Problems and controversies in the management of childhood sarcomas

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Multidisciplinary care and advances in chemotherapy have dramatically improved the prognosis of paediatric sarcoma patients, but much work remains. There are new techniques for molecular diagnosis of Ewing’s sarcomas and alveolar rhabdomyosarcomas, with molecular techniques of staging and subclassification under development. Osteosarcoma is a clinically heterogeneous disease which continues to resist biologic diagnosis, classification, or staging. In chemotherapy, the roles of ifosfamide and doxorubicin in rhabdomyosarcoma treatment remain unclear. While many children with metastatic or recurrent sarcomas undergo massive therapy with peripheral stem cell or autologous marrow rescue, the efficacy of these manoeuvres is debatable. Osteosarcoma appears to respond best to regimens containing doxorubicin and cisplatin, while the roles of alkylating agents, high-dose methotrexate, and carboplatin remain unclear. Ewing’s sarcoma treatment increasingly includes surgery because of the risk of secondary osteosarcoma after radiation. Most osteosarcoma patients now have limb-sparing excisions, though amputation may provide better function and cosmesis with less risk of complications in some patients. The role of multimodal treatment including chemotherapy for the miscellaneous soft tissue sarcomas remains uncertain.

The past 25 years have witnessed dramatic changes in the management of childhood sarcomas. Coordinated, multidisciplinary care incorporating ever more intense chemotherapy, sophisticated radiotherapy, and reconstructive surgery has moved us far beyond the dark days when amputation or high-dose, large-field radiation was followed by a wait for almost inevitable death. Molecular biology has begun to come to the bedside, offering improved methods of diagnosis and perhaps staging, though therapeutic applications remain distant. Correspondingly, children with sarcomas have seen their chances for survival soar from about 1 in 5 in the 1960s to about 3 in 4 today. This progress has been far from linear though, and intense debates swirl around how the available knowledge and technology can be applied to benefit future patients best. Recognizing the impossibility of providing an encyclopedic overview of sarcoma management in less than a hefty monograph, a few of the issues producing the most ferment and controversy will be considered.
The role of molecular biology in diagnosis and staging

Molecular diagnosis of small round cell tumours

Ewing’s sarcomas and alveolar rhabdomyosarcomas have characteristic chromosomal translocations, which are found in the patient’s tumour cells but not in other cells of the body. These tumour-specific translocations interrupt genes coding for transcription factors, proteins which regulate the activity of other genes in the nucleus, and fuse the interrupted genes into novel ones which encode chimeric (and presumably dysfunctional) transcription factors. The most common translocation in alveolar rhabdomyosarcoma, between chromosomes 2 and 13 (t(2;13) fuses the 5' end of PAX3 on chromosome 2 with the 3' end of the FKHR on chromosome 13. The prevailing Ewing’s sarcoma translocation, t(11;22), fuses portions of the genes encoding the transcription factors EWS and ERG, forming another chimeric transcription factor.

While the ways these translocations contribute to malignancy are currently subjects of speculation and experimentation, their identification and molecular cloning are becoming valuable diagnostic tools in distinguishing the various ‘small round blue cell tumours’ of childhood. RNA-based polymerase chain reactions can detect the chimeric gene messenger RNAs with much greater sensitivity than tumour cytogenetics permitting quick and reliable distinction of alveolar rhabdomyosarcomas and Ewing’s sarcomas from other small round blue cell tumours of childhood. Such distinctions are often difficult, and expert histopathologic review is important for sarcomas in general and rhabdomyosarcomas in particular, since primary pathologists and experts disagree in about one-third of cases. Molecular identification of tumour-specific gene fusions is much quicker than, and at least as accurate as, expert review of microscope slides by remote pathologists. There are unusual cases in which the histopathologic and molecular diagnoses diverge; only the accumulation of more experience will teach us which technique is of the greatest clinical relevance.

