High	OP/CT	NED (59)	0
9	18	M	Femur	7.0	OB	High	OP/CT	NED (53)	0
10	61	F	Femur	11.0	FB	High	OP	NED (48)	0
11	42	F	Rib	5.0	OB	High	OP/RT	DOD (17)	0
12	67	F	Femur	8.0	OB	High	OP/RT	NED (13)	0
13	66	F	Femur	12.0	OB	High	OP	AWD (2)	0
14	12	F	Femur	13.0	FB	High	OP/CT	DOD (13)	0
15	13	F	Tibia	8.0	OB	High	OP/CT/RT	DOD (51)	0
16	18	M	Femur	5.0	OB	High	CT	DOD (3)	0
17	21	M	Femur	14.0	OB	High	OP/CT	NED (24)	0
18	13	M	Femur	8.5	OB	High	OP/CT	NED (76)	0*
19	9	F	Femur		OB	High	OP/CT	NED (17)	0
20	18	M	Femur	10.0	CB	High	OP/CT	NED (48)	3+
21	10	F	Femur	13.0	CB	High	OP/CT	NED (47)	3+
22	22	M	Femur	10.0	CB	High	OP/CT	AWD (51)	3+
23	18	M	Pubis	15.0	CB	High	OP/CT/RT	DOD (16)	3+
24	16	M	Tibia	11.0	CB	High	OP/CT	NED (16)	0
25	9	M	Femur	7.5	CB	High	OP/CT	NED (75)	3+
26	8	F	Tibia	6.0	OB	High	OP/CT	NED (16)	0
27	29	F	Tibia		LGC	Low			0
28	23	F	Femur		LGC	Low	OP	NED (87)	0
29	66	M	Ulna		LGC	Low			0
30	9	M	Tibia	9.0	IC	Low	OP/CT	NED (96)	0

AWD, alive with disease; CB, chondroblastic; COX 2, cyclo-oxygenase 2; CT, chemotherapy; DOD, dead of disease; F, female; FB, fibroblastic; IC, intracortical; LGC, low-grade central; M, male; NED, no evidence of disease; OB, osteoblastic; OP, operation; RT, radiotherapy; 0, negative staining; 3+, strong staining.
*<9% of the tumour cells show COX 2 positivity, but they are all chondroblastic cells.

have reported that a large percentage of OS showed increased COX 2 expression,[17 18] but the staining patterns and histological types were not specified. By contrast, the expression of COX 2 in our series was only observed in a limited number of OSs, all of which were of the chondroblastic type. The discrepancy between these results may be due to several reasons, such as different sources of antibodies used, differences in immunohistochemical techniques or different consensus judgement criteria adopted. Moreover, most COX 2-positive OSs are stained heterogeneously even in the same tissue section, and a chondroblastic component in some conventional OSs are also COX 2 positive. These facts may also lead to a different result if one evaluates the COX 2 staining in one tissue section or on whole tumour sections. COX 2 expression was also detected in a limited number of OS cell lines by using cytogenetic methods,[19] but the histological type was not described in detail. It is noteworthy that staining for COX 2 was only observed in chondroblastic cells of these OSs showing COX 2 immunoreactivity. Staining for COX 2 in chondroblastic cells was also shown in chondroblastoma[10] and chondrosarcoma.[22 23] Although we do not know exactly the incidence of OB that may be impossible to distinguish from OS by classic diagnostic methods, rare borderline tumours between OB and OS do exist.[1-3 7 24] In this situation, the application of COX 2 immunohistochemistry would be valuable in making a definite assignment.

COX 2 expression in many tumours, in particular those of the gastrointestinal tract, has been strongly implicated in carcinogenesis.[25] Pharmacodynamic studies showed that selective inhibitors of COX 2 have the effects of antiangiogenesis and proapoptosis, and therefore suppress tumour growth.[26] COX 2-based treatment is of growing interest and has emerged for clinical use.[27] Osteosarcoma is a highly aggressive bone tumour and has a high mortality even when systemic chemotherapy is given. A study of COX 2 inhibitors in OS cell lines showed a possible therapeutic role in counteracting the tumorigenicity of this tumour.[19] Since COX 2 inhibitors inhibit tumour growth through both COX 2-dependent and independent pathways,[19 28] further in vitro and in vivo studies are warranted to reveal the roles of COX 2 inhibitors in these tumours without regarding whether they have COX 2 expression. Our immunohistochemical findings, however, suggest that COX 2 would be beneficial in distinguishing between OB and OS in a clinical setting.

