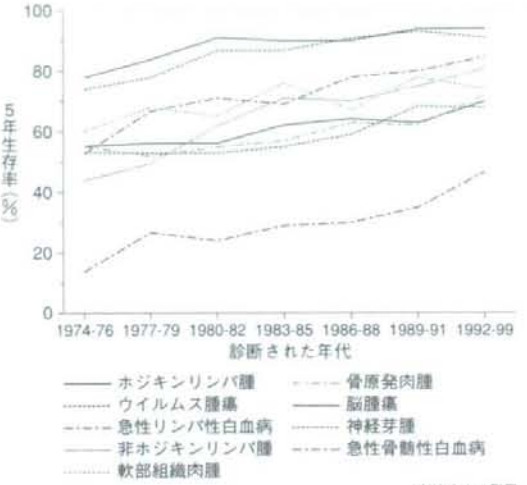
●図1　15歳未満の小児がん患者の5年生存率の傾向



文献4）より引用

基本的には延命が目的であるために、副作用が少ない治療法が望まれます。一方で、小児がんの場合は、たとえ固形腫瘍の転移例であっても治癒を目指して強力な「集学的治療法」を行うことが基本だと考えられており、実際に治癒できる患者も少なからずいます。最近でこそ、成人のがんでも「集学的治療法」が主流となってきていますが、**図1**の治療成績を見れば、この流れは小児がんで始まり、小児がんで初めて成功したと言ってよいことがわかるでしょう。小児がんの患者と家族は常に「治癒」という大目標を目指して闘病しており、治療効果への期待も、その代償として高度な副作用を許容するという考え方も、成人のがんとは大きく異なることに注意が必要です。

小児造血器腫瘍の治療

小児造血器腫瘍には、白血病と悪性リンパ腫が含まれます。

1．白血病の治療

小児の白血病の内訳は、約70％が急性リンパ性白血病（ALL）、約25％が急性骨髄性白血病（AML）、2－3％が慢性骨髄性白血病（CML）と推定されます。

急性白血病の治療[5,6]は、見かけ上の腫瘍細胞が消失する「寛解」と呼ばれる状態を目指す寛解導入療法と、残された細胞を完全に撲滅するために行う寛解後療法に大きく分けられます。

また、中枢神経に浸潤する白血病を予防するために行う治療として、メトトレキサートやシタラビンを用いた髄腔内化学療法が併用されます。

1）急性リンパ性白血病（ALL）

寛解導入療法としては、プレドニゾロンなどのステロイドホルモンにビンクリスチンおよびL-アスパラギナーゼを加えた3剤併用療法（VPL）が基本で、予後が不良と考えられる群に対しては4剤目にダウノルビシンなどのアントラサイクリン系薬剤を加えます。これは病初期から1カ月以上続く長い治療であり、この間に重症感染症で生命の危険にさらされる場合も少なくありません。

寛解後療法として、骨髄回復期からはシタラビン、シクロホスファミドなど、骨髄毒性の強い薬剤を併用した地固め療法、メトトレキサートや6-メルカプトプリンを用いた中間維持療法、と続き、再度、寛解導入療法と地固め療法を繰り返した後に、経口メトトレキサートや6-メルカプトプリンを中心とした維持療法を2－3年継続します。ALLのタイプによっても異なりますが、全体では70％以上の患者が治癒すると考えられています。

ALLの中で最も予後が不良と考えられるフィラデルフィア染色体陽性ALLや、最初の寛解導入療法で寛解に至らない患者（寛解導入不良症例）に対しては、強力な寛解後療法のオプションとして血縁ドナーや骨髄バンクドナーからの同種造血幹細胞移植術が考慮されます。

2）急性骨髄性白血病（AML）

一方、AMLの治療に関しては、成人とほぼ同じ薬剤選択がなされます[7,8]。すなわち、シタラビンとアントラサイクリン系薬剤を基本とし、小児では特にエトポシドを併用する医師が多く、より強力に行われる傾向にあります。ALLと異なり、5～10日間薬剤を固めて投与して3－4週間ごとに繰り返すブロック型治療が行われます。合計で4－5コース、6カ月弱で治療を終了します。AML全体の長期生存率は約50％と考えられています。

AMLについても、予後不良と考えられる特徴がある場合には、寛解後療法のオプションとして同種造血幹細胞移植術が考慮されます。

3）再発の場合

白血病の再発に対しては、再度寛解に導入できるかどうかが最も重要なポイントです。そのために、新しい薬剤の開発が進められています。

ALLの再発に対しては、通常、初発時に類似した寛解導入療法を行って再度の寛解導入を図りますが、最近、クロファラビンという薬剤が欧米で承認され、日本でも治験の開始が検討されています。また、ALLのうちT細胞性ALLの再発に対しては、ネララビンという薬剤が2007年に承認され、その効果が期待されています。

AMLの再発に対しては、ゲムツズマブオゾガマイシンという白血病細胞の表面にあるCD33というタンパク質に特異的に作用する分子標的薬剤が開発され、使用可能です。

2．悪性リンパ腫の治療

小児悪性リンパ腫[9,10]については、成人ほど多くの種類を想定する必要はありません。その90％以上が、リンパ芽球性リンパ腫（LBL）、バーキットリンパ腫（BL）、大細胞型リンパ腫（LCL）の3種類のいずれかで、頻度はほぼ30％ずつの割合と考えてよいでしょう。

LBLは、ALLに極めて類似した細胞が腫瘤を形成した状態と考えてよく、治療方針もALLとほとんど同じになります。一方、BLとLCLは、ALLに類似した薬剤を使用するものの、5日間薬剤を固めて投与して3－4週間ごとに繰り返すブロック型治療が行われます。合計で4－6コース、4－6カ月で治療を終了します。悪性リンパ腫の長期生存率は全体で80％を超えると言われています。

再発リンパ腫に対する新しい薬剤としては、T細胞性LBLに対しても有効で、また、B細胞性リンパ腫に対してはリンパ腫細胞の表面にあるCD20というタンパク質に特異的に作用するリツキサンが使用されます。

小児固形腫瘍の治療[11]

上述の小児造血器腫瘍の治療においては、中枢神経への浸潤例を除き、化学療法のみで治癒が望めます。一方、小児固形腫瘍の治療においては、手術による主要病巣を摘出する「局所療法」が治療の基軸となります。例外として、一部の腫瘍においては、放射線治療を適切に行うことで手術を行わなくても治癒が得られる場合もありますので、手術が困難な部位にある腫瘍の場合には放射線単独の治療が選択される場合があります。また、横紋筋肉腫や神経芽腫など、周囲組織やリンパ節への浸潤傾向の強い腫瘍では、手術を行い、さらに放射線治療が必要となる場合が多々あります。

1．術前・術後化学療法の目的

固形腫瘍における化学療法の役割は、手術を行う前に腫瘍を小さくして切除が確実に行われ、機能的または美

容的な障害を抑えるために行う「術前化学療法」と、局所療法の後に全身転移を予防・治療するために行う「術後化学療法」があります。小児固形腫瘍では、転移のない症例で確実な局所療法を行ったとしても、術後化学療法の追加がなければほとんどの症例で数カ月以内に遠隔転移が生じ、いずれは死に至ることがわかっています(表4)。すなわち、術前化学療法は必須の治療手段と言えます。

一方、術前化学療法は、ほとんどの患者において腫瘍縮小という目的にはかないますが、大きな腫瘍を残したままでは血流やリンパ流への腫瘍細胞の散らばりまでは予防することができないので、手術を遅らせれば遅らせるほど遠隔転移のリスクを増大し、治療成功率が落ちる可能性が高くなります。また少数ですが、化学療法を行いながらも腫瘍が増大してしまう危険性を考慮する必要があります。

診断後、早期の手術が重要であることの医学的根拠は、横紋筋肉腫[12]と腎芽腫で示されています。これらの腫瘍では診断後早期の手術に引き続く術後化学療法が望ましいと言えます。一方、骨肉腫とユーイング肉腫では、適切な術前化学療法によって生存率を落とさずに患肢温存手術の可能性を高めることができるとされています[13]。

2. 化学療法の内容

小児固形腫瘍に対して標準的に用いられる薬剤の組み合わせとその治療期間を表5に示します。この他によく用いられる薬剤としては、イホスファミド、アドリアマイシン、カルボプラチン、エトポシドなどがあり、各がん種間である程度、共通性があります。横紋筋肉腫とユーイング肉腫では約1年間、その他の腫瘍で約半年間の治療期間を要します。