Subclassification of rhabdomyosarcomas

Rhabdomyosarcoma is at least two diseases, embryonal rhabdomyosarcoma and alveolar rhabdomyosarcoma. These types are not homogeneous, either: within embryonal rhabdomyosarcoma, in particular, the myriad sites, patterns of spread, histologies, and clinical behaviours make classification difficult. Clinically-based schemes for classification and treatment assignment became very complex, making the conduct of
Fig. 1 The staging and treatment assignment scheme for the Third Intergroup Rhabdomyosarcoma Study (IRS-III) reflected the complexities of patient classification for this highly heterogeneous tumour.

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Clinical studies difficult (Fig. 1). The questions arose: is a simple clinical system of classification possible? Or, can rhabdomyosarcomas be classified biologically in a way that predicts their clinical behaviour?

There have been many attempts to devise a simple, yet useful, clinical classification system. The culminating effort was an international, retrospective analysis of 951 non-metastatic rhabdomyosarcoma cases. On multivariate analysis, site and invasiveness emerged as the key prognostic variables. Surprisingly, histology (embryonal vs alveolar) was not significant in the multivariate analysis; two possible explanations are that the imperfect and evolving histologic criteria for alveolar rhabdomyosarcoma are difficult to apply to a very large retrospective study, and that there is no such thing as a non-invasive ('good') alveolar tumour, while there are such things as invasive ('bad') embryonal tumours. Invasiveness is difficult to assess, however, so size was substituted as a
Biological Staging for Rhabdomyosarcoma

Variable in the Intergroup Rhabdomyosarcoma Study IV and other studies. A more precise biological marker for good and bad embryonal tumours would be valuable.

Several groups of investigators have found that prognosis correlates with tumour cell DNA content (ploidy), with diploid and tetraploid tumours being unfavourable, and hyperdiploid tumours favourable. Since alveolar tumours are either diploid or tetraploid, and embryonal tumours diploid or hyperdiploid, the unfavourable diploid-tetraploid category contains both embryonal and alveolar tumours, and once again histology loses its prognostic significance on multivariate analysis.\textsuperscript{8,9} A Pediatric Oncology Group study focusing on localized, unresected embryonal tumours found that patients with hyperdiploid tumours had a much better prognosis than those with diploid tumours.\textsuperscript{10} Comparison of ploidy with invasiveness would be an interesting experiment.

The intellectually unsatisfying aspect of ploidy is that its biologic basis and implications are unclear. Many embryonal rhabdomyosarcomas have triploidy of chromosome 2, and sometimes other chromosomes,\textsuperscript{11,12} which may account for the extra DNA. How this extra DNA is associated with transformation or good prognosis, or why its absence is associated with transformation and a poor prognosis, remain matters for speculation.

Combining molecular diagnosis with ploidy may provide a means of classifying rhabdomyosarcomas into two prognostic groups without complex clinical algorithms (Fig. 2). The hypothesis behind this classification is that the current intermediate prognosis group actually
Cancer in children

Cancer in children consists of two subgroups, one of which has an excellent prognosis (the localized, hyperdiploid embryonal tumours) and the other of which has a very poor prognosis (the invasive, diploid embryonal tumours and the alveolar tumours, which are all invasive and either diploid or tetraploid). It also assumes that certain sites are favourable because predominantly hyperdiploid embryonal tumours occur in them. Such a scheme, while appealingly simple, will require the data from a fairly large clinical study for validation.

Complexity may be inevitable in rhabdomyosarcoma classification, though: alveolar rhabdomyosarcoma may represent more than one disease, as well. While the large majority of alveolar rhabdomyosarcomas have the t(2;13) that fuses PAX3 with FKHR, some have a t(1;13) that fuses PAX7 with FKHR. These different fusion genes may be associated with different biologic behaviours and prognoses: the t(1;13) tumours appear associated with younger ages, more peripheral locations, and a better prognosis than the t(2;13) tumours.