In summary, we studied the expression profile of COX 2 in OB and OS and found that there was strong and diffused expression of COX 2 in OB, but it was only observed in the chondroblastic cells of OS. Our findings suggested that in addition to histopathological evaluation, COX 2 is a valuable immunohistochemical marker in the differential diagnosis between OB and OS.

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Take-home messages

- All the osteoblastomas (OB) showed unequivocally strong immunoreactivity for cyclo-oxygenase (COX) 2. Expression of COX 2 was observed in 5 of 26 (19%) high-grade osteosarcomas (OS), all chondroblastic. In one osteoblastic-type OS, COX 2 was only expressed in the chondroblastic component.
- The application of COX 2 immunohistochemistry would be helpful in making a definite assignment in case it is difficult to make an accurate diagnosis between OB and OS.

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Accuracy of ^{18}F Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography in Staging of Pediatric Sarcomas

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Summary: The present study was conducted to clarify the diagnostic accuracy of ^{18}F-fluoro-2-deoxy-D-glucose (^{18}FDG) positron emission tomography (PET)/computed tomography (CT) in the staging in pediatric sarcomas. Fifty pediatric patients with histologically proven sarcomas who underwent ^{18}FDG PET/CT before treatment were evaluated retrospectively for the detection of nodal and distant metastases. Diagnostic accuracy of ^{18}FDG PET/CT in detecting nodal and distant metastases was compared with that of ^{18}FDG PET and conventional imaging (CI). The images were reviewed and a diagnostic consensus was reached by 3 observers. Reference standard was histologic examination in 15 patients and confirmation of an obvious progression in size of the lesions on follow-up examinations. Nodal metastasis was correctly assessed in 48 patients (96%) with PET/CT, in contrast to 43 patients (86%) with PET, and 46 patients (92%) with CI. Diagnostic accuracies of nodal metastasis in 3 modalities were similar. Using PET/CT, distant metastasis was correctly assigned in 43 patients (86%), whereas interpretation based on PET alone or CI revealed distant metastasis in 33 patients (66%) and 35 patients (70%), respectively. Diagnostic accuracy of distant metastasis with PET/CT was significantly higher than that of PET ($P = 0.002$) or CI ($P = 0.008$). False negative results regarding distant metastasis by PET/CT in 7 patients (14%) were caused by subcentimetric lesions (n = 4), bone marrow lesion (n = 2), and soft tissue lesions (n = 1). PET/CT is more accurate and probably more cost-effective than PET alone or CI regarding distant metastasis in pediatric sarcomas.

Key Words: PET/CT, pediatric sarcoma, stage

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Pediatric sarcoma remains uncommon neoplasm but contributes significantly to the burden of morbidity and mortality. The success of aggressive therapy with multiagent chemotherapy and radiotherapy resulted in a significant improvement of the prognosis. However, patients with metastasis continue to have a poor prognosis.[1–3] Therefore, the diagnosis of nodal and distant metastases is crucial to determine the therapeutic plan and prognosis in patients with pediatric sarcomas.

The conventional imaging (CI) for initial staging of bone and soft tissue sarcomas consists of clinical examination, magnetic resonance imaging (MRI) of the primary lesion, chest x-ray, computed tomography (CT), and bone scintigraphy. Positron emission tomography (PET) with ^{18}F-fluoro-2-deoxy-D-glucose (^{18}FDG) has been used in the evaluation of bone and soft tissue sarcomas,[4–11] and most of these studies report that ^{18}FDG PET is advantageous in the assessment of grading and therapy monitoring compared with CI. A hybrid imaging of PET/CT can allow accurate anatomic localization of tumors, and thus has an important advantage over ^{18}FDG PET alone for the staging of tumors.[12]

However, the exact role of ^{18}FDG PET/CT in the staging of pediatric sarcomas has not been elucidated. To further clarify the role of ^{18}FDG PET/CT, the comparison with ^{18}FDG PET/CT, PET alone, and CI are needed. The aim of the current study was to clarify diagnostic accuracy of ^{18}FDG PET/CT for the staging of pediatric sarcomas.

