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# Paediatric Update

# Soft Tissue Sarcomas

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## INTRODUCTION

THE SOFT tissue sarcomas of childhood are dominated by one diagnosis, rhabdomyosarcoma. Thus, any discussion of these tumours is similarly dominated. In rhabdomyosarcoma, there has been considerable biological and clinical progress, although a few very important biological, pathological and therapeutic questions are still unanswered. The other ('non-rhabdo' or 'miscellaneous') soft tissue sarcomas, while not subject to great therapeutic ferment, are beginning to fall under systematic clinical scrutiny and several have had their tumour-specific translocations cloned.

## RHABDOMYOSARCOMA

The management of rhabdomyosarcoma is at a crossroads. There has been tremendous progress in understanding the biology of rhabdomyosarcoma and molecular diagnosis is now available for the identification and classification of alveolar tumours, although embryonal tumours still lack a biological 'handle' and biology has yet to influence therapy. Therapeutically, recent gains have been small and the toxicity is mounting. The prognosis for patients with widespread metastases at diagnosis is still dismal and evidence of progress is scant. Yet there is progress to be made using existing approaches, and several ongoing investigations may yield entirely new approaches.

### *Aetiology and pathogenesis*

The name 'rhabdomyosarcoma' denotes an origin in skeletal muscle, but this is not the clinical situation in most cases. One-third of patients have their primary tumours in such non-muscular locations as the orbit, nasopharynx, paratestis and vagina, or in organs containing smooth rather than striated muscle, such as the bladder. Only alveolar tumours are found in areas of skeletal muscle with any great frequency. Thus, a more accurate view is that rhabdomyosarcomas are mesenchymal tumours with some evidence of striated muscle differentiation, and that they are a family of different diseases with some histological and perhaps biological, similarities.

The best-known histological and biological distinction is between embryonal and alveolar tumours. Alveolar tumours tend to have a distinctive histological appearance (although it may be subtle), primary tumours tend to occur in the trunk and limbs, there is a tendency towards widespread dissemination, and they have poorer prognosis than embryonal tumours. They also have charactersitic chromosomal translocations, t(2;13) or t(1;13), which have been molecularly characterised [1, 2].

The relationship between alveolar histology and molecular biology is intriguing. The mouse homologue of the *PAX-3* gene on human chromosome 2, which is broken and joined to part of the *FKHR* gene on chromosome 13 in the tumour-specific t(2;13) translocation, is active in embryogenesis: it is expressed as the somites differentiate and polarise and is expressed in primitive mesenchymal tissue as it begins to migrate into the limb buds [3]. *PAX-7* is expressed in the developing dermatomyotome and unlike *PAX-3* is expressed in normal myoblasts [4]. Both mouse *Pax-3* and the *PAX-3-FKHR* fusion inhibit muscle differentiation in mouse myoblasts [5] and downregulation of the *PAX* genes promotes apoptosis in one alveolar and one embryonal rhabdomyosarcoma cell line [6]. Thus, the gene abnormally expressed in most alveolar rhabdomyosarcomas is embryologically associated with cell migration and inhibition of differentiation and programmed cell death.

There have been some recent insights into the origin of the alveolar rhabdomyosarcoma translocations: it appears that the regions of chromosomes 2 and 13 involved in the translocations are rich in binding sites for translin, a DNA-binding protein associated with chromosomal translocations in a variety of lymphoid malignancies [7]. What translin is doing there and why, are unanswered questions, as are the nature and causes of the remaining 'hits' involved in the conversion of a primitive mesenchymal cell into an alveolar rhabdomyosarcoma cell. Also awaiting illumination are the targets of the PAX-FKHR fusion proteins, which as transcription factors act through other genes.