冒頭で述べたように、これらの薬剤は細胞毒性が強く、がん細胞に対する効果も高い代わりに血液毒性や臓器毒性が高度に現れるものが主流です。その結果、高度の血液毒性やそれにともなう感染症、粘膜障害を含む消化管毒性など、化学療法中の支持療法に特別な配慮が必要となります。このように、強力な化学療法は小児固形腫瘍治療の特徴の一つですが、それは抗がん剤を大量に投与すればするほど効果が高く現れる「用量強度」が実際の抗腫瘍効果に反映されやすい化学療法高感受性腫瘍が多いからです。

●表4 主な小児固形腫瘍における術後化学療法の効果

がん種	横紋筋肉腫	ユーイング肉腫	ウイルムス腫瘍	骨肉腫
手術のみの生存率(%)	10～20	5	40	15
術後化学療法を追加した場合の生存率(%)	65	50～60	90	65

このような小児固形腫瘍の特徴を活かした治療として、通常の数倍以上の用量の抗がん剤を併用した「大量化学療法」の有効性が1980年代から試験されてきました。大量の抗がん剤による血液毒性を回避するために、患者自身の骨髄細胞または末梢血幹細胞を凍結保存しておき、「大量化学療法」に引き続いて患者の体内に戻す「自家造血幹細胞移植」という手技を併用するものです。現在、神経芽腫の予後不良群に対しては標準治療の一部と位置づけられるものの、他のがん種に対する有効性は証明されていません[14]。

初発の小児固形腫瘍患者に適切な化学療法と局所療法がなされた場合、転移のない腫瘍ではおよそ70%、転移がある腫瘍でも20～30%が長期生存すると言われています。

日本では疾患によって、まだこの水準に達していないものもあり、今後、小児科、小児外科、放射線科、整形外科、眼科、耳鼻咽喉科など、多数の専門家の協同によるチーム医療がますます重要になってくる分野と考えられます。

◉表5 小児固形腫瘍に対する代表的な薬物療法レジメン

がん種	神経芽腫	横紋筋肉腫	ユーイング肉腫	ウイルムス腫瘍	肝芽腫
レジメン名	New A1	VAC	VDC	EE-4A	PLADO
使用薬剤	VCR 1.5mg/m² 静注 THP 40mg/m² 点滴静注 CDDP 90mg/m² 120時間点滴静注 CPA 1200mg/m² 点滴静注	VCR 1.5mg/m² 静注 CPA 2200mg/m² 点滴静注 Act-D 0.015mg/kg 静注	VCR 1.5mg/m² 静注 CPA 2200mg/m² 点滴静注 DOX 75 mg/m² 48時間点滴静注	Act-D 0.045mg/kg（体重30kg未満）静注を3週ごとに投与 VCR 0.05mg/kg（体重30kg未満）静注を1週ごとに投与	CDDP 80mg/m² 24時間点滴静注 DOX 60mg/m² 48時間点滴静注
推奨治療期間	6コース＝24週間	42週間	52週間	24週間	6コース＝18週間

Act-D：アクチノマイシンD，CDDP：シスプラチン，CPA：シクロホスファミド，DOX：ドキソルビシン，THP：ピラルビシン，VCR：ビンクリスチン

3．再発の場合

小児固形腫瘍の再発には大きく2つの様式があり、もともと主病巣があった場所（原発巣）からの再発と、肺や骨などの遠隔転移での再発です。前者では初発時と同様に手術や放射線治療などの局所療法が治療の基本となります。

再発様式にかかわらず、化学療法で選択される薬剤は、腫瘍細胞の薬剤耐性を考慮して初回の治療で使われていない薬剤が選択されることが多く、イホスファミド、エトポシド、カルボプラチンなどの組み合わせが最もよく使われます。現在、再発固形腫瘍に対する化学療法のオプションは、保険適応の面から非常に限られており、欧米で臨床試験が進んでいるイリノテカンについては日本で医師主導治験が行われており、同じくノギテカンについては研究者主導臨床試験が行われています。これらの結果が有望であった際には、小児固形腫瘍に対する保険適応拡大が厚生労働省に申請される予定です[15]。

おわりに

小児がんは47種類ものがん種の総称であるため、本稿の中ではすべての治療を十分に解説することはできませんでした。特に小児がんの約20％を占める脳腫瘍に関しては触れることができませんでしたが、私たち小児がんの化学療法の専門家が薬物療法を施す場合の考え方をできるだけ平易に解説するよう心がけました。未来ある子どもたちが難病を克服して立派に社会復帰するため、その支援に重要な役割を担う看護師の皆さんの理解に少しでもお役に立てれば、存外の幸せです。

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LETTER TO THE EDITOR

Segregated graft-versus-tumor effect between CNS and non-CNS lesions of Ewing's sarcoma family of tumors

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For patients with the localized Ewing's sarcoma family of tumors (ESFT), first-line multimodal treatment, including intensive multi-agent chemotherapy, local radiation therapy and surgery, produces 70–75% of the long-term survival rate.[1,2] However, once patients relapse, there is no effective treatment that yields a 5-year survival rate exceeding 20%, even with high-dose chemotherapy (HDC) with autologous stem cell rescue.[3,4] Therefore, a new and more effective treatment approach is clearly needed for this population. Several reports have described patients with ESFT who had bone marrow metastases and underwent allogeneic SCT instead of autologous SCT,[5] including a rare patient who exhibited evidence of a graft-versus-tumor (GVT) effect.[6] To accumulate further knowledge, we report the case of a patient with recurrent ESFT who responded to allogeneic SCT from a sibling donor. A unique aspect of this case was that the manifestation of the GVT effect differed in different organs, with involvement of central nervous system (CNS) and non-CNS lesions. The GVT effect is rare in CNS diseases.

A 28-year-old woman was diagnosed with ESFT of the right chest wall. The tumor size was $10 \times 11 \times 8$ cm and no metastases were shown on computed tomography (CT) or bone scans. Histology revealed small, round cells positive for the cell-surface glycoprotein CD99 and negative for desmin, myoD1, S100 protein, CD45 and CD30. Primary treatment comprised of two courses of chemotherapy with vincristine, doxorubicin and cyclophosphamide (VDC), followed by two courses of ifosfamide, and then HDC with thiotepa 300 mg/m^2 for 2 days and etoposide 300 mg/m^2 for 3 days with autologous peripheral blood stem cell rescue. Local radiation therapy with 50 Gy X-ray was also administered. The patient remained well without evidence of recurrent disease until 20 months after the autologous SCT, when she presented with chest pain and a recurrent tumor in the original site was observed on CT scanning (Figure 1a). After four courses of re-induction chemotherapy, including one course of VDC, one course of ifosfamide and etoposide (IE), and two courses of irinotecan, and HDC consisting of etoposide 200 mg/m^2 for 4 days and melphalan 90 mg/m^2 for 2 days with autologous peripheral blood stem cell rescue, she achieved partial remission (Figure 1b). The patient then entered a phase I/II clinical trial of reduced-intensity allogeneic SCT. After

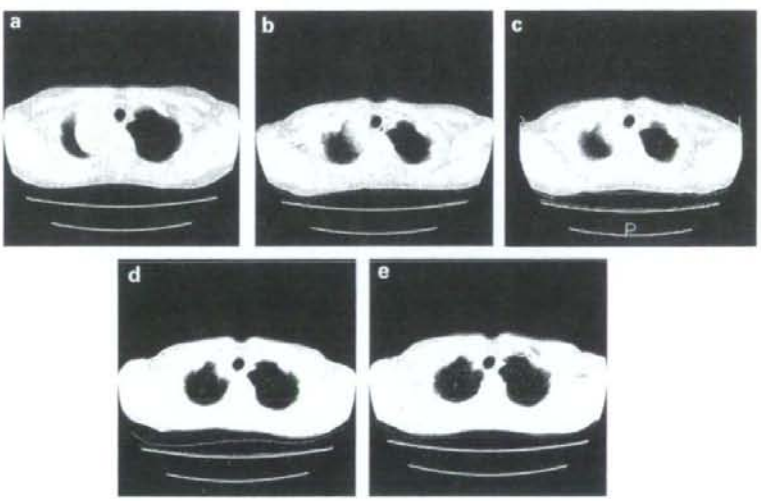

Figure 1 (**a**) Computed tomography (CT) images of a primitive neuroectodermal tumor in the apical lesion on relapse after autoperipheral blood SCT. (**b**) After four courses of chemotherapy, the patient achieved partial remission. A CT scan taken 1 month after the allogeneic SCT, the tumor size was almost no change (**c**), but 4 months after, it showed 50% reduction of the apical tumor (**d**). CR was confirmed at 8 months (**e**).