MATERIALS AND METHODS

Patient

We retrospectively reviewed ^{18}FDG PET/CT images since June 2005 to August 2006 for staging (n = 40, 80%) and restaging (n = 10, 20%) of pediatric sarcomas. ^{18}FDG PET/CT was performed for initial staging in all patients. The study population consisted of 26 males and 24 females with a mean age of 13 years (range, 3 to 17 y). The clinical records of all the patients were available for review. This study was conducted in accordance with the amended Helsinki declaration and the protocol was approved by the Institutional Review Board. All the patients had provided their written

informed consent to participate in the present study and to review their records and images.

PET/CT

PET/CT was performed within mean 2 weeks (range, 0 to 2 wk) before therapy and mean 6 weeks (range, 4 to 11 wk) after initiation of therapy. We used premedication with oral intake of chloral hydrate in 4 patients. Scans were acquired with a PET/CT device (Aquiduo; Toshiba Medical Systems, Tokyo, Japan) that consisted of a PET scanner (ECAT HR+; CTI, Knoxville, TN) and 16-section CT scanner (Aquilion V-detector; Toshiba Medical Systems) with a whole-body mode implemented as the standard software. Before PET/CT study, the patients fasted for at least 6 hours. CT was performed from the skull vertex to the toes according to a standardized protocol with the following setting: axial 3.0-mm collimation × 16 modes; 120 kVp; 80 mAs; and a 0.5-second tube rotation, 11.0 mm/s table speed. Patients maintained normal shallow respiration during the acquisition of CT scans. No intravenous or oral contrast material was administered. Emission scans from the skull vertex to the toes were obtained starting mean 67 minutes (range, 55 to 86 min) after the intravenous administration of mean 7 mCi (range, 2 to 10 mCi) of ^{18}FDG. The acquisition time for PET was 2 minutes per table position. Images were reconstructed with attenuation-corrected ordered-subset expectation maximization with 2 iterations and 8 subsets using emission scans and CT data.

CI

Patients in the present study underwent CI studies, which were performed within a week of PET/CT either before or after therapy. CI studies included ^{99m}Tc-hydroxymethylene diphosphonate bone scintigraphy, chest radiography, diagnostic CT of the chest and abdomen, and locoregional MRI. ^{99m}Tc-hydroxymethylene diphosphonate bone scintigraphy was obtained with a dual-headed gamma camera (E.CAM; Siemens). Diagnostic CT was performed separately from PET/CT using a multidetector scanner (Aquilion V-detector; Toshiba Medical Systems) with the following setting; axial 4.0-mm × 4 modes; 120 kVp, automated electric current; 0.5-second tube rotation; and 5.0 mm/s table speed. Images were reconstructed with 10.0-mm slice thickness by means of a standard algorithm. Intravenous contrast agent was administered in all patients. Nonionic contrast material (Oiparomin 370 mg of iodine/mm; Konica-Minolta, Tokyo, Japan) was administered intravenously. The injection dose was 2.0 mL/kg of body weight with an upper limit of 100 mL. No oral contrast material was administered. Scan delay was set at 60 seconds after injection of contrast media. CT images were reviewed in lung, bone, and soft tissue windows in each patient. MRI of the primary site was performed using a 1.5 Tesla system (Signa Horizon; GE Medical Systems; Milwaukee, WI or Visart; Toshiba Medical Systems). Pulse sequences comprised T1-weighted spin echo (SE) or fast SE images, T2-weighted fast SE images, and also postcontrast T1-weighted SE images with fat suppression after injection of 0.1 mmol/kg of gadopentate dimeglumine (Magnevist, Schering, Berlin, Germany).

