●表3 主な小児固形腫瘍に対する第一選択および第二選択の抗がん剤

		神経芽腫	横紋筋肉腫	ESFT	骨肉腫	ウイルムス腫瘍	肝芽腫	網膜芽腫
ビンカアルカロイド	ビンクリスチン	◎	◎	◎		◎	◎	◎
アルキル化剤	シクロホスファミド	◎	◎	◎	○	○		◎
	イホスファミド	○	○	○	○		○	○
抗生物質	アドリアマイシン	◎	○	○	○	○	◎	
	アクチノマイシンD		◎	◎		◎		
プラチナ製剤	シスプラチン	◎	○	○	◎	○	◎	○
	カルボプラチン	◎	○	○	○			
トポイソメラーゼ阻害剤	エトポシド	◎	○	◎	○			◎

ESFT：ユーイング肉腫ファミリー腫瘍
　◎：第一選択薬として教科書に記載、○：第二選択薬として日常的に使用

胞に大きな突然変異が起こるために発生すると考えてよいでしょう。すなわち小児がんは、健康な子どもの身体にある日突然降ってわいたように生じるものであり、その頻度は低いながらも、どの子どもにも起こり得る病気であるという認識が大切です。また、小児がんは、ごく一部の疾患を除いて遺伝することはありません。ウイルスなどの感染症の関連が指摘されるがんもありますが、伝染することはありません。

この2つの事実は、小児がんに対して一般の人が抱いている大きな誤解であり、治療にともなうボディイメージの変化と相まって、がんの子どもたちの社会復帰を妨げる一因となっているようです。小児がんはどの子どもにも起こり得る病気であるので、がんの子どもを特別視するのではなく、病態や治療合併症に十分に配慮しながらも、我々医療者が社会全体と協力しながら、彼らの日常生活を支援していく体制が望まれます。
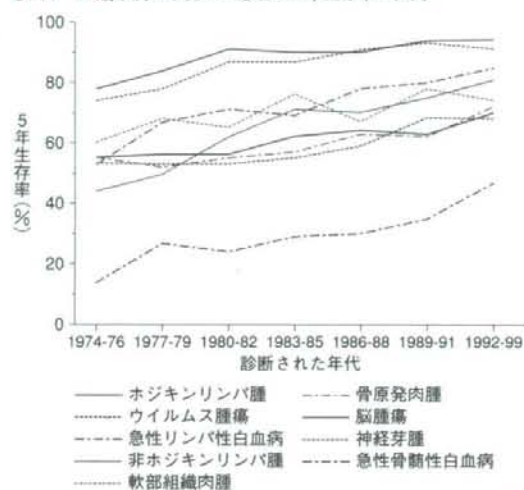
小児がんの特徴[2,3]

小児がんは、上述の染色体異常をともなうことと関連

しますが、病理組織型としては体の深部から発生する「肉腫」が多く、体の表面（上皮）から発生する成人の「癌」と違い、抗がん剤を用いた化学療法にとてもよく反応します。ところが、これらの抗がん剤を単剤で使用しても、初めは効果を認めるもののいずれ再発し、がんの治癒には至らないことが判明しました。このため、小児がんに対する化学療法は、1970年代から併用療法を用いることを基本として発展しました。

現在、小児固形腫瘍に用いられている標準的な化学療法薬剤を表3に示しますが、そのほとんどの薬剤は1990年代前半までに確立されたものであり、アルキル化剤やアントラサイクリン系薬剤など、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となっています。造血器腫瘍の場合は薬剤の用量や組み合わせを最適化することによって、また、固形腫瘍の場合は薬剤と手術や放射線療法とをうまく組み合わせる「集学的治療法」の開発によって、その治療成績を向上させてきました（図1）[4]。日本では遅れている分野もあります、このように小児がんは、おしなべて治療成績が改善されています。

一般的な成人のがんで化学療法が適応となる患者は、手術による根治が望めない進行したがんの患者が多く、

●図1　15歳未満の小児がん患者の5年生存率の傾向

5年生存率（％）

1974-76　1977-79　1980-82　1983-85　1986-88　1989-91　1992-99
診断された年代

――― ホジキンリンパ腫　　------ 骨原発肉腫
……… ウイルムス腫瘍　　　――― 脳腫瘍
――― 急性リンパ性白血病　――― 神経芽腫
――― 非ホジキンリンパ腫　----- 急性骨髄性白血病
……… 軟部組織肉腫