Unfortunately, a useful genetic marker for embryonal rhabdomyosarcoma is still elusive. A large body of evidence implicates the chromosome region 11p15.5, with loss of heterozygosity, loss of imprinting, or loss of function of a tumour suppressor gene all being possible mechanisms [8]. The involvement of the same region in the Beckwith–Wiedemann syndrome, which is associated with an increased risk of rhabdomyosarcoma (as well as Wilms' tumour) is intriguing,

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as is the presence of the *IGF-II* genes, which are abnormally expressed in rhabdomyosarcomas [9]. The exact genes involved and their mechanisms of disruption are still unclear even after a decade of scrutiny. Attempts to indict malfunctioning *PAX* genes have been largely unsuccessful, despite their involvement in alveolar rhabdomyosarcoma and even though the relevant region on chromosome 2 is frequently abnormal in embryonal rhabdomyosarcomas [10, 11].

*Investigation and staging*

The histopathological diagnosis of rhabdomyosarcoma is extremely difficult, and in a variety of studies approximately one-third of rhabdomyosarcoma diagnoses are revised upon central or expert review. Even among expert pathologists, distinction between the subtypes is inconsistent [12]. While minimally-invasive biopsy techniques are increasing in popularity, the samples from needle biopsies are often inadequate because of distorted tumour architecture, the presence of necrotic or normal tissue and insufficient material for immunohistochemical and molecular analyses—not to mention inadequate excess material for research. This has made the development of reliable methods of molecular diagnosis valuable.

Molecular identification of alveolar rhabdomyosarcomas, Ewing's sarcomas and other small round blue cell tumours is fast and accurate, though alignment with histopathological diagnoses in large numbers of patients is still necessary [13]. Within alveolar rhabdomyosarcomas, we have demonstrated that alveolar rhabdomyosarcomas containing the *PAX7-FKHR* fusion associated with a t(1;13) are more likely to occur in the limbs, are less likely to be metastatic at diagnosis and have a better prognosis than the more common *PAX3-FKHR* containing tumours [14].

Therefore, we can divide rhabdomyosarcomas into histologically, clinically and biologically distinct types, embryonal and alveolar and we can further divide alveolar tumours into two molecularly and clinically distinct subtypes. That leaves the embryonal tumours undivided and whether or how to divide them is perhaps the major current question in rhabdomyosarcoma.

Definition of risk groups or prognostic categories in rhabdomyosarcoma is made difficult by the many interactions among variables: site, size, histology, invasiveness, nodal status and patient age all have prognostic significance, but are bafflingly interconnected. There is a strong association between primary site and clinical behaviour, which appears to transcend the relationship between site and histological type. For example, tumours of the orbit very rarely metastasise or invade through the skull, although tumours arising a few centimetres away, in the nasopharynx, frequently invade the central nervous system and metastasise. Tumours arising in the paratestis have an excellent prognosis in prepubertal boys, a less favourable prognosis in postpubertal boys and in both cases a better prognosis than tumours arising a few centimetres away in the pelvic floor.

Thus some of the division is easy on clinical grounds, as with tumours in the orbit, paratestis and vagina (very good prognosis), or tumours which are metastatic at diagnosis (very poor prognosis). This leaves two-thirds of cases, which are currently associated with an intermediate prognosis, and for which the prognosis has not improved very much in the last decade. There are at least two biological possibilities for these intermediate risk tumours. First, they may be a homogeneous population, with patient survival a matter of unknown host factors and chance; or second, they may be two different tumours biologically, one associated with an excellent prognosis and one associated with a very poor prognosis.

Many have examined tumour cell ploidy as the much-sought-after biological discriminator between more- and less-aggressive rhabdomyosarcomas. Several small studies have shown that diploid tumours have a worse prognosis than hyperdiploid tumours, with one multivariate analysis finding ploidy and site to be the most important prognostic variables [15] and another assigning prime importance to ploidy and stage [16]. However, ploidy and histology are also related, with alveolar tumours being either diploid or tetraploid and embryonal tumours being diploid or hyperdiploid and the difficulties and inconsistencies inherent in these histological distinctions complicate the analyses. Only one group has examined embryonal rhabdomyosarcomas confirmed by central pathologic review and found ploidy to be prognostically important [17]. What is needed is an analysis of rhabdomyosarcomas shown to be embryonal by the absence of a *PAX-FKHR* fusion and then subjected to ploidy analysis.