Imaging Analysis

All images were reviewed and a diagnostic consensus was reached by 2 board-certified radiologists and a nuclear medicine physician who were unaware of any clinical or other radiologic information using a multimodality computer platform. In attempt to reduce bias of image analysis, review process was performed in random order and the interval between reviews of various studies on each patient was 2 weeks. PET and coregistered PET/CT images were analyzed with dedicated software (e-soft; Siemens). The initial review of the attenuation-corrected PET images was performed using transaxial, coronal, and sagittal planes. A pixel region of interest was outlined in the peak activity within regions of increased ^{18}FDG uptake and measured on each transaxial, coronal, and sagittal slice. For quantitative interpretations, maximum standardized uptake value (SUV max) was determined according to the standard formula, with activity in the region of interest given in Bq/mL/injected dose in Bq/weight (kg). However, time decay correction for whole-body image acquisition was not conducted.

Image Interpretation

The presence or absence of nodal or distant metastasis was evaluated for study analysis. The assessment of the T stage was verified histopathologically using specimens obtained by surgical resection of the primary tumors in all patients. For bone tumors, T1 is assigned when the tumor is less than or equal to 8 cm in greatest dimension and T2 is assigned when the tumor is greater than 8 cm in greatest dimension. For soft tissue tumor, T2b is assigned when the deep tumor is greater than 5 cm in greatest dimension. The reference standard of nodal and distant metastases was histologic examination in 15 patients and confirmation of an obvious progression in size of the lesions on follow-up examinations in 35 patients. The reviewers recorded the presence or absence of nodal or distant metastasis and nodal stations and metastatic organs for each modality. For diagnosing bone marrow metastasis, bone marrow biopsy was used as the reference standard in all patients. The presence or absence of abnormal uptake at a site where bone marrow biopsy had been performed was also recorded. Focal ^{18}FDG uptake was considered to be abnormal when it was substantially greater than that of the surrounding normal tissue. The SUV max of the lesion was categorized by comparing with that of normal adjacent tissue: slight uptake was assigned when the SUV max of the lesion was less than 1.5 times that of surrounding normal adjacent tissue; moderate uptake was assigned when the SUV max of the lesion was greater than or equal to 1.5 times but less than 3.0 times that of surrounding normal adjacent tissue; marked uptake was assigned when the SUV max of the lesion was greater than or equal to 3.0 times that of

surrounding normal adjacent tissue. Lymph nodes with abnormal uptake were deemed positive for metastases even when they were smaller than 10.0 mm in short axis nodal diameter. Lung nodules without abnormal uptake but depicting multiple well-defined or ill-defined nodules throughout parenchyma on the chest CT were considered to be positive for metastases. For interpretation of abnormal nodes on CI, the presence of lymph nodes greater than 10.0 mm in short axes was considered positive.

Statistical Analysis

All valuables were assessed on patient-by-patient basis. The McNemar test was used for paired comparisons between 3 modalities. To address the problem of multiple comparisons, Bonferroni correction was applied. Statistical analysis was performed with the SPSS version 11 software program (SPSS Inc, Chicago, IL).

RESULTS

In 50 patients, there were 26 bone sarcomas (52%) and 24 soft tissue sarcomas (48%, Table 1). Among 20 Ewing sarcomas, 8 tumors were bone origin and 12 tumors were soft tissue origin. All patients had increased ^{18}FDG uptake of the primary lesion [average SUV max ± standard deviation (SD); 7.6 ± 3.7: range; 1.7 to 19.0]. Clinical T stages of primary staging tumors (n = 40, 80%) were as follows: T1 (n = 12, 24%), T2 (n = 15, 30%), and T2b (n = 13, 26%). Nodal metastases in 5 patients (10%) and distant metastases in 10 patients (20%) were confirmed by pathologic examinations using biopsy specimens. For suspected nodal metastases in 2 patients (4%) and suspected distant metastasis in 14 patients (28%), diagnosis was confirmed by an obvious progression in size of the lesions on follow-up examinations. The mean follow-up period was 8 months (range, 0 to 14 mo).