preconditioning with busulfan (4 mg/kg/day, orally from day −4 to day −3) and fludarabine (30 mg/m^2/day, intravenously from day −8 to day −3), peripheral blood cells containing 2.4×10^6/kg CD34$^+$ cells from her HLA-matched sister were infused. Prophylactic immunosuppression with cyclosporine-A was started on day −1. Her post transplant course was uncomplicated, except for transient grade 1 GVHD of the skin, which began on day +64 and resolved by day +67 without any specific treatment. Cyclosporine-A was tapered from day +70 and discontinued on day +106. A CT scan taken 1 month after the allogeneic SCT when the tumor size was almost unchanged (Figure 1c), but 4 months later, there was 50% reduction of the apical tumor (Figure 1d). CR was confirmed at 8 months (Figure 1e). The patient had headache and was found to have CNS disease on magnetic resonance imaging at 14 months. She died of the disease 5 months after the second relapse. The patient relapsed after initial treatment including HDC with autologous stem cell support, but thereafter, the tumor disappeared coincidently with the occurrence of GVHD, and at least for the primary lesion, the regression period exceeded the period of initial remission. Hence, a graft-versus-ESFT effect seems likely.

In this case, we followed the patient mainly by CT scanning. Although the CT findings showed the tumor status fairly well, they could not provide information regarding viability of the residual tumor. In this regard, PET scanning would be very helpful.

Interestingly, although the GVT effect was exerted in the primary lesion in the chest wall, it was not effective for the prevention of CNS recurrence in this case. The speculated reason for this observation is that the CNS is essentially an immunologically privileged site and theoretically, donor-derived immunocompetent cells carrying the GVT effect mechanism cannot cross the blood–brain barrier.[7] Hence, the application of additional therapeutic intervention to the CNS might become necessary after any systemic manifestations of a GVT effect.

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ORIGINAL ARTICLE

Comparative study of FDG PET/CT and conventional imaging in the staging of rhabdomyosarcoma

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Abstract
Objective The current study was conducted to compare the diagnostic accuracy between ^{18}F-fluoro-2-deoxy-D-glucose (FDG) positron emission tomography (PET)/computed tomography (CT), and conventional imaging (CI) for the staging and re-staging of patients with rhabdomyosarcomas.
Methods Thirty-five patients who underwent FDG PET/CT prior to treatment were evaluated retrospectively. CI methods consisted of ^{99m}Tc-hydroxymethylene diphosphonate bone scintigraphy, chest radiograph, whole body CT, and magnetic resonance imaging of the primary site. The images were reviewed and two board-certified radiologists reached a diagnostic consensus. Tumor stage was confirmed by histological examination and/or follow-up examinations.
Results Interpretation on the basis of FDG PET/CT, and CI, diagnostic accuracies of the T and N stages were similar. Using FDG PET/CT, the M stage was correctly assigned in 31 patients (89%), whereas the accuracy of CI in M stage was 63%. TNM stage was correctly assessed with FDG PET/CT in 30 of 35 patients (86%) and with CI in 19 of 35 patients (54%). The overall TNM staging and M staging accuracies of FDG PET/CT were significantly higher than that of CI ($P < 0.01$).
Conclusions FDG PET/CT is more accurate than CI regarding clinical staging and re-staging of patients with rhabdomyosarcomas.

Keywords FDG PET/CT · Rhabdomyosarcoma · Stage

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Introduction

Rhabdomyosarcoma is the most common form of soft tissue sarcoma in young children. The introduction of multi-agent chemotherapy and radiation therapy has improved the prognosis of the patients with rhabdomyosarcoma. Combined therapy results in higher progression-free survival for children with localized tumor. However, patients with prolonged survival often have recurrent disease. Approximately, 26% of patients with rhabdomyosarcomas will experience tumor recurrence following primary therapy [1]. Therefore, the more precise staging and re-staging for these patients are important for adequate therapy.

The general diagnostic tools for staging soft tissue sarcomas are clinical examination, magnetic resonance imaging (MRI), chest X-ray or chest computed tomography (CT), and bone scintigraphy [2]. Positron emission tomography (PET) with ^{18}F-fluoro-2-deoxy-D-glucose (FDG) has been used in the evaluation of patients with soft tissue sarcomas [3–8], and most of these studies report that FDG PET is advantageous in grading assessment and therapy monitoring compared to conventional imaging. In addition, diagnostic accuracy to detect recurrent disease as a re-staging of patients with prolonged survival is unclear. To completely elucidate the role of FDG PET, the comparison with FDG PET and conventional imaging modalities are needed.

A PET/CT can allow accurate anatomic localization of tumors [9]. This hybrid technique has an important advantage over FDG PET alone due to better localization of tumors for confident interpretation. The aim of the current study was to clarify the role of FDG PET/CT in the staging of rhabdomyosarcoma compared with that of conventional imaging (CI).

Materials and methods

Patients

We retrospectively reviewed FDG PET/CT results since December 2004 to December 2007 for patients with rhabdomyosarcomas, who subsequently underwent chemotherapy, radiotherapy, and/or surgical resection. FDG PET/CT was performed for initial staging in 24 patients (69%) and for re-staging of recurrent disease in 11 patients (31%). The study population consisted of 22 men (63%) and 13 women (37%) with a mean age of 19.8 years (range 3–38 years). The clinical records of all the patients were available for review. All the patients had provided their written informed consent to participate in the current study and to review their records and images.

PET/CT

Studies were performed with the LSO-based whole-body PET/CT scanner (Aquiduo, Toshiba, Medical Systems, Tokyo, Japan). The CT component of the scanner was same as Aquillion 16, which has 16-rows detector. The PET component of the scanner has a transaxial field of view of 68.3 cm, and an axial field of view of 16.2 cm without septa and rotating rod source. The scanner was used in three-dimensional mode with image resolution of 4.0 mm in full width at half maximum (FWHM). Prior to the FDG PET/CT study, the patients fasted for at least 6 h. CT was performed from the head to the mid-thigh according to a standardized protocol with the following setting: axial 2.0-mm collimation × 16 modes; 120 kVp; Auto-Exposure Control (SD10); and a 0.5-s tube rotation, a table speed of 11.0 mm/s. Patients maintained normal shallow respiration during the acquisition of CT scans. No iodinated contrast material was administered. Emission scans from the head to the mid-thigh were obtained starting 60 min following the intravenous administration of 18.5–370 MBq of FDG. The acquisition time for PET was 2 min per table position. For two patients with tumors arising from the lower legs, CT scans, and emission scans were obtained from the head to the legs. Images were reconstructed with attenuation-corrected ordered-subset expectation maximization with 4 iterations, and 14 subsets using emission scans and CT data.

PET, CT, and co-registered PET/CT images were analyzed with dedicated software (e-soft, Siemens Medical Solutions, Knoxville, TN, USA). The initial review of the attenuation-corrected PET images was performed using transverse, coronal, and sagittal planes. The images were reviewed and two board-certified radiologists who were unaware of any clinical or radiologic information using a multimodality computer platform reached a diagnostic consensus. Focal FDG uptake was considered abnormal when it was substantially greater than that of the surrounding normal tissue. For FDG PET/CT, the tumor sizes, and T staging were determined by the CT part of PET/CT. FDG-avid lymph nodes or distant metastases on PET/CT were interpreted as positive for metastases regardless of size. 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 nodule with abnormal uptake was considered positive for metastasis regardless of nodular size. When multiple lung nodules without abnormal uptake depict random distribution on the CT portion of PET/CT, they are considered positive for metastases. A pixel region of interest (ROI) was outlined in the peak activity within regions of increased FDG uptake and was measured on each slice. For quantitative interpretations, maximum standardized uptake value (SUV max) was determined according to the standard formula, with activity in the ROI given in Bq per milliliter per injected dose in Bq per weight (kg). However, time decay correction for whole-body image acquisition was not conducted.