Molecular staging of Ewing's sarcoma and rhabdomyosarcoma

A skilled microscopist can detect tumour infiltration of bone marrow when 5–10% of the cells are malignant. Since RNA-based PCR is capable of detecting 1 tumour cell in 100,000 normal cells, identification of residual alveolar rhabdomyosarcoma or Ewing's sarcoma in surgical margins, marrow, and even peripheral blood is possible with unprecedented sensitivity. Thus the questions arise: does it make a difference if a patient has microscopically negative, but molecularly positive, bone marrow? A further question is whether or not the disappearance or reappearance of tumour cells in the peripheral blood is of any prognostic value. In an initial study at The Children's Hospital of Philadelphia, however, 2 of 2 alveolar rhabdomyosarcoma patients with molecularly positive, histologically negative marrows suffered marrow relapse and died, while 5 of 6 patients with molecularly and microscopically negative marrows are alive.

Osteosarcoma diagnosis and staging

While the greatly improved prognosis for patients with osteosarcoma is one of the most striking achievements of paediatric oncology, it is far from a complete victory. About one-quarter of patients have metastases at diagnosis, and their prognosis remains poor, with perhaps one-quarter surviving. Of the patients with localised tumours, about one-fifth could be cured by surgery alone (could we identify who they are) and at least a quarter die of disease despite chemotherapy and surgery. A few minutes
of arithmetic leads to the sobering conclusion that we are treating only about 40% of osteosarcoma patients adequately and appropriately. This clinical behaviour of osteosarcoma indicates that it, too, is more than one disease.

Molecular diagnostic techniques for alveolar rhabdomyosarcoma, Ewing's sarcoma, and several other malignancies grew from identification of tumour-specific translocations and their accompanying gene rearrangements. Osteosarcomas, unfortunately, have a bizarre and highly variable karyotype with no consistent pattern\textsuperscript{18}. Lacking any convenient cytogenetic or molecular "handles", molecular diagnosis and classification for osteosarcoma have barely begun. Recent evidence indicates that P-glycoprotein expression at diagnosis, implying resistance to doxorubicin, is a poor prognostic sign\textsuperscript{19}, and the current POG-CCG osteosarcoma study in the US is investigating whether the addition of ifosfamide can overcome this feature.

**Optimising chemotherapy in childhood sarcomas**

**Rhabdomyosarcoma**

**The role of ifosfamide**

The 'VAC' combination of vincristine, actinomycin and cyclophosphamide, in various doses and schedules, has been the standard chemotherapeutic approach to moderate and high-risk rhabdomyosarcoma for 20 years. Until the ongoing Fourth Intergroup Rhabdomyosarcoma Study (IRS-IV), assaults on VAC's primacy have been few and poorly organized. The IRS compared VAC with vincristine--doxorubicin--actinomycin--cisplatin--cyclophosphamide ± etoposide in IRS-III, providing muddled results in which no arm emerged as being superior in intermediate-risk patients. During the last decade in Europe, ifosfamide has displaced cyclophosphamide, yielding the 'IVA' combination. While it is clearly a highly effective regimen\textsuperscript{20}, it has not been subjected to randomised controlled comparisons. Ifosfamide has the disadvantage of substantial nephrotoxicity, which may be severe and irreversible especially in small children\textsuperscript{21}.

Asking whether ifosfamide is actually superior to cyclophosphamide in rhabdomyosarcoma, IRS-IV in the US is comparing three combinations: VAC, IVA, and VIE (vincristine--ifosfamide--etoposide) for patients with intermediate-risk (stage II and III) tumours. VIE is a promising combination because of the remarkable effectiveness of ifosfamide and
etoposide in resistant and recurrent rhabdomyosarcoma. The earliest results of this study probably will not be available until 1998.