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。

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

●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 $300 \, \text{mg/m}^2$ for 2 days and etoposide $300 \, \text{mg/m}^2$ 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 $200 \, \text{mg/m}^2$ for 4 days and melphalan $90 \, \text{mg/m}^2$ 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
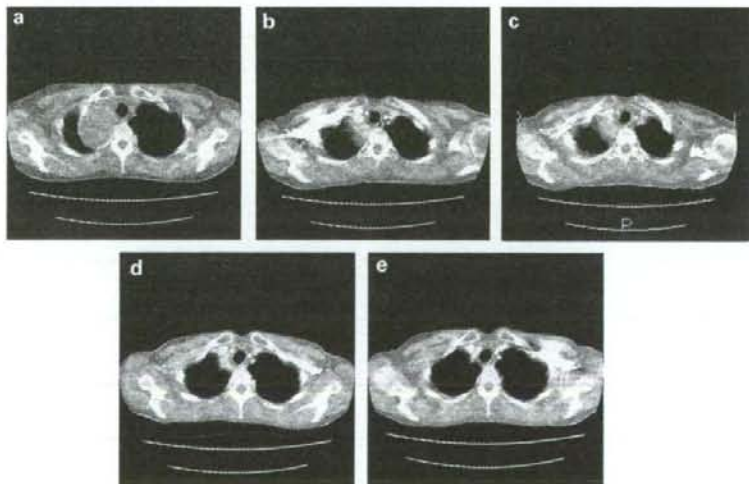

Figure 1 (a) Computed tomography (CT) images of a primitive neuroectodermal tumor in the apical lesion on relapse after autoperipheral blood SCT. (b) After four courses of chemotherapy, the patient achieved partial remission. A CT scan taken 1 month after the allogeneic SCT, the tumor size was almost 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/m²/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-
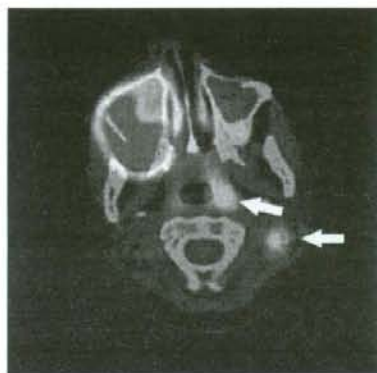

Fig. 1 A 12-year-old boy with primary alveolar rhabdomyosarcoma. Transverse FDG PET/CT image reveals hypermetabolic focus in the right maxillary sinus. FDG accumulation is seen in the left parapharyngeal and deep cervical lymph nodes (9 mm, *arrows*). FDG PET/CT findings were verified at histopathologic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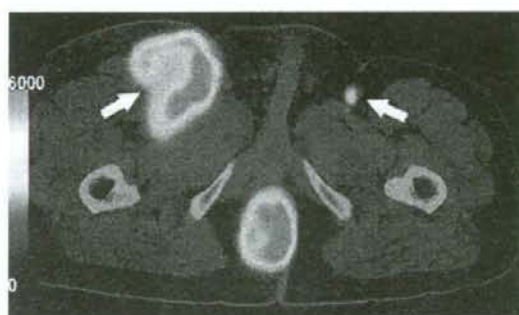

Fig. 2 A 38-year-old man with metastatic alveolar rhabdomyosarcoma. Transverse FDG PET/CT image depicts abnormal uptake in the tumor arising from the perineum. Abnormal uptake of FDG is also noted in both inguinal metastatic lymph nodes: *right* 45 mm, left 9 mm (*arrows*). Lymphedema is seen in the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

Table 2 Sites of lymph node involvement

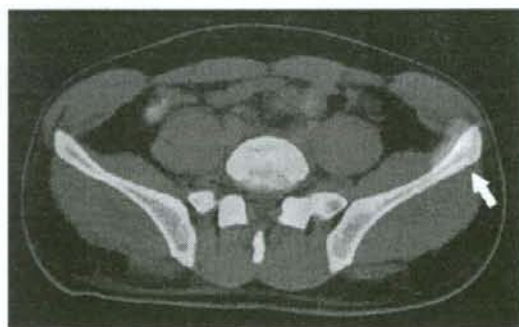| Primary	Lymph node	n
Head and neck ($n = 8$)	Deep cervical node	5
	Parapharyngeal node	4
	Submandibular node	3
	Supraclavicular node	2
	Parotid node	1
Trunk ($n = 4$)	Inguinal node	2
	Internal iliac node	2
	External iliac node	1
	Common iliac node	1
	Paraaortic node	1
Extremities ($n = 3$)	Axillary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