Thus, the ideal of being able to separate embryonal rhabdomyosarcomas on the basis of simple biological characteristics is still elusive and we are left with complex clinical methods of characterisation. Metastasis at diagnosis is the strongest poor prognostic variable, with a variety of analyses showing bone and marrow metastases to be the worst. Currently, bone scans, chest CT scans, plain radiographs and microscopically inspected bone marrow specimens are the available tools, although some early results indicate that submicroscopic (i.e. molecular) marrow positivity by RT–PCR may portend doom [18].

Among non-metastatic tumours, besides site, invasiveness has been shown to be the most important prognostic variable for rhabdomyosarcoma in multivariate analyses [19]. Histology was not a significant factor on multivariate analysis, perhaps because alveolar tumours are virtually always invasive and in unfavourable sites. However, this classification has been difficult to apply clinically because invasiveness is difficult to define accurately enough for multi-institutional studies.

While several schemes (mostly quite complex) are in use or in development, there is a general consensus emerging around three risk groups. For the purposes of further discussion, and while more biological investigations continue, we will consider them as follows:

- Low risk: non-invasive tumours, embryonal histology, favourable sites (orbit, superficial head and neck, paratestis, vagina, bladder dome);
- High risk: metastatic at diagnosis, or extremity tumours with invasion or positive nodes (grossly or microscopically) [20];
- Intermediate risk: all others, including invasive or alveolar tumours in favourable sites and all tumours in unfavourable sites.

## TREATMENT

*Chemotherapy*

In patients with localised embryonal tumours in favourable sites, chemotherapy with vincristine and actinomycin-D produces overall survival rates of at least 90%, with few or no chemotherapy-related late effects. While it may be possible in

the future to identify some patients who do not need any chemotherapy at all, it is unlikely that any study will ever improve upon these overall results.

Patients with high-risk tumours have not demonstrably benefited from the striking changes in chemotherapy intensity over the last 20 years. Even with autologous bone marrow or stem cell rescue, only approximately a quarter of patients with metastatic-at-diagnosis rhabdomyosarcomas survive, and almost none of the survivors have marrow or bone metastases. The strategy most often applied to high-risk rhabdomyosarcomas (as well as other high-risk tumours in children and adults) is myeloablative chemotherapy and radiotherapy, with autologous marrow or peripheral stem cell rescue. While many institutions have been performing these procedures for many years and approximately 12 abstracts report the approach as 'promising' in small numbers of patients, peer-reviewed manuscripts demonstrating efficacy are non-existent. At the U.S. National Cancer Institute, intense induction chemotherapy (by the standards of 10–15 years ago, when the patients were treated) followed by high-dose consolidation chemotherapy and total body irradiation failed to increase the event-free survival of patients with metastatic rhabdomyosarcoma above its traditional 20% [21]. A recent European consensus conference found no evidence of any benefit of autologous transplant on survival in rhabdomyosarcoma [22]. This group of patients needs the most creative therapeutic attention.

For intermediate-risk tumours, the chemotherapeutic standards for over a decade have been 'IVA' (ifosfamide–vincristine–actinomycin-D), in the Old World and 'VAC' (vincristine–actinomycin-D–cyclophosphamide) in the New World. The Fourth Intergroup Rhabdomyosarcoma Study, which will complete its accrual shortly, is performing a randomised comparison of VAC, IVA and 'VIE' (vincristine–ifosfamide–etoposide) in intermediate-risk patients, with cyclophosphamide and ifosfamide given at equally toxic doses but by different schedules (cyclophosphamide as a single dose, ifosfamide divided over 5 days). Until the results of this study are available sometime in 1998 or 1999, there is no evidence at all of one alkylating agent's superiority over another [23].