The IRS-IV study is addressing the substitution of ifosfamide for cyclophosphamide, but not the alternation of cyclophosphamide and ifosfamide-containing therapy. This is an issue that deserves to be addressed. The recently completed Third Intergroup Ewing's Sarcoma Study in the US demonstrated that a regimen of alternating vincristine-doxorubicin-cyclophosphamide and ifosfamide-etoposide provided strikingly better results than vincristine-doxorubicin-cyclophosphamide alone. In rhabdomyosarcoma, a single-arm 27-patient study of intermediate risk rhabdomyosarcoma treatment using alternating vincristine-doxorubicin-cyclophosphamide and ifosfamide-etoposide, headquartered at the Mayo Clinic, has yielded 25 progression-free survivors (93%) at a median of 21 months. An alternating, non-cross-reactive chemotherapy strategy is ripe for study in a randomised controlled trial in rhabdomyosarcoma.

The role of doxorubicin

More controversial than the relative merits of cyclophosphamide and ifosfamide are the comparative value of doxorubicin and actinomycin. In every other sarcoma in children and adults, doxorubicin is the single most active agent; there is no reason to believe this is not the case in rhabdomyosarcoma as well. Even if it is not superior in all subtypes, it is possible that doxorubicin provides an advantage in unfavorable embryonal or alveolar tumours.

The Intergroup Rhabdomyosarcoma Studies have included doxorubicin in several regimens, but with few clear-cut results. Two comparisons have shown no differences between regimens with and without doxorubicin: IRS-I compared VAC to VAC + doxorubicin in clinical group III and IV patients, with no resulting evidence of a difference in efficacy. VAC was compared to alternating VAC and vincristine-doxorubicin-cyclophosphamide in clinical groups III and IV in IRS-II, producing another dead heat. In IRS-III, VAC was compared with two doxorubicin-containing regimens in clinical groups III and IV, with no apparent differences in efficacy; however the experimental regimens also included cisplatin and etoposide, muddying the comparison. In each of these studies, doxorubicin was substituted for some actinomycin, added to an actinomycin-containing regimen, or included in a regimen with many other confounding chemotherapeutic variables.

The most direct IRS test of doxorubicin was in group III patients in IRS-II, which compared 1 year of vincristine-actinomycin with a regimen of vincristine-doxorubicin for about 4 months, followed by vincristine-
actinomycin for the balance of the year of treatment. The doxorubicin-containing regimen was superior in survival (89 vs 54% at 5 years, \( P=0.03 \))\(^{24} \). The Mayo Clinic results with vincristine-doxorubicin-cyclophosphamide alternating with ifosfamide-etoposide have already been discussed; it is unclear what are the relative contributions of doxorubicin and ifosfamide-etoposide to this regimen's success. A two-by-two, factorial study of VAC versus VDC, with and without IE, would efficiently answer both questions, but require many patients.

**High dose therapy with ‘rescue’ in rhabdomyosarcoma and Ewing’s sarcoma**

The dose intensity of chemotherapy, defined as the amount of an agent given per unit of time, has gained wide acceptance as an important determinant of the efficacy of a regimen. The highest dose-intensity regimens require ‘rescuing’ the patient’s marrow with previously harvested autologous marrow or peripheral blood stem cells, or allogeneic marrow. These ‘transplant’ protocols have become popular as therapies of last resort in many high-risk malignancies, including leukemias and metastatic solid tumours, in children and adults.