Conventional imaging (CI)

CI methods performed within 1 week of FDG PET/CT, either prior to or following, were chest radiograph,

whole body CT, and MRI of the primary site, and ^{99m}Tc-hydroxymethylene diphosphonate (HMDP) bone scintigraphy. ^{99m}Tc-HMDP bone scintigraphy was performed 2 h following intravenous injection of 370–740 MBq of ^{99m}Tc-HMDP. Both anterior and posterior whole body planar images were simultaneously obtained with a dual-headed gamma camera (E.CAM, Siemens Medical Solutions). Whole body CT was performed on a separate CT device 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; and a 0.5-s tube rotation; and a table speed of 5 mm/s. Iodinated contrast material (Oiparomin 370 mg of iodine per milliliter; Konica-Minolta, Tokyo, Japan) was administered intravenously in all patients. Images were reconstructed with 5.0-mm slice thickness by means of a standard algorithm. 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) images, T2-weighted fast spin echo (FSE) images, as well as post-contrast T1-weighted SE images with fat suppression following injection of 0.1 mmol/kg gadopentate dimeglumine (Magnevist, Schering, Berlin, Germany). Standard pulse sequence parameters and slice orientation varied with the examined anatomic site. The images were reviewed and a diagnostic consensus was reached by two board-certified radiologists who were unaware of any clinical or radiologic information using hard-copy films and multimodality computer platform. Two readers for FDG PET/CT and those for conventional imaging were not the same persons.

Imaging analysis

Each tumor was staged according to the SIOP-International Union Against Cancer TNM classification of pretreatment disease or IRS pretreatment N staging classification [10]. T, N, and M stages were assigned for both FDG PET/CT and conventional imaging. T staging was confirmed by pathologic evaluation using specimens obtained from surgical resection of the primary tumors. When surgical resection was not feasible at sites of the disease, T staging was not determined. N staging was confirmed by pathologic examinations in six patients (40%) using specimens obtained from sampling of regional nodes. In terms of suspected nodes in nine patients (60%), nodal staging was confirmed by an obvious progression in number and/or size of the lesions on follow-up examinations. The mean follow-up period was 374 days (range 47–1000 days). Cerebral spinal fluid (CSF) examination was performed for all head and neck tumors to check the presence or absence of tumor dissemination. Bone marrow aspirate was performed in all cases for the detection of bone marrow metastasis.

Statistical analysis

All valuables were assessed on patient-by-patient basis. The McNemar test was used for paired comparisons between FDG PET/CT and conventional imaging. Statistical analysis was performed with the SPSS version 16 software program (SPSS, Chicago, IL, USA).

Results

There were 22 patients with alveolar subtype, 12 patients with embryonal subtype, and 1 patient with botryoid subtype (Table 1). The primary sites included head and neck (n = 19), trunk (n = 8), and extremities (n = 8). Histologic grade of tumors is grade 2 (n = 1), and grade 3 (n = 34). All patients of initial staging had increased FDG uptake of the primary lesion [average maximal SUV ± SD: 5.48 ± 3.60 (range 1.69–13.47)].

Pathologic T stages available in 24 patients with initial staging are as follows: T1b (n = 3), and T2b (n = 21).

Table 1 Patient demographics

Age	
Mean ± SD	19.8 ± 8.5
Range	3–38
Sex	
M/F	22/13
Subtype	
Alveolar	22 (63)
Embryonal	12 (34)
Botryoid	1 (3)
Distribution	
Head and neck	19 (54)
Paranasal or nasal sinus	14 (40)
Pharynx	1 (3)
Middle ear	1 (3)
Orbit	1 (3)
Temporal muscle	1 (3)
Cheek	1 (3)
Trunk	8 (23)
Chest wall	1 (3)
Groin	1 (3)
Perineum	1 (3)
Vagina	1 (3)
Penis	1 (3)
Testis	1 (3)
Prostate	1 (3)
Retroperitoneum	1 (3)
Extremities	8 (23)
Hand	4 (11)
Lower extremities	2 (6)
Thigh	1 (3)
Elbow	1 (3)

The values in the parentheses are percentages

T stages in patients with re-staging except one are T1a ($n = 7$), T2a ($n = 1$), and T2b ($n = 2$). Complete resection of the primary site was performed in one patient at re-staging. Both FDG PET/CT and conventional imaging classified the T stage correctly in all patients.

Fifteen of 35 patients (43%) had pathological nodal involvement in 11 regions (Table 2). Using FDG PET/CT, the N stage was correctly assigned in 34 patients (97%, Figs. 1, 2), whereas the accuracy of conventional imaging in N stage was 31% ($P = 0.375$, Table 3). No patients were understaged on FDG PET/CT. FDG PET/CT revealed one patient with an overstage. Conventional imaging revealed two patients with an overstage and two patients with an understage. In these patients, the cause of overstage was found in the cervical lymph nodes and pathologic examination of these nodes revealed reactive lymph nodes.

Using FDG PET/CT, the M stage was correctly assigned in 31 patients (89%, Fig. 3), whereas the accu-

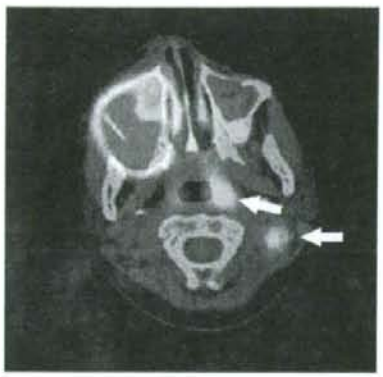

Fig. 1 A 12-year-old boy with primary alveolar rhabdomyosarcoma. Transverse FDG PET/CT image reveals hypermetabolic focus in the right maxillary sinus. FDG accumulation is seen in the left parapharyngeal and deep cervical lymph nodes (9 mm, *arrows*). FDG PET/CT findings were verified at histopathologic examination

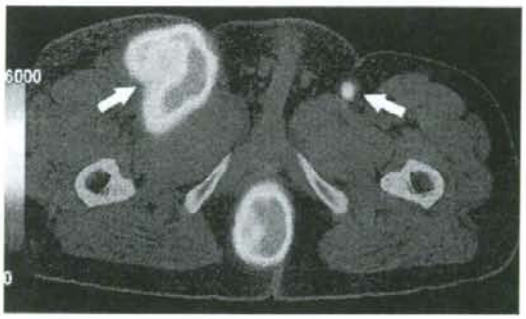

Fig. 2 A 38-year-old man with metastatic alveolar rhabdomyosarcoma. Transverse FDG PET/CT image depicts abnormal uptake in the tumor arising from the perineum. Abnormal uptake of FDG is also noted in both inguinal metastatic lymph nodes: *right* 45 mm, left 9 mm (*arrows*). Lymphedema is seen in the right femoral soft tissue

Table 2 Sites of lymph node involvement

Primary	Lymph node	*n*
Head and neck ($n = 8$)	Deep cervical node	5
	Parapharyngeal node	4
	Submandibular node	3
	Supraclavicular node	2
	Parotid node	1
Trunk ($n = 4$)	Inguinal node	2
	Internal iliac node	2
	External iliac node	1
	Common iliac node	1
	Paraaortic node	1
Extremities ($n = 3$)	Axillary node	2
	Supraclavicular node	1
	Inguinal node	1
	Internal iliac node	1
	Paraaortic node	1

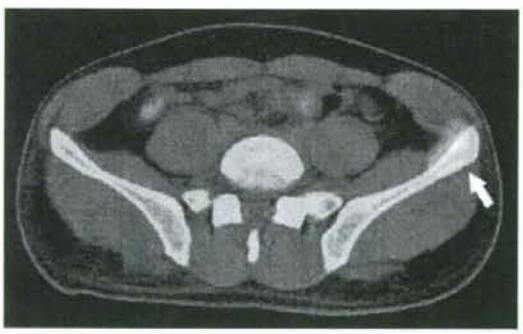

Fig. 3 A 21-year-old man with metastatic alveolar rhabdomyosarcoma. Transverse FDG PET/CT image depicts abnormal uptake of the left ilium (*arrow*). Corresponding CT showed slightly osteoblastic change