TABLE 1. Patient Characteristics

Parameter	Value (%)
Age	
Mean ± SD	13 ± 4
Range	3-17
Sex	
M/F	26 (52)/24 (48)
Primary site	
Bone tumor	26 (52)
Femur	8 (16)
Tibia	8 (16)
Rib	4 (8)
Vertebra	2 (4)
Others*	4 (8)
Soft tissue tumor	24 (48)
Back	6 (12)
Head and neck	4 (8)
Thigh	3 (6)
Groin	2 (4)
Chest wall	2 (4)
Calf	2 (4)
Others†	5 (10)
Histologic diagnosis	
Ewing sarcoma	20 (40)
Osteosarcoma	18 (36)
Synovial sarcoma	5 (10)
Rhabdomyosarcoma	3 (6)
Fibrosarcoma	1 (2)
Epithelioid sarcoma	1 (2)
Pleomorphic MFH	1 (2)
Angiosarcoma	1 (2)

The numbers of the parentheses are percentages.
*Others include mandible (n = 2), ilium (n = 1), and humerus (n = 1).
†Others include abdomen (n = 1), abdominal wall (n = 1), scalp (n = 1), and hand (n = 1).
MFH indicates malignant fibrous histiocytoma.

Among 7 patients with nodal metastasis, the lesion was found only in soft tissue sarcomas: Ewing sarcoma (n = 2), synovial sarcoma (n = 2), rhabdomyosarcoma (n = 2), and angiosarcoma (n = 1). Using CI, nodal metastasis was correctly assigned in 46 patients (92%). On the other hand, nodal metastasis was correctly diagnosed by PET/CT in 48 patients (96%) and by PET in 43 patients (86%, Table 2). The average SUV max ± SD of nodal metastasis was 6.5 ± 1.0 (range, 4.9 to 9.5). One patient was understaged by PET/CT, 2 patients by PET, and 3 patients by CI, respectively (Table 3). Lymph node, which could not be discriminated from the adjacent primary tumor, was a cause of an understage by all modalities. The causes of an understage on CI were due to lymph nodes whose diameter of the short axis were less than 8 mm. The causes of nodal understage by PET were due to a lack of FDG avidity or inability to localize the activity to a lymph node. PET/CT revealed 1 patient with an overstage, while overstaged patients were identified by PET (n = 5) and by CI (n = 1). Reason for an overstage was due to inflammatory reactive lymph nodes on PET/CT, PET, and CI. There was no significant difference found in diagnostic accuracy of nodal metastasis between 3 modalities. The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy were summarized in Table 2.

Among 24 patients with distant metastasis, the lesion was correctly assigned in 43 patients (86%) with PET/CT. The average SUV max ± SD of distant metastasis was 4.2 ± 0.5 (range, 3.0 to 8.0). Distant metastasis was correctly diagnosed in 33 patients (66%) by PET and 35 patients (70%) by CI. The numbers of understaged patients were 7 on PET/CT, 17 on PET, and 15 on CI (Table 3). Reasons for patients of an understage by PET/CT were pleural or peritoneal metastases (n = 4), bone marrow metastasis (n = 2), and soft tissue metastasis (n = 1). The causes of an understage by PET were lung metastases (n = 6), soft tissue metastases (n = 6), pleural or peritoneal metastases (n = 3), and bone marrow metastasis (n = 2). The causes of an understage by CI were due to soft tissue metastases (n = 6), pleural or peritoneal metastases (n = 4), bone metastases (n = 3), and bone marrow metastasis (n = 2). The understage of distant metastases by PET/CT, PET, or CI was due to a lack of FDG avidity or inability to localize the activity to the lesion. Three patients with pleural or peritoneal metastases, 2 patients with bone marrow metastases, and

TABLE 2. Diagnostic Accuracy of Nodal and Distant Metastases in Pediatric Sarcomas