The popularity of these regimens for advanced sarcomas is not supported by evidence of effectiveness, and their widespread use over at least 15 years has produced strikingly few publications. In a study of 91 high-risk rhabdomyosarcoma and Ewing’s sarcoma patients undergoing their initial treatment at the US National Cancer Institute between 1981–1986, Horowitz and colleagues used vincristine-doxorubicin-cyclophosphamide induction followed by total body irradiation, high doses of the same agents, and autologous marrow rescue. The results are comparable to what was achieved with less dramatic therapy in similar patients, previously and subsequently: about 20% of patients with metastases at diagnosis survived 6 or more years\(^{25} \). A review of 10 years of European experience with megatherapy for Ewing’s sarcoma produced an actuarial relapse-free survival rate of 21% for patients with metastases at diagnosis and treated in first remission\(^{26} \), also not notably better than the dismal results achieved with conventional chemotherapy. The only really promising report is of a series of 17 German Ewing’s sarcoma patients treated with total-body irradiation and different chemotherapy protocols; 6 were in continuous remission 2 or more years after autograft\(^{27} \). The value of this report is diminished by the patients’ varied clinical circumstances (some initial treatment, some subsequent treatment, some in remission, some not) and the varied chemotherapy regimens.
Chemotherapy for osteosarcoma did not become well-established until the mid-1980s, almost 15 years after it became an accepted part of therapy for rhabdomyosarcoma, Ewing’s sarcoma, Wilms’ tumour, and lymphoma. There was a dearth of clearly active agents, probably arising from a peculiarity of osteosarcomas: they usually calcify in response to chemotherapy and shrink little, if at all. Chemotherapy studies which assess response by changes in the size of lesions on examination or radiographs probably have underestimated the efficacy of drugs against osteosarcoma; this includes traditional phase II studies on relapsed patients and ‘phase II window’ studies on newly diagnosed patients. Indeed, none of the widespread methods of imaging (plain radiographs, computed tomography, magnetic resonance imaging, technetium pyrophosphate bone scans) accurately and reliably predicts the degree of necrosis found on microscopic examination of an excised tumour after preoperative (or ‘neoadjuvant’) chemotherapy. The advent of positron emission tomography (PET) and thallium scanning may improve this situation.

Nonetheless, methotrexate, doxorubicin, mitomycin, and cyclophosphamide produced a few recognizable responses in patients with metastases in the 1960s, and many small and medium-sized studies of adjuvant and preoperative chemotherapy were conducted during the 1970s. They emphasised high-dose methotrexate and doxorubicin; cisplatin was introduced late in that decade. Most showed improved survival compared to historical controls, but none were randomised controlled trials until the Mayo Clinic compared adjuvant high-dose methotrexate with surgery alone, and found 42% relapse-free survival in both arms.

Thus the early 1980s found two contending schools of thought in the treatment of osteosarcoma: one held that chemotherapy was indispensable, while the other attributed the observed improvements in survival in the 1970s to advances in imaging, patient classification, resection of pulmonary metastases, and even changing tumour biology instead. Stephen Carter, reviewing the situation in 1984, called it ‘a massive indictment of the historical control methodology as a failure’. The Multi-Institutional Osteosarcoma Study (MIOS) finally settled the issue with a well-designed randomised controlled trial, demonstrating vastly better event-free survival in patients who received adjuvant chemotherapy compared to patients treated with surgery and observation (66 vs 17% relapse-free survival at 2 years).

The MIOS used chemotherapy containing doxorubicin, cisplatin, methotrexate, bleomycin, actinomycin, and cyclophosphamide; other regimens incorporated vincristine, ifosfamide, and melphalan. Distin-
guishing active from inactive drugs became an urgent priority. The German-Austrian Cooperative Osteosarcoma Study (COSS-82) performed a randomised comparison of high-dose methotrexate with either doxorubicin–cisplatin or bleomycin–cyclophosphamide–actinomycin in preoperative chemotherapy, and found the doxorubicin–cisplatin combination markedly superior. Malcolm Smith and his colleagues at the US National Cancer Institute conducted a meta-analysis of osteosarcoma preoperative chemotherapy, using the degree of tumour necrosis at excision or amputation as the end-point variable. They found that the efficacy of chemotherapy was closely related to the dose-intensity of doxorubicin in the chemotherapy regimen; that high-dose methotrexate had either a negative influence or no influence on efficacy, and that the bleomycin–actinomycin–cyclophosphamide combination detracted from efficacy. The methotrexate–doxorubicin–cisplatin combination became the control arm for the first intergroup osteosarcoma study now underway in the US, and the recently concluded European intergroup osteosarcoma study. Current clinical research in osteosarcoma chemotherapy is moving in different directions in the US and Europe: simplifying chemotherapy further by focusing on doxorubicin and cisplatin in Europe, and adding alkylating agents to the standard therapy in the US.

