# Philosophy of treatment and the role of chemotherapy in paediatric soft tissue sarcomas

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## Introduction

Soft tissue sarcoma (STS) accounts for 7–8% of cancers in children. The most common diagnostic subtype is rhabdomyosarcoma (RMS) (50–65%). Fibrosarcoma, neurofibrosarcoma and other fibromatous neoplasms account for 10–20%; and a group of various other specified non-rhabdomyosarcoma STS accounts for 10–25%, of which the most frequent diagnoses are peripheral neuroectodermal tumour and synovial sarcoma. The remaining cases represent unspecified STS (5–10%).

## Rhabdomyosarcoma (RMS)

RMS is a chemosensitive tumour with an overall survival rate of approximately 70%. Although occurring at all ages in childhood and adolescence, this tumour is rare in adult life and the median age at diagnosis is only about 5 years. This very young age profile creates significant concerns about the late effects of therapy, especially in relation to the use of radiation therapy. Some of the current issues which contribute to the different philosophies of treatment for RMS include such questions as: What is the optimal chemotherapy strategy? What are the most important prognostic factors and how should therapy differ for different subtypes of the disease? Do all children with RMS need radiotherapy? Children with metastatic RMS have a very poor prognosis: what new approaches to treatment are available?

### *Staging and pathological subtypes*

Attempts to understand and compare the results of clinical trials involving RMS have been confused by the lack of standard terminology for staging and pathological classification, although recent collaboration between major international collaborative groups has begun to address these difficulties and there is international agreement for a standard approach to the criteria used both for staging and for pathological classification [1,2] (Table 1). Two principal staging systems have been in use for some years — the SIOP (International Society of Paediatric Oncology) TNM Clinical and Post-Surgical system (Figs. 1 and 2) and the North American IRSG (Intergroup Rhabdomyosarcoma Study Group) Clinical Grouping system (Table 2).

### *Approaches to treatment for non-metastatic rhabdomyosarcoma*

Multimodality therapy involving surgery, chemotherapy and radiotherapy is important for RMS. How-

Table 1
International pathology classification for rhabdomyosarcoma

| Prognostic group | Prognosis | Histological subtype |
|---|---|---|
| I | Superior | Botryoid RMS<br>Spindle cell RMS |
| II | Intermediate | Embryonal RMS |
| III | Poor | Alveolar RMS<br>Undifferentiated sarcoma |
| IV | Uncertain | RMS with rhabdoid features |

Table 2
IRS clinical grouping system

| Group | | Extent of disease | Tumour resection |
|---|---|---|---|
| I | A | Localised to site of origin | Completely resected |
| | B | Localised but infiltrating | Completely resected |
| II | A | Local disease | Microscopic residual |
| | B | Regional disease | Completely resected and nodes completely resected |
| | C | Local ± Regional | Microscopic residual and nodes completely resected |
| III | | Any non-metastatic disease ± nodes | Incomplete resection/ biopsy only |
| IV | | Metastatic disease | Any |

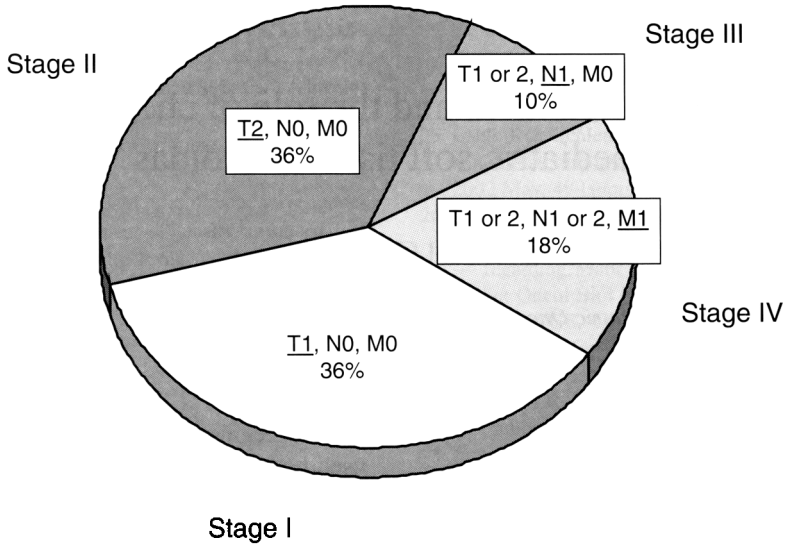


Fig. 1. SIOP TNM clinical stage. Stage I = T1 tumour, localised in the organ or tissue of origin. Stage II = T2 tumour, involving one or more contiguous organs or tissues. Stage III = any T, N1 (evidence of regional lymph node involvement). Stage IV = any T, any N, M1 (metastatic disease).