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.
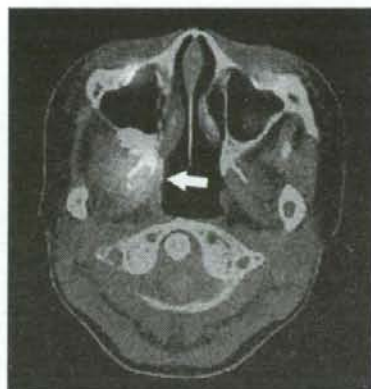

Fig. 4 A 13-year-old girl with second primary osteosarcoma following remission of embryonal rhabdomyosarcoma. Transverse FDG PET/CT image shows abnormal uptake in the right masticator space, which corresponds to previously irradiated area for primary tumor (*arrow*). Also noted is abnormal ossification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

Table 5 Diagnostic accuracy of distant metastasis		Sensitivity	Specificity	PPV	NPV	Accuracy
PPV positive predictive value, *NPV* negative predictive value	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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SPECIAL ARTICLE

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The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).

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The International Neuroblastoma Risk Group (INRG) Staging System: An INRG Task Force Report

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A B S T R A C T

Purpose
The International Neuroblastoma Risk Group (INRG) classification system was developed to establish a consensus approach for pretreatment risk stratification. Because the International Neuroblastoma Staging System (INSS) is a postsurgical staging system, a new clinical staging system was required for the INRG pretreatment risk classification system.

Methods
To stage patients before any treatment, the INRG Task Force, consisting of neuroblastoma experts from Australia/New Zealand, China, Europe, Japan, and North America, developed a new INRG staging system (INRGSS) based on clinical criteria and image-defined risk factors (IDRFs). To investigate the impact of IDRFs on outcome, survival analyses were performed on 661 European patients with INSS stages 1, 2, or 3 disease for whom IDRFs were known.

Results
In the INGRSS, locoregional tumors are staged L1 or L2 based on the absence or presence of one or more of 20 IDRFs, respectively. Metastatic tumors are defined as stage M, except for stage MS, in which metastases are confined to the skin, liver, and/or bone marrow in children younger than 18 months of age. Within the 661-patient cohort, IDRFs were present (ie, stage L2) in 21% of patients with stage 1, 45% of patients with stage 2, and 94% of patients with stage 3 disease. Patients with INRGSS stage L2 disease had significantly lower 5-year event-free survival than those with INRGSS stage L1 disease (78% ± 4% v 90% ± 3%; P = .0010).

Conclusion
Use of the new staging (INRGSS) and risk classification (INRG) of neuroblastoma will greatly facilitate the comparison of risk-based clinical trials conducted in different regions of the world.

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INTRODUCTION

The International Neuroblastoma Risk Group (INRG) classification system was developed to facilitate the comparison of risk-based clinical trials conducted in different regions of the world by defining homogenous pretreatment patient cohorts. As described in the companion article by Cohn and Pearson et al,[1] the INRG classification system was based on survival tree regression analyses of data collected on 8,800 patients. Because the International Neuroblastoma Staging System (INSS) stage of locoregional tumors is based on the degree of surgical resection, this staging system is not suitable for the INRG pretreatment risk classification system. Therefore, the INRG Task Force[1] (see Appendix, online only, for participants) developed a new staging system

based on tumor imaging rather than extent of surgical resection.

The INSS was developed in 1986 after a meeting that was held to establish international consensus for a common staging system and response to therapy.[2,3] Although many countries around the world adopted the INSS, difficulties have been encountered. For example, according to the INSS, the same tumor can be either stage 1 or 3 depending on the extent of surgical excision, making direct comparison of clinical trials based on INSS stages difficult.[4] Furthermore, patients with localized disease who are observed because tumor regression is anticipated cannot be properly staged using INSS criteria.[5] An additional limitation of the INSS is that assessment of lymph node involvement is necessary for proper staging. However, lymph node sampling is subject to the

thoroughness of the individual surgeon, and the assessment of extra-regional lymph node involvement is difficult to apply uniformly.[2-4]

Image-Defined Risk Factors

Since 1994, the International Society of Pediatric Oncology Europe Neuroblastoma Group (SIOPEN) has classified locoregional tumors as resectable or unresectable dependent on the absence or presence of "surgical risk factors," but independent of INSS stage.[6] Surgical risk factors are features detected on imaging that make safe, total tumor excision impracticable at the time of diagnosis.[6,7] The SIOPEN principle for stratifying patients with locoregional tumors by imaging features was adopted by the INRG Task Force at a conference in Whistler, Canada, in 2005, and used in the design of the INRG Staging System (INRGSS). However, to avoid confusion with the INSS, the terms resectable and unresectable are not used in the INRG system.