Table 3 Diagnostic accuracy of nodal staging

PPV positive predictive value, *NPV* negative predictive value

	Sensitivity	Specificity	PPV	NPV	Accuracy
PET/CT	100	95	94	100	97
Conventional imaging	87	90	87	90	87

racy of conventional imaging in M stage was 63% ($P < 0.01$, Tables 4, 5). Three patients were overstaged on FDG PET/CT. One of these patients had a tumor in his elbow 10 years ago. FDG PET/CT showed an abnormal uptake in the elbow, which was suspicious lesion of bone metastasis. Pathologic examination revealed a fracture associated with osteoporosis following chemotherapy. Two patients, who were overstaged on FDG PET/CT, had spotty uptake of rib caused by trauma. Four patients were overstaged on conventional imaging. Three patients had a fracture following chemotherapy, and the other had second primary tumor arising in the cheek adjacent to the primary site. The latter patient had a tumor in her middle ear 12 years ago. CT showed osteoblastic change in the posterior wall of the right maxillary sinus, which corresponded to an abnormal uptake on FDG PET/CT. This lesion was considered as bone metastasis of rhabdomyosarcoma. Pathologic examination revealed a second primary osteosarcoma arising in the cheek in the previously irradiated field for the primary tumor (Fig. 4). Nine patients (43%) were understaged on conventional imaging. The most frequent cause of an understage was bone metastasis ($n = 6$, 67%). These six patients had too minimal osteoblastic change to be detected on CT (Fig. 3). One patient with bone metastasis also had bone marrow metastasis and spinal dissemination. Other causes were soft tissue metastases ($n = 2$) and pancreatic metastasis ($n = 1$) which were confirmed by pathologic examinations. The latter patient had a tumor in the paranasal sinus and received subsequent chemoradiotherapy 2 years ago. In the re-staging FDG PET/CT, abnormal uptake was found in the pancreatic head, but the tumor was difficult to detect by conventional imaging (Fig. 5).

Table 4 Sites of distant metastasis

Primary	Lymph node	*n*
Head and neck ($n = 7$)	Bone	6
	Soft tissue	1
	Pancreas	1
Trunk ($n = 3$)	Bone	3
	Bone marrow	2
	Pleura	1
Extremities ($n = 4$)	Bone	2
	Bone marrow	1
	Soft tissue	1
	Lung	1

The complete stage of all patients were stage 1 ($n = 8$), stage 2 ($n = 3$), stage 3 ($n = 4$), and stage 4 ($n = 20$). TNM stage was correctly assessed with FDG PET/CT in 30 of 35 patients (86%), and with conventional imaging in 19 of 35 patients (54%, $P < 0.01$, Table 6). Conventional imaging assigned an incorrect TNM stage in 16 patients (46%) because of fracture following chemotherapy, second primary osteosarcoma, and reactive lymph nodes.

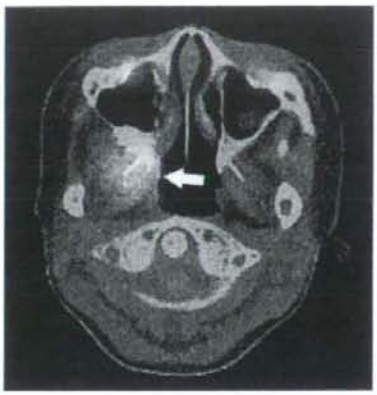

Fig. 4 A 13-year-old girl with second primary osteosarcoma following remission of embryonal rhabdomyosarcoma. Transverse FDG PET/CT image shows abnormal uptake in the right masticator space, which corresponds to previously irradiated area for primary tumor (*arrow*). Also noted is abnormal ossification with the tumor

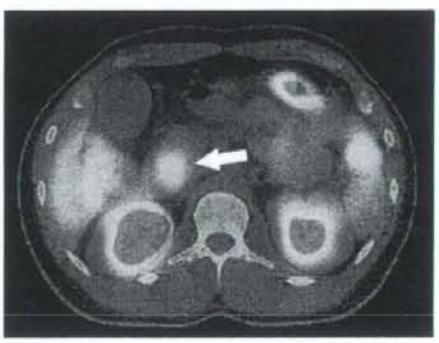

Fig. 5 A 27-year-old man with metastatic alveolar rhabdomyosarcoma. Transverse FDG PET/CT image shows abnormal accumulation of FDG in pancreatic head, which is metastasis at pathologic examination (*arrow*)

Table 5 Diagnostic accuracy of distant metastasis

PPV positive predictive value, *NPV* negative predictive value

	Sensitivity	Specificity	PPV	NPV	Accuracy
PET/CT	90	88	75	96	89
Conventional imaging	20	80	29	71	63

Table 6 Overall staging performance

Variables	Conventional imaging	PET/CT
Overall stage†		
Correct diagnosis	19 (54)	30 (86)
Understaged	10 (29)	1 (3)
Overstaged	6 (17)	4 (11)
N stage		
Correct diagnosis	31 (89)	34 (97)
Understaged	2 (6)	0
Overstaged	2 (6)	1 (3)
M stage†		
Correct diagnosis	22 (57)	31 (89)
Understaged	9 (26)	1 (3)
Overstaged	4 (11)	3 (9)

The numbers in the parentheses are percentages
Significant difference is found between PET/CT and CI by McNemar test (†$P < 0.01$)

Ten patients (29%) with an understage by conventional imaging were attributable for metastases of bone, soft tissue, and pancreas. FDG PET/CT correctly determined TNM stage in 11 patients (31%) in whom the stage derived from conventional imaging was incorrect.

Discussion

The results of the current study show that FDG PET/CT improves the accuracy of staging in patients with rhabdomyosarcoma compared to conventional imaging. Specifically, FDG PET/CT has potentially significant implications for detecting distant metastases at overall staging. Reports about the efficacy of FDG PET/CT in the localization and detection of soft tissue sarcomas are still limited [2, 11]. In our study, 11 of the 35 patients had distant metastases detected by FDG PET/CT, which were not identified by conventional radiologic evaluation.

MRI of the primary tumor, chest radiograph or chest CT, and bone scintigraphy are currently performed as conventional imaging to evaluate the baseline initial and follow-up imaging in the assessment of soft tissue sarcomas. The ability of FDG PET to depict increased metabolism in malignancies has greatly improved the accuracy in detecting neoplasms. However, compared with conventional imaging studies, use of FDG PET alone results in a lack of substantial detail. FDG PET/CT device permits sequential acquisition of anatomic CT and functional FDG PET images in a single scanning session. Morphologic characterization of scintigraphic lesions by FDG PET/CT resulted in a lower percentage of equivocal interpretations compared with that of conventional imaging. Tumor detection with FDG PET/CT technology is rapidly growing. However, there are only limited data available on staging of soft tissue sarcomas with FDG PET/CT.

To our knowledge, only few studies regarding FDG PET or FDG PET/CT for staging rhabdomyosarcoma have been reported. McCarville and colleagues described that FDG PET/CT is useful for identifying and localizing unusual sites of soft tissue and bony metastases not appreciated by conventional imaging [2]. Ben Arush and colleagues reported three cases with alveolar rhabdomyosarcoma arising from the extremities who underwent FDG PET/CT [11]. Two cases had metastatic lymph nodes, which were identified on FDG PET/CT. Peng and colleagues reported a case presenting persistent abnormal FDG uptake following treatment, which results in relapse of rhabdomyosarcoma [12]. These results from the previous studies were consistent with our results and might suggest potential usefulness of FDG PET/CT for the staging of rhabdomyosarcoma.

Combined cancer therapy results in higher progression-free survival more than 5 years for children who had been diagnosed with rhabdomyosarcoma. The development of second primary neoplasms is one of the latest effects of cancer therapy for survivors. The risk of developing a subsequent malignancy is increased among patients with rhabdomyosarcoma [13]. Rich and colleagues reported that most primary tumors were rhabdomyosarcoma which occurred in an extremity and the most common second malignancy was bone sarcoma [14]. In our study, one patient who had been treated a tumor in the middle ear 12 years ago developed a mass in the cheek. Pathologic examination revealed a second primary osteosarcoma within the previously irradiated field for the primary rhabdomyosarcoma. Although both of FDG PET/CT and conventional imaging could not correctly determine the diagnosis of second primary tumor, FDG PET/CT could demonstrate abnormal uptake as a malignant tumor. Second primary tumor often arises from irradiated fields, which is related directly to initial treatment [15]. In our case, the second primary osteosarcoma arose from the irradiated field for the initial treatment of rhabdomyosarcoma occurred in the middle ear. Initial therapy of combined radiotherapy and chemotherapy may play an additional role in the development of second primary malignancies.

Our study has limitations. FDG PET/CT was performed to diagnose the purpose of re-staging in patients enrolled in this study and may differ from the patient population of initial staging studies. Our study was intended to examine the staging accuracy as a potential role of FDG PET/CT; therefore, patient population for both initial staging and re-staging tumors may explain the significant difference of diagnostic accuracy in overall staging compared to conventional imaging. A study with

a larger patient population would clarify the influence of FDG PET/CT on sampling.