The role of high-dose methotrexate

High-dose methotrexate is the drug with the longest record of use against osteosarcoma. Several apparently effective chemotherapy regimens, particularly those developed at the Memorial-Sloan Kettering Cancer Center, emphasised the use of high doses of the drug, usually 12 g/m². Some authors contend that the serum level achieved is more critical than the dose, with 1000 micromolar being the critical level. Using doses in this range in pre-operative chemotherapy alone resulted in about 20% of patients having a good histologic response in the primary tumour; in combination with bleomycin–cyclophosphamide–actinomycin the proportion of patients having a good histologic response is about one-third.

Though high-dose methotrexate has some activity against osteosarcoma, the intensity of that activity and its value in multi-agent chemotherapy have long been debated. In the 1970s, the US Children’s Cancer Study Group randomly assigned 166 newly diagnosed osteosarcoma patients to regimens containing two methotrexate doses (300 mg or 7.5 g/m²) along with vincristine and doxorubicin, and found no difference in outcome. Smith’s meta-analysis found either a negative
or no effect, depending upon the model used to analyse the data\textsuperscript{35}. Recently, the European Osteosarcoma Intergroup published the results of its study which randomly assigned patients to methotrexate-doxorubicin-cisplatin or just doxorubicin and cisplatin, holding the length of therapy constant so that patients in the methotrexate arm received two fewer cycles of doxorubicin-cisplatin. The event-free survival in the methotrexate arm was significantly worse (57 vs 41\% at 5 years, $P = 0.05$), indicating that high-dose methotrexate cannot replace two courses of doxorubicin and cisplatin\textsuperscript{36}.

The question remains whether methotrexate adds to the efficacy of osteosarcoma chemotherapy, holding the doses of other drugs constant between the two arms. It could be settled through a randomised controlled trial in which methotrexate was added (or not) to similar doses of doxorubicin-cisplatin, but there are no firm plans in place for such a study. This is unfortunate, since methotrexate is expensive, inconvenient, potentially highly toxic, and reduces the dose intensity of other drugs which appear to be more effective.

Meanwhile the MRC and SIOP, abandoning methotrexate entirely, have chosen to explore further increasing the dose intensity of doxorubicin and cisplatin through a randomised study in which chemotherapy is given every 2 weeks in the experimental arm. This study is still accruing patients.

**The role of alkylating agents**

Ifosfamide has also gained recognition as an effective drug against osteosarcoma\textsuperscript{35,40}. The American-based Children's Cancer Group and Pediatric Oncology Group are collaborating in a randomised controlled trial testing whether ifosfamide contributes to the efficacy of the three-drug combination of methotrexate, doxorubicin, and cisplatin (Fig. 3). This study is also evaluating the role of a biologic agent, MTP-PE, which may decrease the risk of relapse by stimulating pulmonary macrophages to ingest osteosarcoma cells\textsuperscript{41}. Simultaneously, tumours are being assayed for *MDR-1* expression, to test the hypothesis that ifosfamide contributes to survival primarily in patients whose tumours express *MDR-1*, and thus are relatively resistant to doxorubicin. Though accrual is running well ahead of expectations, the answer to the question probably will not be available until at least 1998. The relative efficacy of cyclophosphamide and ifosfamide in osteosarcoma is unknown, as is the case in other sarcomas.
Childhood sarcomas

CCG-7921 / POG-9351: Intergroup Osteosarcoma Study
What does ifosfamide contribute to combination chemotherapy?
Can a biologic response modifier improve prognosis?

Fig. 3 Design of the current US intergroup osteosarcoma study, which uses two randomisations to study the roles of ifosfamide and the biologic agent MTP-PE in the context of multi-agent chemotherapy.

Biopsy-proven osteosarcoma

- Methotrexate
- Doxorubicin
- Cisplatin

Randomize

Methotrexate
Doxorubicin
Cisplatin

Randomize

Methotrexate
Doxorubicin
Cisplatin
Ifosfamide

Randomize

Methotrexate
Doxorubicin
Cisplatin
MTP-PE
None

Carboplatin versus cisplatin

Cisplatin has considerable toxicity, with high-frequency hearing loss and renal dysfunction being long-lasting side-effects. However, it is not very myelosuppressive, and thus is easy to combine with doxorubicin. Carboplatin has much less ototoxicity and nephrotoxicity, but is much more myelosuppressive than cisplatin; it is thus harder to combine with other agents.