The premise is that a staging system based on preoperative, diagnostic images will be more robust and reproducible than one based on operative findings and approach. Furthermore, because digital radiographs can be reviewed centrally, the images can be evaluated uniformly. As the surgical risk factors are based on radiographic images, it was decided to use the term

"image-defined risk factors" (IDRFs), and consensus was reached for the IDRFs listed in Table 1. The IDRFs and the INRGSS are designed for use at the time of diagnosis, but they may also be used at reassessments during treatment. Although not needed for staging patients with disseminated disease, it is recommended that the IDRF status of the primary tumor be recorded in all patients (including patients with metastatic disease), so that the impact of IDRFs on surgical resection, surgical complications, and outcome can be prospectively evaluated in all patients.

Staging Investigations

Diagnosis. In the INRG classification system, the diagnosis of neuroblastoma will be made using INSS criteria.[3] A tissue diagnosis of neuroblastoma can be made by conventional histology (with or without immunohistology and increased urine or serum catecholamine or metabolites). A diagnosis can also be made if unequivocal tumor cells are seen in bone marrow samples and increased urine or serum catecholamines or metabolites are present.

Involvement of bone marrow. Bone marrow involvement should be assessed by two aspirates and two biopsies from bilateral sites according to the recommendations of the INSS.[3] Biopsy is not required for infants younger than 6 months of age. Bone marrow disease is determined by morphology on smears and biopsies. Biopsies should be complemented by immunohistochemical techniques. Immunocytologic and/or molecular techniques are also recommended to evaluate the presence of tumor cells in the bone marrow at the time of diagnosis, although the results of these assays are not used for staging (Beiske et al, manuscript in preparation on behalf of the INRG Task Force).

Required imaging studies. Computed tomography (CT) and/or magnetic resonance imaging (MRI) with three-dimensional measurements and of sufficient quality to address IDRFs is mandatory for imaging the primary tumor. The presence or absence of each individual IDRF should be evaluated and recorded (Table 1). When possible, metastatic sites should also be measured by CT and/or MRI, as this information may be needed to evaluate treatment response.

Iodine-123 metaiodobenzylguanidine (MIBG) scintigraphy is mandatory, and it is recommended that the study is performed before tumor excision and according to the Standard Operating Procedure previously described.[8] One unequivocal MIBG-positive lesion at a distant site is sufficient to define metastatic disease. A single equivocal lesion on MIBG requires confirmation by another imaging modality (plain radiographs, and if negative, MRI) and/or biopsy.

Technetium-99 bone scintigraphy is required only exceptionally, but in all age groups, if MIBG positivity of the primary tumor cannot be confirmed (ie, the primary tumor is removed or is not MIBG-avid). An isolated bone uptake should be confirmed by another imaging modality and/or biopsy.

Staging Definitions

The short-version definitions of the four INRGSS stages are listed in Table 2.

Table 1. Image-Defined Risk Factors in Neuroblastic Tumors

Ipsilateral tumor extension within two body compartments
  Neck-chest, chest-abdomen, abdomen-pelvis
Neck
  Tumor encasing carotid and/or vertebral artery and/or internal jugular vein
  Tumor extending to base of skull
  Tumor compressing the trachea
Cervico-thoracic junction
  Tumor encasing brachial plexus roots
  Tumor encasing subclavian vessels and/or vertebral and/or carotid artery
  Tumor compressing the trachea
Thorax
  Tumor encasing the aorta and/or major branches
  Tumor compressing the trachea and/or principal bronchi
  Lower mediastinal tumor, infiltrating the costo-vertebral junction between T9 and T12
Thoraco-abdominal
  Tumor encasing the aorta and/or vena cava
Abdomen/pelvis
  Tumor infiltrating the porta hepatis and/or the hepatoduodenal ligament
  Tumor encasing branches of the superior mesenteric artery at the mesenteric root
  Tumor encasing the origin of the coeliac axis, and/or of the superior mesenteric artery
  Tumor invading one or both renal pedicles
  Tumor encasing the aorta and/or vena cava
  Tumor encasing the iliac vessels
  Pelvic tumor crossing the sciatic notch
Intraspinal tumor extension whatever the location provided that:
  More than one third of the spinal canal in the axial plane is invaded and/or the perimedullary leptomeningeal spaces are not visible and/or the spinal cord signal is abnormal
Infiltration of adjacent organs/structures
  Pericardium, diaphragm, kidney, liver, duodeno-pancreatic block, and mesentery
Conditions to be recorded, but *not* considered IDRFs
  Multifocal primary tumors
  Pleural effusion, with or without malignant cells
  Ascites, with or without malignant cells