In our study, lymph node sampling was not performed in all patients because lymph nodes suspicious for metastasis in 9 of 15 patients (60%) were not accessible. In these lymph nodes, nodal staging was confirmed by an obvious progression in number and/or size of the lesions on follow-up examinations. This might be sampling bias in the statistical analysis.

In summary, the use of FDG PET/CT in patients with rhabdomyosarcoma increases the accuracy of overall staging and M staging compared to conventional staging. Our study suggests that whole-body FDG PET/CT should be the preferred modality with greater diagnostic accuracy for staging and re-staging in patients with rhabdomyosarcoma.

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Epidemiology Note

Trends of Centralization of Childhood Cancer Treatment Between 1975 and 2002 in Osaka, Japan

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Objective: To analyze the tendency to centralize childhood cancer treatment among cancer treatment hospitals in Osaka, Japan over a 28-year period.
Methods: The subjects were patients under the age of 15, newly diagnosed with cancer in Osaka between 1975 and 2002 ($n=4738$). They were categorized into three groups by the time diagnosed (1975–84, 1985–93 and 1994–2002). The International Classification of Childhood Cancer was used as the disease classification. The degree of centralization was examined using a Pareto analysis, the Gini coefficient and the annual average number of cases per hospital.
Results: During this period, the number of children with cancer in Osaka has decreased by nearly half, from 2.1 to 1.2 million and the number of hospitals treating childhood cancer decreased from 37 to 20. However, the Pareto curve and Gini coefficient were almost constant (0.747, 0.737, 0.756 in Gini coefficient for the three diagnosed periods). The annual average numbers of cases per hospital were much low and marginally increased from 5.6 during 1975–84 to 6.1 during 1994–2002 in the hospitals that treated 90% of all cancers.
Conclusions: The degree of centralization appeared to be almost constant from 1975 to 2002 regardless of the decrease in hospitals treating cancer patients.

Key words: childhood cancer – centralization – population-based cancer registry

INTRODUCTION

Recent studies have suggested that there is a relation between better survival and hospital procedure volume (1–3). There also seems to be a relation between childhood cancer patients under the age of 15 referred to specialist centers and better survival (4–5).

The incidence rates of childhood cancer are very low and almost the same worldwide, and were 154 per million for boys and 158 per million for girls in Osaka in 2004 (6). So, centralization is thought to be particularly important to attain better survival for rare childhood cancers (4–5).

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In fact, childhood cancer treatment has been centralized in the UK, Georgia and Germany (7–10), although the child and family are heavily burdened with ambulant treatment and hospital stays. For example, at 244 820 km^2 and with 11.1 million children in 2001, the UK has only 22 treatment centers, which have treated ~90% of newly diagnosed cases (~1350 cases per year in the early 2000s) (7–8). In Osaka with an area of 1898 km^2 and 1.3 million children in 1995, nine specific hospitals had treated ~70% of cases (~180 cases per year) during 1989–98 (11). This information suggests that childhood cancer treatment had been decentralized in Osaka (7–10).

The child population in Osaka has reduced by about half, from 2.1 million in 1975 to 1.2 million in 2005, because of a decreasing birth rate. According to this decline, the

number of childhood cancer patients and the annual treatment volume per hospital should also have decreased. On the other hand, childhood cancer treatment was supposed to have been centralized to specific hospitals in 1990s mainly because of following three factors. First, the number of medical lawsuits increased and this led doctors to refer patients that were difficult to diagnose to specialists (12). Second, multi-center cooperative studies began to conduct larger scale investigations into childhood cancer so that patients could be treated at specific hospitals (13). Third, two large and specialized hospitals for pediatric medicine were built and a university hospital relocated to Osaka in the early 1990s.

We investigated the trend of centralization of cancer patients to specific hospitals from 1975 to 2002 using the data from the population-based Osaka Cancer Registry (OCR).

PATIENTS AND METHOD

Data Sources

Osaka Prefecture is an area with 8.8 million people, and the population covered by the OCR was the largest in Japan till 2006. The proportion of death certificate only (DCO) cases was <2.9% for children under the age of 15 between 1981 and 89, and that of registered patients was estimated to be from 85 to 94% (14). We used this OCR as our source database.

Subjects

Our subjects were patients under the age of 15 and newly diagnosed with cancer between 1975 and 2002 (5291 cases). We then excluded carcinoma *in situ* (two cases), patients who had no information on a treatment (153 cases), those who did not specify both treating hospital code and diagnosing hospital code (three cases), and those that received treatment in other prefectures (417 cases). The final number of subjects for our study was 4738.

We needed to know the number of patients by treatment hospital in order to investigate the degree of centralization. For the analysis, we principally used the treating hospital code (3741 cases). The diagnosing hospital codes were used only when the patients had no information on the treating hospital (997 cases).

The patients were then divided into three period groups by the diagnosed year: 1975–84 (1976 cases), 1985–93 (1661 cases) and 1994–2002 (1101 cases). We then used these data to investigate the centralization tendency.

Classification of Childhood Cancer

Childhood cancer is histologically very diverse and some histological types occur in many different sites. Since 1996, the International Classification of Childhood Cancer (ICCC) has been used for international comparisons of statistical analyses (15). We used twelve diagnostic groups on the basis of ICCC in this research for our classification of childhood cancer.

Method

A Pareto analysis was used to investigate the centralization tendency for childhood cancer treatment. The process for the Pareto analysis was as follows.

A table was prepared to list the number of patients that each hospital treated, and the rows were arranged in descending order of the number of the patients. A column was added to this table that shows the cumulative percentage of the patients in descending order.

In order to find how many hospitals have treated childhood cancers, we counted up the cumulative frequency of hospitals when the cumulative percentage of patients was upper 50 and 75% and when it was 100% by year, diagnosed period and ICCC. We also plotted the Pareto curves with the cumulative percentage of hospitals and patients for the three diagnosed periods.

The Gini coefficient was also calculated as an index of the centralization of treatment for the three diagnosed period groups and the ICCC group. This is defined as follows (16):

$$\text{Gini} = \frac{1}{2n^2\bar{y}} \sum_{i=1}^{n} \sum_{j=1}^{n} |y_i - y_j|$$

Graphically, the Gini coefficient covers twice the area between the Pareto curve and the line of equality. The Gini coefficient ranges between 0 and 1. A 'one' means all the patients were treated at one specific hospital.

Furthermore, the annual average number of cases per hospital was calculated and compared with those of European countries and the USA (8–10).

We used R version 2.4.0 for all the analysis in this study.

RESULTS

The number of children in Osaka during this 28-year period decreased to nearly half, from 2.1 to 1.2 million. That of the hospitals treating childhood cancer also decreased from 37 in 1975 to 20 in 2002, and in particular, decreased from 37 in 1993 to 32 in 1994. After 1993, the number of the newly diagnosed patients drastically decreased from 161 in 1993 to 107 in 2002.

Figure 1 shows the change in the Pareto curve and the Gini coefficient for all childhood cancer cases for the diagnosed period. The Gini coefficients were almost constant (0.747, 0.737, 0.756 for the three periods), and a weak centralization can be found during 1994–2002 when looking at the Pareto curve.

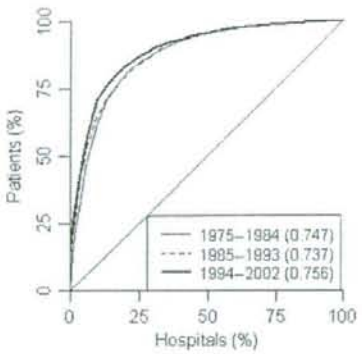

Figure 1. Pareto curve and Gini coefficient by diagnosed period. The Pareto curve shows a weak concentration between the periods of 1975–84 and 1994–2002; however, the Gini coefficient varied very little.

Table 1 shows each cumulative frequency of hospitals and the Gini coefficient by the ICCC and diagnosed period. Each cumulative frequency of hospitals slightly increased or was constant during 1975–84 and 1985–93, but reduced by about half during 1994–2002, except for the hospitals treating upper 50% of malignant bone tumors (VIII). The variations in Gini coefficient were small throughout all three periods. The Gini coefficients by the ICCC groups ranged from 0.275 to 0.665. The rarer the ICCC group was, the smaller the Gini coefficient was. In particular, the low level of centralization was shown for the rarely diagnosed groups: retinoblastoma (V), renal tumors (VI), hepatic tumors (VII), malignant bone tumors (VIII), carcinomas and other malignant epithelial neoplasms (XI) and other and unspecified malignant neoplasms (XII).