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
PET/CT					
Nodal metastasis	6/7 (86)	42/43 (98)	6/7 (86)	42/43 (98)	48/50 (96)
Distant metastasis	17/24 (71)*†	26/26 (100)	17/17 (100)	26/33 (79)	43/50 (86)*†
PET					
Nodal metastasis	5/7 (71)	38/43 (88)	5/10 (50)	38/40 (95)	43/50 (86)
Distant metastasis	7/24 (29)*	26/26 (100)	7/7 (100)	26/43 (60)	33/50 (66)*
CI					
Nodal metastasis	4/7 (57)	42/43 (98)	4/5 (80)	42/45 (93)	46/50 (92)
Distant metastasis	9/24 (38)†	26/26 (100)	9/9 (100)	26/41 (63)	35/50 (70)†

Data of the parentheses are percentages.
Significant difference was found between 2 modalities by McNemar test with Bonferroni correction (*$P = 0.002$; †$P = 0.008$).
NPV indicates negative predictive value; PPV, positive predictive value.

1 patient with soft tissue metastasis were not detected by any modality. In 2 patients with bone marrow metastasis, the iliac crest where bone marrow biopsies had been performed was also negative on PET or PET/CT. No patients were overstaged by PET/CT, PET, or CI. Diagnostic accuracy of distant metastasis by PET/CT was significantly higher than that of PET ($P = 0.002$) or that of CI ($P = 0.008$). The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy were summarized in Table 2.

DISCUSSION

We have demonstrated a significant difference in diagnostic accuracy for the detection of distant metastasis by PET/CT, PET, or CI in pediatric sarcomas. The improvement of diagnostic accuracy in detecting distant metastasis can affect tumor stage before treatment.

The magnitude of diagnostic accuracy of PET/CT in detection of distant metastasis is unclear, because its efficacy and performance in staging of pediatric sarcomas is still limited.[12–16] In our study, 8 of the 50 patients (16%) had distant metastases detected by PET/CT which were not identified by PET alone or CI. McCarville et al[12] described that PET/CT was useful in identifying and localizing unusual sites of soft tissue and bony metastases not appreciated by CI. These results from the previous studies were consistent with our results.

TABLE 3. Diagnostic Performance in Nodal and Distant Metastases in Pediatric Sarcomas

Parameter	CI	PET	PET/CT
Nodal metastasis			
Correct	46 (92)	43 (86)	48 (96)
Overstaged	1 (2)	5 (10)	1 (2)
Understaged	3 (6)	2 (4)	1 (2)
Distant metastasis			
Correct	35 (70)	33 (66)	43 (86)
Overstaged	0	0	0
Understaged	15 (30)	17 (34)	7 (14)

The numbers of the parentheses are percentages.

There was a significant difference in diagnostic sensitivity, reflected by the 42% difference between PET/CT and PET and 33% difference between PET/CT and CI. PET/CT device permits sequential acquisition of anatomic CT and functional PET images in a single scanning session. Morphologic characterization of active lesions by PET/CT resulted in a lower percentage of equivocal interpretations compared with that of PET alone. This may have been causally linked to the improvement of sensitivity to detect distant metastases in the present study.

In the present study, correct diagnosis of distant metastasis was found in 43 patients (86%) by PET/CT. However, false negative results by an understage were caused by pleural or peritoneal metastasis, bone marrow metastasis, and soft tissue metastasis. Importantly, 3 patients with pleural or peritoneal metastasis; 2 patients with bone marrow metastases, and 1 patient with soft tissue metastasis were not detected by any modality. It is difficult to detect such distant metastases when the lesion gets smaller in size, owing to limited spatial resolution of PET or PET/CT. However, further studies are needed to be conducted for addressing the ability of PET or PET/CT to evaluate metastasis of pleura, peritoneum, bone marrow, and soft tissue in patients with pediatric sarcomas.