Abbreviation: IDRFs, image-defined risk factors.

Table 2. International Neuroblastoma Risk Group Staging System

Stage	Description
L1	Localized tumor not involving vital structures as defined by the list of image-defined risk factors and confined to one body compartment
L2	Locoregional tumor with presence of one or more image-defined risk factors
M	Distant metastatic disease (except stage MS)
MS	Metastatic disease in children younger than 18 months with metastases confined to skin, liver, and/or bone marrow

NOTE. See text for detailed criteria. Patients with multifocal primary tumors should be staged according to the greatest extent of disease as defined in the table.

Stage L1 tumors are localized tumors that do not involve vital structures as defined by the list of IDRFs (Table 1). The tumor must be confined within one body compartment, neck, chest, abdomen, or pelvis. The isolated finding of intraspinal tumor extension that does not fulfill the criteria for an IDRF (Table 1) is consistent with stage L1.

Stage L2 tumors are locoregional tumors with one or more IDRFs. The tumor may be ipsilaterally continuous within body compartments (ie, a left-sided abdominal tumor with left-sided chest involvement should be considered stage L2). However, a clearly left-sided abdominal tumor with right-sided chest (or vice versa) involvement is defined as metastatic disease.

Stage M is defined as distant metastatic disease (ie, not contiguous with the primary tumor) except as defined for MS. Nonregional (distant) lymph node involvement is metastatic disease. However, an upper abdominal tumor with enlarged lower mediastinal nodes or a pelvic tumor with inguinal lymph node involvement is considered locoregional disease. Ascites and a pleural effusion, even with malignant cells, do not constitute metastatic disease unless they are remote from the body compartment of the primary tumor.

Stage MS is metastatic disease in patients younger than 18 months (547 days) with metastases confined to skin, liver, and/or bone marrow. Bone marrow involvement should be limited to less than 10% of total nucleated cells on smears or biopsy. MIBG scintigraphy must be negative in bone and bone marrow. Provided there is MIBG uptake in the primary tumor, bone scans are not required. The primary tumor can be L1 or L2 and there is no restriction regarding crossing or infiltration of the midline.

Special Conditions

In addition to the IDRFs, and independent of the patient's INRGSS stage, three special conditions should be recorded: multifocal primary tumors, pleural effusion, and ascites (Table 1). Patients with multifocal primary tumors should be staged according to the greatest extent of disease as defined above (ie, stage L1, L2, M, or MS).

Relationship of INSS and INRG Stage

The INSS system is not in keeping with the INRG goal of a pretreatment classification system because the INSS assessment is made after the completion of the initial surgical procedure, and the INSS assessment is strongly dependent on the approach of the individual surgeon. To address these limitations, the INRGSS was developed. However, the survival tree regression analysis that forms the basis for the INRG classification system[1] could not be performed in terms of INRGSS because the sample size of patients with known surgical risk factors (analogous to the IDRFs that define INRGSS) in the INRG database[1] (< 850) was too small relative to patients with known INSS stage (> 8,500). Posthoc statistical analyses were therefore performed to determine whether it was reasonable to assign staging in terms of IDRFs of INRGSS instead of INSS, and if the prognostic ability of clinical stage was preserved if INRGSS was used. The analyses were restricted to patients with INSS stages 1, 2, or 3 disease because by definition, INSS stage 4 is equivalent to INRGSS M, and INSS stage 4S is very similar to INRGSS MS. Simon et al[9] have previously demonstrated the prognostic value of using IDRFs to define stage in a retrospective review of German neuroblastoma studies. The only other available data that can be used to validate the clinical significance of IDRFs and the INRGSS are those from SIOPEN in the INRG database.[1] The posthoc analysis of the SIOPEN data was performed in an attempt to validate the findings of the German study.