The VAC combination has been changing as improved supportive care has made possible ever-higher doses of cyclophosphamide. The dose intensity of cyclophosphamide, expressed as the dose per square metre in the first 12 weeks of therapy, has risen from 900 mg in IRS-I to 8800 mg in IRS-IV, but the gains in survival have been much more modest, and potentially attributable to many factors other than cyclophosphamide dose. With the prognosis in metastatic rhabdomyosarcoma remaining bleak despite heroic doses of alkylating agents, and with the risk of secondary acute myeloid leukaemia and myelodysplasia darkening the horizon for high-dose therapy [24], further dose increases are unlikely to lead to progress.

Alternatively, two potentially profitable strategies are the substitution of doxorubicin for actinomycin-D, and the incorporation of etoposide. The IRS results with doxorubicin partially substituted for actinomycin are unclear, except in IRS-III patients who have microscopic residual disease at diagnosis (Clinical Group II), where the doxorubicin-containing regimen was superior for survival (89% versus 54% at 5 years, $P = 0.03$) [25]. The risk of anthracycline cardiomyopathy, which has limited the use of doxorubicin in small children, may diminish with the use of dexrazoxane (also termed ICRF-187 or ADR-529). Since doxorubicin is the single most effective drug against all other paediatric and adult sarcomas, this would seem worth investigating.

Etoposide is another drug whose potential is yet largely unexplored. It was included in one regimen of IRS-III, but in a poor design that makes identification of its effect impossible. The combination of ifosfamide and etoposide was very effective against resistant and relapsed rhabdomyosarcoma in phase II studies [26] and it greatly augmented the efficacy of vincristine–doxorubicin–cyclophosphamide–actinomycin-D in Ewing's sarcoma [27]. In a group of 48 patients with intermediate-risk rhabdomyosarcomas treated with an alternating regimen of vincristine–doxorubicin–cyclophosphamide and ifosfamide–etoposide, progression-free survival was over 85% at 3 years [28] and ifosfamide–etoposide combined with VAC has provided good preliminary results in metastatic tumours [29]. How best to use etoposide and other topoisomerase inhibitors, and what their role might be, are interesting and promising paths for future investigation.

*Primary tumour surgical and radiation treatment*

Since the first Intergroup Rhabdomyosarcoma Study demonstrated that the extent of surgical excision at the time of diagnosis was a key prognostic feature [30], control of the primary tumour has been an area of controversy. The extent of original excision ('clinical group' in IRS parlance) is the result of a convergence of other variables, both definable (site, invasiveness, size) and not definable (surgical adventuresomeness, patient and family tolerance of disfigurement and disability). Debate continues over what combination of surgery and radiotherapy is best, what doses and methods of radiotherapy administration should be used and even whether local control measures are necessary at all in an era of fairly effective chemotherapy.

The most extreme position, that primary tumour treatment is often unnecessary with adequate chemotherapy, is held by the investigators of the SIOP MMT studies. Using ifosfamide-containing chemotherapy, the MMT-84 study avoided surgical excision or radiation therapy in 22 of 31 patients with orbital rhabdomyosarcomas [31]. This approach has also been applied to other sites, although the results are not yet published. Critics argue that this approach, with the use of ifosfamide (sometimes at high total doses), a 50% local recurrence rate, a 25% orbital exenteration rate and a disease-related mortality rate of 9%, is inferior to the more traditional combination of vincristine, actinomycin-D and radiation therapy [32].

Clearly, the use of effective chemotherapy has permitted a decrease in both the extent of surgery and the extent and dose of radiation therapy. It is now usually possible to avoid pelvic exenteration or cystectomy in patients with rhabdomyosarcoma of the bladder, although the function of the salvaged organs is often impaired and reconstructive urological surgery is often necessary [33–35]. Delaying primary tumour treatment until induction chemotherapy has had a chance to shrink the tumour is now a common strategy and appears to be safe even in parameningeal tumours with cranial nerve involvement or invasion into the brain [28].

The doses of radiation therapy applied to rhabdomyosarcomas are also decreasing. Work at St Jude Children's Research Hospital and at the Memorial Sloan-Kettering Cancer Center, U.S.A. demonstrate that 40 Gy is more than

enough to treat patients with microscopic residual disease [36], and that 30–36 Gy is probably sufficient [37]. The German CWS studies are attempting to adjust radiation therapy fields and doses according to the response of the primary tumour to chemotherapy.