The annual average numbers of cases per hospital were less 2.2 in all hospitals during the three diagnosed periods (1975–84: 2.17, 1985–93: 2.15, 1994–2002: 2.18). In hospitals that treated upper 90% of all cancers, those were 5.6 during 1975–84, 5.5 during 1985–93 and 6.1 during 1994–2002. In the early 2000s, those were ~61.4 in the UK, ~60.9 in Georgia and ~32.4 in Germany (8–10). Even hospitals that treated upper 50% of all cancers, the annual average numbers of cases were 14.1 during 1975–84, 15.4 during 1985–93 and 20.4 during 1994–2002. Those were one-third the number compared with ~56.3 in Germany (10). In addition, during 1994–2002, for 10 out of 12 ICCC groups, the annual average number of cases per hospital was less than one person.

DISCUSSION

The trend of centralization of childhood cancer treatment was studied based on the population-based cancer registry in Osaka. Little was previously known about this trend. Our study is valuable because we used population-based data that had about an 85–94% registration rate for children, and we looked at the information for a 28-year period (14).

After 1993, each cumulative frequency of hospitals decreased to about half along with the number of newly diagnosed cancers, and the degree of centralization was almost constant during the three diagnosed periods. These results suggest that childhood cancers have continually been treated at many different hospitals, and the reduction in the number of cases also reduced each cumulative frequency of hospitals. From 1993 to 1994, each cumulative frequency of hospitals reduced approximately by one-third. Around 1993, three large hospitals completed or relocated, so this was supposed to have influenced the trend of hospitals that accessed childhood cancer.

The annual number of cases by the ICCC deserves attention in terms of absolute smallness (Table 1). Despite this smallness, patients were treated at many different hospitals. And the annual average number of cases per hospital has remained very small, which was much lower compared to that in the UK, Georgia and Germany. In addition, each diagnostic group includes many types of cancer and their different treatments. So, centralization to specific hospitals is necessary to improve survival.

Looking at the results, the rarer the ICCC group was, the smaller the Gini coefficient was. Of the types of cancer found in children, clinical trials have been mainly conducted on the more common tumors, such as leukemia (I) or lymphomas and reticuloendothelial neoplasms (II) (13,17). This would have helped to more centralize the more common types of childhood cancer. More influential reasons for doing this would be as follows. Patients were able to freely select and attend treatment hospitals in the Japanese medical system, although they did not usually have enough information on where were specialists. Of total 566 hospitals in Osaka, patients had to find an appropriate one under uncertainty and incomplete information (18). Regretfully, general practitioners had not strictly referred cancer patients to childhood cancer specialists.

From a statistical point of view, the Gini coefficient for a small sample is known to include a downward bias (19,20). The Gini coefficients of each category may have a downward bias, and look to lower centralization, particularly during 1994–2002. Each cumulative frequency of hospitals for sympathetic nervous system tumors (IV) was exceptional compared with those of the other diagnostic groups. This was due to the mass screening at 6 months of age for neuroblastoma (IVa) that was introduced in 1985 and had continued into the 2000s across Japan. As a result of overdiagnosis, the annual age-standardized incidence rate increased by about three times in children from the periods of 1970–84 to 1985–94 (21). Table 1 also shows the increase in the total number of cases of sympathetic nervous system tumors (IV). However, as <10 hospitals carried out mass screening in Osaka, each cumulative frequency of hospitals during 1985–93 is about equal to those during 1994–2002.

Table 1. Cumulative frequency of hospital, Gini coefficient, and number of cases by the International Classification of Childhood Cancer, and diagnosed period

	Diagnosed period	Cumulative frequency of hospitals			Gini coefficient	Annual no. of cases	Total no. of cases
		50%	75%	100%			
I Leukemia	1975–1984	8	17	63	0.619	57.3	573
	1985–1993	7	15	53	0.607	49.0	441
	1994–2002	4	8	36	0.631	37.1	334
II Lymphomas and reticuloendothelial neoplasms	1975–1984	7	16	48	0.524	18.3	183
	1985–1993	7	12	41	0.544	19.0	171
	1994–2002	4	9	26	0.487	11.6	104
III Central nervous system and miscellaneous intracranial and intraspinal neoplasms	1975–1984	5	11	43	0.642	40.9	409
	1985–1993	6	14	47	0.591	33.9	305
	1994–2002	4	10	33	0.564	19.2	173
IV Sympathetic nervous system tumors	1975–1984	4	8	24	0.552	11.9	119
	1985–1993	3	7	28	0.657	22.9	206
	1994–2002	1	3	15	0.665	17.8	160
V Retinoblastoma	1975–1984	2	4	8	0.431	7.6	76
	1985–1993	2	3	9	0.463	4.0	36
	1994–2002	1	2	5	0.357	3.9	35
VI Renal tumors	1975–1984	4	9	19	0.441	7.0	70
	1985–1993	5	11	25	0.451	7.1	64
	1994–2002	2	5	12	0.448	3.9	35
VII Hepatic tumors	1975–1984	4	7	16	0.404	4.1	41
	1985–1993	3	6	15	0.471	4.8	43
	1994–2002	2	4	9	0.370	2.6	23
VIII Malignant bone tumors	1975–1984	3	6	21	0.589	7.5	75
	1985–1993	3	7	23	0.575	8.6	77
	1994–2002	3	5	11	0.402	5.2	47
IX Soft-tissue sarcomas	1975–1984	6	14	34	0.484	9.7	97
	1985–1993	6	15	36	0.472	12.1	109
	1994–2002	3	6	19	0.518	8.1	73
X Germ-cell, trophoblastic and other gonadal neoplasms	1975–1984	7	17	44	0.505	13.9	139
	1985–1993	6	16	42	0.501	15.0	135
	1994–2002	4	10	23	0.413	7.1	64
XI Carcinomas and other malignant epithelial neoplasms	1975–1984	4	8	16	0.382	3.4	34
	1985–1993	5	10	16	0.275	3.0	27
	1994–2002	3	6	10	0.275	2.2	20
XII Other and unspecified malignant neoplasms	1975–1984	9	18	46	0.476	16.0	160
	1985–1993	5	12	23	0.383	5.2	47
	1994–2002	4	10	18	0.306	3.7	33
Total	1975–1984	7	15	91	0.747	197.6	1976
	1985–1993	6	15	86	0.737	184.6	1661
	1994–2002	3	8	56	0.756	122.3	1101

With the exception of neuroblastoma (IVa), the survival of many diagnostic groups in Osaka was lower than that in England and Wales and in the USA, and the report suggested that the reason for this was insufficient introduction and practice of chemotherapy (22). Our study suggested that the low centralization of patients is also related to the lower survival. Previous studies also suggested that the lower survival will also related to the treatment volume in the field of surgery or radiotherapy, although these subjects were adult cancers (23,24). Therefore, to centralize childhood cancer to specific hospitals and to perform a higher volume of procedures are important to ensure better survival. For the centralization of treatment, however, the burden children and their families must deal within their daily lives would increase. A social support system would be needed to achieve and maintain centralization.

In our study, although the identification of treating hospitals was the point, 997 cases did not have treating hospital codes so that the diagnosing hospital code was alternatively adopted. The bias derived from this substitution is assumed minor, because the proportion of cases that the diagnosing hospital code was same as the treating hospital one was 91.8% (3435 cases).

These data included newly diagnosed patients only, so that the specialists might feel that the small degree of centralization would not reflect the realization for childhood cancer treatment. Further study would be needed to investigate the centralization taking into account the succession of treatment.

We confirmed that the hospitals that treated childhood cancers decreased approximately by half during the 1990s, because childhood cancer decreased because of a lower birth rate. The degree of centralization seemed almost constant from 1975 to 2002. The annual average number of cases per hospital marginally increased, although it still was much lower compared with European countries and the USA.

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Conflict of interest statement

None declared.