Statistical Considerations

Cross-tabulation of INRGSS and INSS was performed. The primary analytic end point for the predictive ability of INRGSS was event-free survival (EFS). Time to event was defined as time from diagnosis until time of first occurrence of relapse, progression, secondary malignancy, or death, or until time of last contact if none of these occurred. Univariate analyses were performed to assess the prognostic ability of INRGSS. Kaplan-Meier curves were generated, and curves were compared using log-rank test, with P values less than .05 considered statistically significant.[10] EFS and overall survival (OS) values were reported at the 5-year time point ± SE (per Peto).[11] It was not the goal of this analysis to compare outcome for INRGSS versus INSS (as was done in the study of Simon et al[9]).

Table 3. Distribution of SIOPEN Patients by INRGSS Versus INSS

INSS Stage	INRGSS L1		INRGSS L2		Total No.
	No.	%	No.	%	
1	239	79	64	21	303
2	81	55	66	45	147
3	12	6	199	94	211
Total	332	50	329	50	661

Abbreviations: SIOPEN, International Society of Pediatric Oncology Europe Neuroblastoma Group; INRGSS, International Neuroblastoma Risk Group Staging System; INSS, International Neuroblastoma Staging System.

RESULTS

A total of 661 patients with INSS stage 1, 2, and 3 disease from SIOPEN met INRG eligibility criteria and had known data for IDRFs. Twenty-one percent of patients with INSS stage 1, 45% of patients with INSS stage 2, and 94% of patients with INSS stage 3 disease had IDRFs (ie, in total, 50% of all localized tumors were INRGSS stage L2; Table 3). The remainder of patients who had no IDRFs were classified as having INRGSS stage L1 disease. Of the 661 SIOPEN patients, 474 patients had available outcome data. Both INSS and INRGSS were found to be highly prognostic. The EFS for patients with INRGSS stage L1 disease (90% ± 3%, n = 213) was statistically significantly higher than for stage L2 (78% ± 4%, n = 261; P = .0010; Fig 1). The OS for patients with INRGSS stage L1 disease (96% ± 2%) was also significantly higher than for patients with INRGSS stage L2 disease (89% ± 3%; P = .0068; Fig 2). The EFS for patients with INSS stage 1 disease (92% ± 3%, n = 209) was statistically significantly higher than for patients with INSS stage 2 (78% ± 6%, n = 103; P = .0005) and INSS stage 3 disease (75% ± 5%, n = 162; P < .0001), whereas patients with INSS stage 2 and 3 disease had similar EFS (P = .6611). The OS rates for patients with INSS stage 1, 2, and 3 disease were respectively 98% ± 2%, 95% ± 3%, and 84% ± 4%.
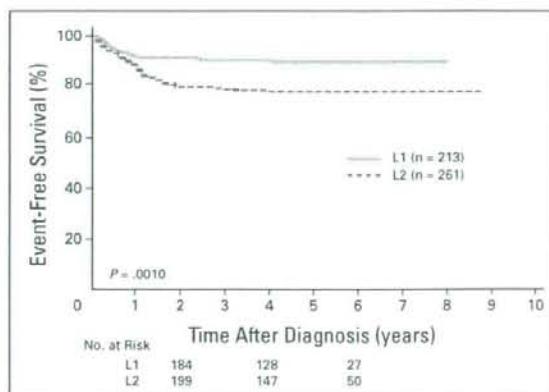

Fig 1. Event-free survival curves for International Society of Pediatric Oncology Europe Neuroblastoma Group patients by International Neuroblastoma Risk Group Staging System stage L1 versus L2 (P = .0010; n = 474). The number of patients at risk for an event are shown along the curves at years 2, 4, and 6.
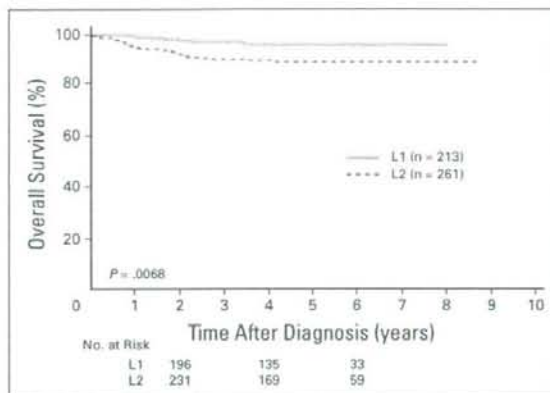
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Fig 2. Overall survival curves for International Society of Pediatric Oncology Europe Neuroblastoma Group patients by International Neuroblastoma Risk Group Staging System stage L1 versus L2 ($P = .0068$; n = 474). The number of patients at risk for death are shown along the curves at years 2, 4, and 6.