There is little experience with carboplatin in osteosarcoma. In a Children's Cancer Group phase II study, there were no responses among 12 evaluable osteosarcoma patients treated, and only 1 patient had stable disease\textsuperscript{42}. In a German phase II study, 17 of 20 patients had progressive disease, making the method of determining response moot\textsuperscript{43}. Since the spectra of activity of cisplatin and carboplatin are very similar, and since the majority of osteosarcoma patients have received cisplatin, these poor results are not surprising. When used as initial therapy the results were promising in one small study\textsuperscript{44}.

Primary tumour management in Ewing’s sarcoma and osteosarcoma

Surgery versus radiation in Ewing’s sarcoma treatment

Ewing’s sarcoma has generally been considered easier to treat than osteosarcoma by virtue of its sensitivity to radiation therapy. Radiation is especially attractive for primary tumour treatment when the lesion is in an unexpendable bone (such as a vertebra), or one whose surgical
removal would be mutilating and disabling (such as the femur or pelvis). Recently, the trend has been away from radiation, and toward surgery for primary tumour control, because of the increasing sophistication of surgery, including complex reconstructions and vascularized bone autografts, increasing doubts about the efficacy of radiation therapy, especially for large tumours, and concern about second malignancies following radiation therapy.

The evidence for better survival with surgical excision is circumstantial; it is difficult to separate the prognostic influences of tumour size and location from the influence of surgery, since the larger and more central tumours are the ones most likely to be irradiated rather than excised. A Mayo Clinic series, examining the records of 36 patients with Ewing’s sarcoma of the pelvis and treated with chemotherapy, found that only 1 of 8 patients who had surgical excision had a local recurrence, while 4 of 13 treated with radiation had local recurrences (statistically not significant). Actuarial 5-year overall survival was 75% in the surgically treated group, and 25% in the irradiated group (P<0.005). An analysis of 144 Italian patients with localized tumours found that surgery contributed importantly to survival, though this may not be the case in the pelvis. Several attempts to design randomized controlled trials of radiation versus surgery have failed because of the many variables and strong opinions involved.

Aside from a possibly higher risk of local recurrence, the most serious drawback to reliance on radiation therapy for treatment of primary Ewing’s sarcomas is the risk of second malignant neoplasms, especially osteosarcomas. The risk of secondary osteosarcoma seems related to both the radiation dose and alkylating agent exposure, both of which are very high in patients treated for Ewing’s sarcoma. Various retrospective studies have found the secondary sarcoma risk in Ewing patients to range from 4.5% at 20 years to nearly 4 times that figure. The patients’ previous intense chemotherapy makes these secondary osteosarcomas very difficult to treat, and they are usually fatal.

These problems have led to the development of combined surgical and radiotherapeutic approaches, including excision with close margins followed by reduced-dose radiation therapy, or radiation therapy followed by surgical excision at the end of therapy, when further chemotherapy will not compromise healing. Both approaches remove the risk of secondary sarcomas by removing the bone in the radiation field.

Limb salvage versus amputation in osteosarcoma treatment

With rare exceptions, osteosarcoma cannot be cured with chemotherapy alone; surgical excision of the involved bone is indispensable. Limb
salvage surgery has displaced amputation as the surgical treatment of choice during the last 10 years. While there are no randomised studies, it appears that local recurrence is about equally likely, though a poor histologic response to preoperative chemotherapy may increase the local recurrence risk with limb salvage\textsuperscript{52}. Even pathologic fracture is no longer considered a contra-indication to limb-sparing surgery. Limb salvage surgery is most strongly indicated in the treatment of upper limb lesions. Since the arms are not ordinarily weight bearing, fragile reconstructions impose relatively little disability, and there is also no satisfactory prosthetic replacement for a hand.