We failed to demonstrate a significant improvement in diagnostic accuracy to detect nodal metastasis by any modality. This may be explained by the small numbers of patients with nodal metastasis in the patient population. Lymph nodes whose diameter in the long axis less than 8 mm resulted in understaged patients on both PET and CI. In the present study, nodal metastasis was found in 7 patients (14%) who had soft tissue sarcomas in the primary sites. The causes of nodal understage by PET were due to a lack of FDG avidity or inability to localize the activity to a lymph node. Most histologic subtypes of sarcomas have a tendency to spread via the vascular system to the lung. However, a few histologic types including epithelioid sarcoma[17] and angiosarcoma[18,19] are often accompanied by nodal metastasis at the initial presentation. Although the exact reasons for rarity of nodal metastasis in sarcomas are unclear, further studies

are needed to clarify the clinical implications of PET/CT for diagnosing nodal metastasis in pediatric sarcomas.[20]

Our study has limitations. Patients enrolled in this study may be relatively small population for specific types of bone and soft tissue sarcomas. Our study was intended to examine the diagnostic accuracy of nodal and distant metastases as a potential role of PET/CT, compared with PET or CI. A study with a larger patient population would clarify the clinical impact of PET/CT on initial staging. In our study, all the lesions were not confirmed by pathologic examination. In 14 patients (28%) with suspected nodal and distant metastatic lesions, diagnosis was based on an obvious progression in size of the lesions on follow-up examinations. This might be sampling bias in the statistical analysis.

In summary, we demonstrate that the use of PET/CT in patients with pediatric sarcomas increases the diagnostic accuracy of distant metastasis compared with PET alone or CI. Further studies are required to assess the exact role and clinical impact of PET/CT on initial staging of pediatric sarcomas.

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ORIGINAL PAPER

Prediction of response and prognostic factors for Ewing family of tumors in a low incidence population

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Abstract
Purpose There is some unknown reason Ewing family of tumors (EFTs) is much less common on Asia and Africa than in the Western Caucasian population. This study analyzed the prediction of response and prognostic factors for Ewing family of tumors (EFTs) in an Asian population with a low incidence.
Methods We retrospectively reviewed 94 patients with EFTs between 1978 and 2006. Fifteen patients received local therapy only. Statistical analyses were performed for 79 patients, including those who received systemic chemotherapy, to identify factors related to chemotherapy responsiveness, event-free survival, and overall survival.
Results Of the 79 patients whose records were analyzed, the 5-year event-free rate and overall survival (OS) rate were 41 and 54%, respectively. The response rate to first-line chemotherapy was 61% in 70 patients with assessable lesions. A significant predictor of response was existence of a non-pelvic primary tumor ($P = 0.04$). Significant prognostic factors for OS were age, performance status, and metastases at the time of diagnosis ($P < 0.01$, respectively). Fifty-four patients had disease progression or recurrence after first-line treatment. The time to progression was 3.4 months after salvage treatment. Progression during first-line treatment was significantly associated with time to progression after salvage treatment ($P = 0.01$). All patients treated without chemotherapy in first-line treatment were recurred with poor prognosis.
Conclusion A non-pelvic primary tumor was a favorable predictor of responsiveness to chemotherapy. Chemoresistant patients might less benefit from second line chemotherapy. Chemotherapy in first-line treatment should not be omitted, even if primary tumor was extirpated completely.

Keywords Ewing family of tumors · Predictive factor · Prognostic factor · Response · Chemotherapy · Asian population

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Introduction

The Ewing family of tumors (EFTs) is a group of rare malignant tumors that mostly arise in bone, although a significant proportion of patients have soft tissue primaries. EFTs share histological, immunohistochemical and

cytogenetic characteristics; in the past, they have also been identified as Ewing sarcomas of bone or soft tissue, malignant peripheral primitive neuroectodermal tumors, primitive neuroepitheliomas or Askin tumors. (Miser et al. 1987) The vast majority of these tumors arise in children and young adults. The treatment of EFTs consists of a multidisciplinary approach including surgery, radiotherapy, and combination chemotherapy. During the past three decades, the prognosis of patients with EFTs has improved considerably, as shown in several clinical trials, mainly because of improved chemotherapy regimens (Burgert et al. 1990; Grier et al. 2003; Jurgens et al. 1988; Nesbit et al. 1990; Paulussen et al. 2001; Sluga et al. 2001).