DISCUSSION

Because excision of the primary tumor is a prerequisite for assigning patients to INSS stages 1 and 2, and because it is possible to downstage patients by surgical treatment at diagnosis,[4] the INSS is not suitable for pretreatment staging and risk assessment. A new clinical staging system (INRGSS) was, therefore, designed specifically to constitute one of seven prognostic factors in the INRG pretreatment classification system.[1] In the INRGSS, locoregional disease is stratified into two stages instead of three (as in INSS). This decision was based on recognition of the increasing importance of biologic prognostic factors and the excellent OS rate for patients with nonmetastatic neuroblastomas.[1,12-16] Although the INRGSS can be used as a separate and independent clinical staging system, its primary function is as a component of the INRG. The INRGSS is not intended to substitute for the INSS, and it is anticipated that most cooperative groups will continue to use INSS in parallel with INRGSS.

Data from European studies show that absence or presence of IDRFs at diagnosis has prognostic significance. Our posthoc analysis of SIOPEN data[6] confirmed the results of Simon et al.[9] In both studies, EFS was lower for patients with INRGSS stage L2 compared with L1 tumors, and the differences were highly statistically significant. These observations support the translation of EFS tree regression results (in terms of INSS stages) into the INRG classification system (in terms of INRGSS): INSS 1 → INRGSS L1; INSS 2 and 3 → INRGSS L2; INSS 4 → INRGSS M; and INSS 4S → INRGSS MS.[1]

Because the treatment effect of tumor excision is an inherent part of the INSS, the prognostic value of specific stages within INRGSS and INSS cannot be directly compared. For example, most readers would agree that a comparison between patients with INRGSS stage L1 and INSS stage 1 is actually a comparison between an untreated group of patients and a cohort in whom nearly all patients have already been cured. However, even if INRGSS is not intended to substitute for the INSS, the distribution of patients between the two systems is of interest. In the retrospective study of Simon et al,[9] 84% of 160 patients with INSS stage 1 disease met the criteria for INRGSS stage L1 (ie, no

IDRFs), whereas only 16% of 139 patients with IDRFs (stage L2) had INSS stage 1 disease. Similarly, our posthoc statistical analyses of 661 SIOPEN patients, in whom the clinical impact of surgical risk factors (= IDRFs) was examined prospectively, confirm the results of Simon et al.[9] In the data from SIOPEN (Table 3), 79% of patients with INSS stage 1 disease met the criteria for INRGSS stage L1, whereas 21% of patients with IDRFs (stage L2) had INSS stage 1 disease. In the SIOPEN LNESG1 study, 99% of 367 patients who met the criteria for INRGSS stage L1 underwent primary tumor excision (with one surgery-related death caused by renal failure). Among the 363 patients who underwent surgery, 75% had INSS stage 1 disease, 22% had INSS stage 2 disease, and 3% had INSS stage 3 disease. In 56% of 352 patients who had presence of one or more surgical risk factors (INRGSS stage L2), the initial surgical approach was limited to a biopsy; no attempt at primary tumor excision was made.[6] Furthermore, both studies referred to above demonstrated that primary operations in patients with IDRFs were associated with significantly lower complete excision rates and greater risks of surgery-related complications.[6,9]

Recommendations on treatment are not part of the INRGSS, nor of the INRG. Treatment policies must be decided by the individual cooperative groups. However, a new staging and risk classification system cannot exclude possible treatment alternatives, as is the case with INSS and the treatment option of observation without surgery. Today, OS in localized neuroblastoma is more than 90%,[1,12-16] and it can be assumed that a certain number of survivors have been overtreated. A main challenge in the years to come will be to maintain survival with reduced treatment. The INRGSS has been designed to permit uniform staging of all patients independent of the treatment alternatives contemplated.