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ORIGINAL ARTICLE

Low-dose MTX for the treatment of acute and chronic graft-versus-host disease in children

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We report the results of a retrospective analysis in 27 pediatric patients who received low-dose MTX as the second-line treatment for steroid-refractory or -dependent acute and chronic GVHD. Between July 2000 and May 2006, 10 patients with aGVHD and 17 with cGVHD were treated with MTX at a dose of 3–10 mg/m^2 weekly. Seven of ten patients (70%) with aGVHD responded well to MTX, thus resulting in the achievement of either a complete response (CR) or a partial response (PR). The dose of prednisone could be reduced to equal to or lower than 1 mg/kg in the responding patients at the end of MTX therapy. The median number of MTX administrations was five (range, 1–7). Ten (58.8%) of seventeen patients with cGVHD achieved CR or PR. The dose of prednisone could be reduced to lower than 0.4 mg/kg in 16 of 17 patients and seven patients could discontinue prednisone. The median duration of MTX administration was 18 months (range, 1–68). The toxicities of grade III to IV occurred in only six patients presenting cytopenias or elevated levels of serum transaminases. Low-dose MTX was tolerable and effective for the steroid-refractory or -dependent GVHD in reducing the dose of steroid without increasing the risk of opportunistic infection.

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Keywords: low-dose MTX; acute GVHD; chronic GVHD; children

Introduction

GVHD is the most common complication after allogeneic hematopoietic stem cell transplantation (HSCT).[1] Methylprednisolone or prednisone have been mainly used as an initial treatment for acute GVHD (aGVHD) and prednisone and CsA are considered as the first-line therapy for chronic GVHD (cGVHD).[2,3] Against steroid-refractory or -dependent GVHD, for which mortality is reported to be very high,[4,5] the standard second-line treatment remains to be established.

MTX has been widely used as the anti-inflammatory and immunomodulatory agent for the treatment of patients with rheumatoid arthritis and other inflammatory disorders by weekly low-dose (7.5–25 mg) administration and its efficacy and safety have been documented in the literature.[6–10] In addition, low-dose MTX has been employed for a long time as part of the prophylaxis for aGVHD after HSCT.[11–14] On the other hand, MTX had also been used as a part of a combined regimen for the treatment of acute and chronic GVHD, however, there are a few published data or prospective trials to evaluate the feasibility of MTX in the treatment of GVHD.[15,16]

MTX is an antifolate and has been used as the high-dose therapy for the treatment of malignancies since 1947. During the 1980s, the use of low-dose MTX began for the treatment of rheumatoid arthritis.[6,10] One of the mechanisms of the immunomodulatory effect of low-dose MTX is mediated by increasing the release of adenosine which inhibits production of tumor necrosis factor-α, IL-6 and IL-8, in addition to promoting the secretion of IL-10 and IL-4 *in vitro*.[6,17] These cytokines are considered to play an important role in the initiation, propagation or regulation of GVHD,[18–21] thus low-dose MTX should be expected to control GVHD by regulating the cytokine network.

Since 2000, we have employed low-dose MTX treatment for steroid-refractory or -dependent acute and chronic GVHD including that of post donor lymphocyte infusion (DLI). In this report, we show the results of retrospective analysis in 27 patients receiving low-dose MTX as second-line treatment for GVHD.

Patients and methods

Patients

Between July 2000 and May 2006, 27 pediatric patients including 10 with aGVHD and 17 with cGVHD were treated with low-dose MTX. One patient received MTX for his acute and chronic GVHD, which occurred after DLI. The reasons for the administration of MTX were that (1) the clinical manifestations of GVHD did not improve, or

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deteriorated despite the treatment with steroids with or without calcineurin inhibitor; (2) the improvement was observed with first-line therapies but the dose-reduction of prednisone was difficult because of the recurrence of GVHD. Characteristics of aGVHD and cGVHD patients are shown in Tables 1 and 2, respectively.

Low-dose MTX administration

MTX was administered either intravenously or orally at a dose of 3–10 mg/m^2 weekly. The dose of MTX was determined at each physician's discretion for the first few patients, and the majority of patients received MTX at a dose of 5–10 mg/m^2. Because only a few adverse events related to the agent had been observed during this period, we thereafter standardized the initial dose at MTX 10 mg/m^2 from January 2002. Leucovorin was not administered to all patients. Unless a toxicity of higher than grade III due to MTX was observed, then the dose of the agent was neither discontinued nor reduced.

Transplantation procedure

All 10 patients with aGVHD received BMT including one from a matched related donor and nine from mismatched related or matched unrelated donors. Seven were HLA-matched while three were mismatched (one with one locus mismatch and two with two locus mismatch) serologically. Thirteen of seventeen patients with cGVHD received BMT and three received peripheral blood stem cell transplantation, and another one received umbilical cord blood stem cell transplantation. Fourteen were HLA-matched while three were one locus mismatched serologically. The pre-transplant conditioning regimen varied according to diagnosis, disease status, stem cell source and HLA disparities. All but one patient received a myeloablative-conditioning regimen. The remaining one patient with CML received a reduced-intensity conditioning regimen. In case of HSCT from a matched unrelated or mismatched related donor, all patients except three received tacrolimus (FK506) plus short-term MTX 15 mg/m^2 on day 1 and 10 mg/m^2 on days 3, 6, 11 as the prophylaxis for aGVHD. The remaining three patients received CsA plus short-term MTX. In case of matched related HSCT, CsA alone was used.

Diagnosis and grading of GVHD

Diagnosis and grading of aGVHD were based on established clinical criteria.[22] Four patients with grade II developed skin stage 3 only. Another six patients suffered grade III including GVHD of the gut that were stage 2–4.

The onset forms and the types of cGVHD were differentiated according to the published classifications.[23] Fourteen of seventeen cases occurred as the quiescent form, and the remaining three as the progressive form. There was no patient with the *de novo* form of cGVHD in this series. The types of cGVHD included two limited and 15 extensive. The most frequently involved organs were the oral mucosa, skin and liver.

Histological diagnoses were made in four of ten patients with acute GVHD of the gut and in one with chronic GVHD of the upper gastrointestinal tract. No other organs

Table 1 Characteristics and outcomes in acute GVHD patients

UPN	*Sex*	*Age*	*Disease*	*Donor*	*HLA disparity*	*Prophylaxis for GVHD*	*At the start of MTX*						*No. of cycles of MTX*	*At the end of MTX*		*Outcome (no. of days follow-up) and disease status*
							aGVHD				*PSL (mg/kg)*	*Other agent*		*Overall response*	*PSL (mg/kg)*	
							Skin	*Liver*	*Gut*	*Grade*						
240	F	4	CML	UBM	1	FK506/sMTX	3	—	—	II	2	FK	6	CR	1	Alive (1347), in CR
245	F	7	ALL	UBM	0	FK506/sMTX	3	—	—	II	2	FK/Pulse	6	CR	0.3	Alive (1237), in CR
257	M	4	WAS	UBM	0	FK506/sMTX	3	—	—	II	2	FK/Pulse	6	CR	1	Alive (1063)
263	F	6	BDA	RBM	0	CsA	3	—	—	II	2	CsA/Pulse	7	PR	1	Alive (982), in CR
180	F	4	NHL	RBM	2	FK506/sMTX	2	—	2	III	2	FK/Pulse	4	CR	0	Died (576) of relapse
214	M	15	AML	UBM/DLI	0	FK506/sMTX	2	—	3	III	2	None	5	CR	0.2	Alive (1760), in CR
291	M	13	AML	UBM	0	FK506/sMTX	—	3	3	III	2	FK/Pulse	1	PR	0.4	Alive (447), in CR
251	M	13	CML	RBM	2	CsA/sMTX	1	3	4	III	2	CsA/Pulse	4	NR	2	Dead (77)
267	F	2	JMML	RBM	1	CsA/sMTX	3	2	3	III	2	FK/Pulse	1	NR	2	Dead (52)
206	M	15	SAA	UBM	0	FK506/sMTX	—	3	4	III	2	CsA/Pulse	5	NR	1	Dead (145)

Abbreviations: SAA = severe aplastic anemia; aGVHD = acute GVHD; BDA = Blackfan-Diamond anemia; CML = chronic myelogenous leukemia; CR = complete response; DLI = donor lymphocyte infusion; F = female; FK506 = tacrolimus; JMML = juvenile myelomonocytic leukemia; M = male; NR = no response; PR = partial response.; PSL = prednisone; NHL = non-Hodgkin's lymphoma; Pulse = steroid pulse therapy; RBM = related bone marrow; sMTX = short-term MTX; UBM = unrelated bone marrow; UPN = unique patient number; Was = Wiskott–Aldrich syndrome.