It is not obvious, however, that limb salvage surgery is always superior to amputation, especially in the lower limb. The complication rate is high, particularly with flap ischemia and infection; complications and recurrences result in the eventual amputation of about one-quarter of salvaged limbs\textsuperscript{53,54}. Revisions or re-operations to compensate for complications, wear, loosening or growth are much more frequent than after amputations\textsuperscript{53}. An analysis of 97 lower limb endoprostheses at Memorial Sloan-Kettering Cancer Center revealed an event-free prosthetic survival (i.e. no complications or revisions) of just over 50% at 5 years. The reconstructions are usually fragile, imposing limitations on activities that chafe many active children and adolescents. A retrospective analysis of 17 children treated with expandable endoprostheses for lower limb bone tumours found all having sports restricted, and only 7 (41\%) walking independently\textsuperscript{55}. Cosmesis is often poor, and disability considerable, especially in excisions of the knee joint with arthrodesis.

The amputee, however, is able to enjoy unrestricted physical activities, including contact sports. Current and former amputated patients at CHOP have enjoyed backpacking, basketball, tennis, soccer, softball, skiing, bicycling, field hockey, wrestling, and even varsity football. With amputations below the upper third of the femur, function and cosmesis with modern prostheses is excellent. Complications and re-operations are rare.

Neither method of surgical treatment appears superior in studies of psychological and social adjustment. Patients with amputations are indistinguishable from patients with limb sparing surgery in terms of education, employment, psychological well-being, and social experience\textsuperscript{53,56}.

Osteosarcoma of a major bone cannot be treated without disability in 1996; limb salvage surgery merely allows patients and families to choose what sort of disability they wish to live with. The choice of surgical procedure should be made only after extended, candid discussions with the patient and family, and thorough acquaintance with their life style and priorities. Visits by successful limb salvage veterans and amputees are very helpful to families and staff, providing a great deal of
information and lysing the horror that often surrounds the subject of amputation.

**Miscellaneous soft tissue sarcomas**

While rhabdomyosarcomas, Ewing’s sarcomas, and osteosarcomas account for most of the connective tissue malignancies in children and adolescents, there is a sizable population of patients with a variety of other connective tissue malignancies. These tumours, which account for about one-third of soft tissue sarcomas in pediatrics, include fibrosarcomas, neurofibrosarcomas, malignant fibrous histiocytomas, synovial sarcomas, and others. When these patients have localized tumours and are treated either with complete excision, or gross total excision and radiation, between half and three-quarters survive. Because of their diversity, small numbers, and fair prognosis, they are a difficult population to study and their optimum management is unclear.

A Pediatric Oncology Group study randomized 83 patients with these non-rhabdomyosarcoma soft tissue sarcomas (NRSTS) between observation and treatment with a chemotherapy combination including vincristine, doxorubicin, actinomycin, and cyclophosphamide; no benefit in survival could be found\(^5\), though the statistical power of the experiment was modest and the chemotherapy gentle by current standards. However, we have seen several patients with metastatic neurofibrosarcoma and synovial sarcoma have complete responses to a regimen of alternating vincristine–doxorubicin–cyclophosphamide and ifosfamide–etoposide, indicating that these tumours are not utterly resistant to chemotherapy. Its proper role still needs definition, preferably through well-organized cooperative group studies.

**Conclusion**

A theme uniting many of the issues discussed is the heterogeneity of pediatric sarcomas, even within diagnoses, and the desirability of finding specific therapies for specific subtypes. The situation in osteosarcoma certainly obtains in the other diseases: we are still treating many patients inappropriately, because we cannot identify the patients who need different treatment until it is too late. Carefully designed studies combining biological and clinical investigations are the only way forward.

Many more issues exist; because of the limited numbers of patients and improving survival, very few will be addressed properly in randomised
controlled trials. During the next 25 years, some of these will be answered, some left unanswered, and many will be rendered irrelevant by further advances that we cannot even dream of in 1996.

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