The INRGSS differs from INSS in four important ways. First, it is based on preoperative imaging and IDRFs, not surgicopathologic findings. Second, the midline is not included in the staging criteria of the INRGSS. Third, lymph node status is not included in the staging of localized disease. Fourth, whereas INSS stage 4S has an upper age limit of 12 months, the Task Force decided to extend the age group for stage MS to patients younger than 18 months. The statistical basis for selecting a cutoff age of 18 months in INRG stages L2, M, and MS is presented and discussed in the companion article by Cohn and Pearson et al.[1] In one German study, the 5-year EFS was 100% in eight patients aged 12 to 18 months with *MYCN* nonamplified tumors who, apart from age, had classical INSS stage 4S disease.[17] The number of patients with "stage 4S disease aged 12 to 18 months" is small, but because the outcome in this patient cohort remains unclear, it is anticipated that the individual cooperative groups will give these patients special attention in prospective studies where careful stopping rules are included. Unlike INSS stage 4S, stage MS includes patients with primary tumors infiltrating the midline (INSS stage 3). The inclusion of all patients with stage L2 primaries is supported by the results of the SIOPEN 99.2 trial (B. De Bernardi, personal communication, February 2008). In this study, all 30 infants with INSS stage 4 disease having primary tumors corresponding to INSS stage 3 disease because of midline infiltration, and with stage 4S metastatic pattern, survived. Eight patients received no chemotherapy, and the remainder received only one or a few courses of chemotherapy to control symptoms. Only five of the patients had their primary tumor excised.

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The effects of treatment on IDRFs are not known, although preliminary data from the SIOPEN Infant Neuroblastoma Study suggests that preoperative chemotherapy (or time) can decrease the incidence of IDRFs by 35% to 40%.[18] It also remains unclear whether the risks of surgical complications are reduced by preoperative chemotherapy when delayed operations are performed in patients who have persistent IDRFs. The impact of individual IDRFs on outcome is currently not known, and the clinical significance of individual IDRFs will need to be analyzed in a larger series of patients to address these questions.

Although surgery is not required for INRGSS staging, the biologic characteristics of the tumor must be known to stratify patients according to the INRG pretreatment classification system.[1] Image-guided core-needle biopsies are acceptable provided adequate material for the histologic and genetic studies are obtained. However, in many cases, complete or partial tumor excision may be a more rational way to obtain tissue for histologic categorization and genetic studies. In the latter case, it must be emphasized that the magnitude of the residual tumor does not influence the INRG stage. Even if completely excised at diagnosis, a localized tumor with (preoperative) one or more IDRFs will still be classified as an INRGSS stage L2.

The Task Force considered using a specific nomenclature to identify subgroups of patients with neuroblastoma with special features like multifocal primary tumors (because of the potential genetic implications of this diagnosis[19,20]). The experience with the INSS does not support a practice of subclassification within a staging system. Although the stage of patients with multifocal primary tumors in the INSS should be given a subscript letter M (stage 1_M, stage $2A_M$, and so on),[3] this subscript has not been widely accepted and only rarely used in published series. The Task Force, therefore, decided not to use subscripts in the INRGSS. This decision implies that patients with important special features not defined by the INRGSS have to be identified by other measures. It is recommended that data regarding the conditions listed in the last portion of Table 1 be collected.

Isolated pleural effusion and ascites are not considered IDRFs in the INRGSS. Although pleural disease is associated with reduced survival rates in patients with metastatic neuroblastoma,[21,22] isolated pleural effusion or ascites is rare in patients with locoregional disease, and its impact on outcome is not clear. In a recent study of 31 patients with neuroblastoma having pleural effusion, none had INSS stage 1 disease and only one had stage 2 disease.[23] It is assumed that the vast majority of patients with ascites also have either metastatic disease or the presence of IDRFs.

The extent of intraspinal tumor extension can range from a small tumor component bulging through one intervertebral foramen to a tumor occupying the majority of the spinal canal. In the SIOPEN studies, intraspinal tumor extension is considered a surgical risk factor if neurologic signs of spinal cord compression are present. However, because clinical signs are not image defined, in INRGSS, it was decided to consider intraspinal tumor extension an IDRF, provided one or more of the imaging criteria listed in Table 1 are present.

In conclusion, the INRGSS is a preoperative staging system that has been developed specifically for the INRG classification system. The extent of disease is determined by the presence or absence of IDRFs and/or metastatic tumor at the time of diagnosis, before any treatment. Use of this pretreatment staging system and the INRG classification system will facilitate the ability to compare results of risk-based clinical trials conducted in different regions of the world, and thereby, provide insight into optimal treatment strategies for patients with neuroblastic tumors.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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