For reasons that remain unknown, EFTs rarely occurs in Asian and African-American populations. The incidence of EFTs in Asian populations is lower than in Western populations (Guo et al. 1999) According to the Japanese Musculoskeletal Tumor Committee, 473 patients with EFTs of bone were registered during 1972–2003, the population of Japan is 120 million (The JOA Musculo-Skeletal Tumor Committee 2003a) Registration of malignant soft tissue tumor had starting from 2003, and 11 patients with EFTs of extra-osseous primary were registered in 2003. (The JOA Musculo-Skeletal Committee 2003b) Only three reports on the clinical outcome of Japanese patients with EFTs have been made (Obata et al. 2007; Ozaki et al. 2002; Yamada et al. 2006). It is controversy that the prognosis of patients with EFTs were relatively poorer compared with the major Euro-American studies. However, the recent report described the clinical outcome of patients with localized EFTs of bone were virtually equivalent (Obata et al. 2007).

Several clinical and biologic characteristics can assist in determining the prognosis and directing the intensity of therapy. These characteristics include age, primary tumor location and size, the presence or absence of metastases, the serum lactate dehydrogenase level, and the response to therapy (Bacci et al. 2000; Catterill et al. 2000; Obata et al. 2007; Rodriguez-Galindo et al. 2003; Sluga et al. 2001). Although chemotherapeutic regimens and treatment strategies based on prognostic factors have been advanced, previous reports from developing countries indicate that similar results were not obtained in non-western population (Cardenas-Cardos et al. 1999; Jenkin et al. 2002; Villarroel et al. 1997) Thus, previously reported prognostic factors may not have the same influence on clinical outcome in patients belonging to populations with a low incidence, even if developed countries.

The aim of this study was to analyze the clinical characteristics and prognostic factors of EFTs in an Asian population with a low incidence.

Methods

Patients

We retrospectively reviewed the records of 94 patients with EFTs; all records were retrieved from a database of patients treated at the National Cancer Center Hospital (Tokyo, Japan) between September 1978 and April 2006. Two experienced musculo-skeletal pathologists (T.H. or K.S.) had diagnosed or reviewed all biopsy or surgical specimens after performing histological or immunohistochemical examinations. Molecular genetic studies such as PCR or FISH had been performed in cases with available specimens (Yamaguchi et al. 2005).

Treatment

In the present study, all the patients had received single modality therapy or various combinations of multi-modality therapy. Therapy for local control was individualized: surgery alone, radiation therapy alone or a combination of surgery and radiotherapy was performed, as suitable. Various systemic chemotherapy regimens were used. The 94 patients were classified into four groups according to their first-treatment systemic therapy regimen: group I consisted of patients treated with systemic chemotherapy, including vincristine, doxorubicin, and cyclophosphamide with or without actinomycin D; group II consisted of patients treated with multi-drug chemotherapy regimens, including vincristine, doxorubicin, actinomycin D and ifosphamide (VAIAdr) or vincristine, doxorubicin, and cyclophosphamide, alternating with ifosfamide and etoposide (VAdrC/IE); group III consisted of patients treated with systemic treatment including various chemotherapy regimens (Meyers et al. 1995, 1998) (T9 protocol, $n = 1$; T11 protocol, $n = 3$; T12 protocol, $n = 1$; vincristine plus etoposide plus cyclophosphamide plus cisplatin, $n = 2$; vincristine plus ifosfamide plus cisplatin, $n = 1$; doxorubicin plus cisplatin, $n = 2$; and etoposide plus cisplatin, $n = 1$); group IV consisted of patients receiving local therapy, including surgery or radiotherapy, without systemic chemotherapy. Some patients received high-dose consolidation therapy and peripheral blood stem cell transplantations or autologous bone marrow transplantations. Salvage treatment after recurrence was classified in the same manner as the first-line treatments.

Response assessment

Objective responses were evaluated according to the WHO criteria (World Health Organization 1979) Patients with no bidimensionally measurable lesions were considered ineligible for the objective response evaluation and were classified as not evaluable (NE). Systemic chemotherapy was