Even in patients requiring full-dose therapy, the use of CT-guided, computerised treatment planning and combinations of brachytherapy and external beam therapy can decrease radiation-associated morbidity [38]. The IRS-IV study is investigating whether hyperfractionated radiotherapy improves local control while decreasing late morbidity in Group III patients.

Local recurrences are still a serious problem in rhabdomyosarcoma, particularly in patients with gross residual disease when chemotherapy is begun (IRS Clinical Group III). Intriguingly, a recent analysis of IRS data showed that the pattern of recurrence varies with the primary site of the tumour [39], indicating that once again biological differences between histologically similar tumours are at work. Presumably these behaviours have identifiable biological correlates for which assays might be possible. Thus, improving local control may not be a matter of increasing radiation therapy fields or doses. Better biological classification could have as beneficial an effect on local control as on chemotherapy.

## OTHER SOFT TISSUE SARCOMAS

The 'miscellaneous' soft tissue sarcomas, including neurofibrosarcoma, fibrosarcoma, synovial sarcoma and malignant fibrous histiocytoma, have been difficult to study because of small patient numbers, curability in the majority of cases with surgery alone and historically poor responses to chemotherapy. The diagnosis of these unusual tumours is advancing rapidly through the application of molecular biology. The synovial sarcoma t(X;18) and the myxoid liposarcoma t(12;16) have both been cloned, offering new opportunities for molecular diagnosis [40]. Perhaps the largest contribution possible from the Pediatric Oncology Group and U.S. Children's Cancer Group studies now being developed is uniforrn central pathological review of all U.S. miscellaneous sarcoma cases, with the application of a panel of molecular and immunohistochemical studies.

Complete surgical excision is the most important component of the care of these tumours, although radiation therapy may be capable of eliminating microscopic residual disease. There is no evidence that chemotherapy contributes to survival, but it may shrink some tumours and make them more amenable to surgical excision.

One distinct, recently recognised entity is the desmoplastic small round cell tumour. This tumour usually arises in the abdomen of adolescents and young adults and is usually widely disseminated within the abdomen by the time of diagnosis. It has a distinctive histological appearance as well as a t(11;22) which fuses the *EWS* gene (also implicated in Ewing's sarcoma) with the *WT1* gene involved in some cases of Wilms' tumour [41]. While this tumour is usually fatal despite aggressive multimodal treatment, a few patients have been cured with chemotherapy, radiotherapy and complete surgical excision [42].

## THE FUTURE

One can view the future of childhood soft tissue sarcoma management optimistically or pessimistically. Optimistically, 20 years from now, molecular diagnosis will provide a complete biological characterisation of a tumour from a fine needle aspiration sample. Patients will then receive chemotherapy tailored to the biological characteristics of their tumours. For example, patients with alveolar tumours will receive drugs aimed at the PAX-FKHR fusion proteins and their target genes. Research into muscle and limb development will have provided new knowledge and technology to apply to embryonal tumours. Patients will be treated on international randomised controlled studies, with international collaborations made necessary because event-free survival will be over 80% for high-risk patients. Radical surgery, high-dose radiation therapy and autologous transplant will be viewed with the same historical fascination with which we now regard bleeding and purging.

A pessimistic outlook finds us, 20 years hence, slogging away with pretty much the same approaches and agents that we now use. There will have been some improvements in survival and reductions in morbidity and we will understand much more about how rhabdomyosarcoma cells arise and function; but scarce research funds, myopic clinical investigations, political squabbling and good (though not excellent) results with existing approaches will have stifled progress and collaboration.

A realistic view would fall somewhere in between.


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# Commentary

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RICHARD WOMER'S commentary makes stimulating reading and reflects the complexity of the management of children with soft tissue sarcoma. The contrasting scenarios he offers for the future of this difficult group of diseases contain elements of truth. However, much is now being done, at a clinical level, to clarify the interpretation of principles of