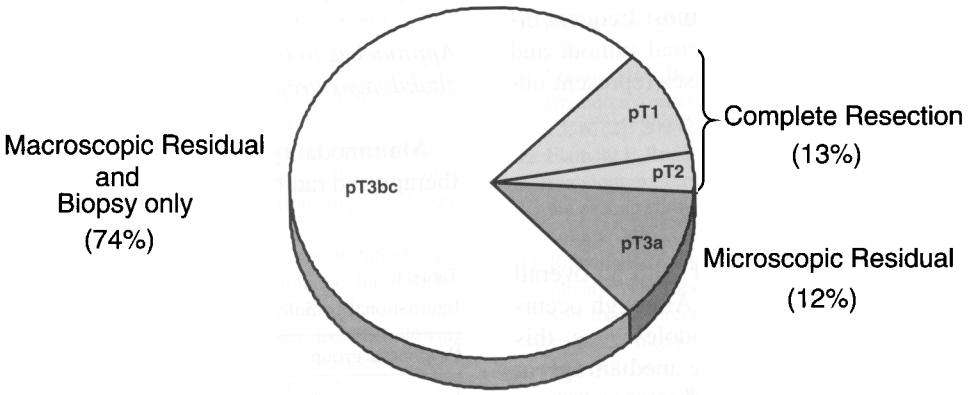


Fig. 2. SIOP pTNM post-surgical stage. pT1 = tumour limited to organ or tissue of origin, excision complete and margins histologically free. pT2 = tumour invasion beyond the organ or tissue of origin, excision complete and margins histologically free. pT3 = tumour incompletely resected. pT3a = evidence of microscopic residual tumour. pT3b = evidence of macroscopic residual tumour or biopsy alone. pT3c = adjacent malignant effusion.

ever, important differences in the philosophy of treatment have emerged in the past 20 years, the most important of which relate to the method and timing of local treatment. More specifically, the debate relates to the place of radiotherapy in guaranteeing local control for patients who appear to achieve complete remission with chemotherapy, with or without significant surgery. When local therapy with surgery and/or radiotherapy is systematically implemented as part of primary treatment, local control is improved and the risk of relapse is less. However, the systematic application of local therapy, particularly in very young children, raises concern about the long-term consequences of such treatment. Recent experience suggests that it may be possible to avoid or reduce the intensity of local therapy depending on response to initial surgery and primary chemotherapy. Clinical studies organised by the International Society of Paediatric Oncology (SIOP) have promoted a selective approach to the use of local therapy [3]. This represents one of the most important philosophical differences from treatment promoted by other international collaborative groups — principally the Intergroup Rhabdomyosarcoma Study Group (IRSG — now the STS Group of the Children's Oncology Group) in North America [4] and the German (CWS) [5] and Italian (ICG) [6] Co-operative Groups in Europe. Local relapse rates are generally higher in the SIOP studies than those experienced elsewhere, although the SIOP experience has also made it clear that a sig-

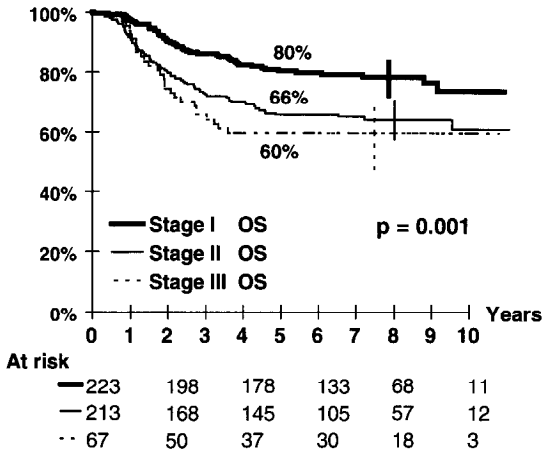


Fig. 3. Rhabdomyosarcoma: overall survival by (TNM) clinical stage.

nificant number of patients who relapse may be cured with alternative treatment. In the context of such differences, overall survival (OS) rather than event-free or progression-free survival (EFS/PFS) becomes the most relevant criteria for measuring outcome.

*Prognostic factors in deciding treatment for RMS*

The most important prognostic factors are stage, site, and pathological subtype. Experience in all studies has confirmed that both of the following predict outcome: staging according to the initial clinical assessment of disease; and the use of a surgical–pathological classification system which groups patients according to the extent of residual tumour after the initial surgical procedure (Fig. 3). The great majority (approximately 75%) of patients without evidence of metastatic disease will have macroscopic residual disease at the primary site at the start of chemotherapy (Fig. 2).

The variability with which RMS presents at different anatomical sites has a particularly strong influence on strategies for treatment. Forty percent of RMS arise in the head and neck and a further 20% in the genitourinary tract (Fig. 4). Such sites do not usually lend themselves to a radical primary surgical approach as complete resection is often impossible or, if it is possible, it is unlikely to be achieved without significant functional or cosmetic consequences. In the majority of cases, initial surgical intervention is limited to diagnostic biopsy and definitive resection attempted only after assessing response to chemotherapy. Site remains one of the most important independent variables predicting survival (Fig. 5).

There is now convincing evidence that the alveolar subtype carries a much less favourable prognosis (Fig. 6). These patients are often older, are more likely to have extremity tumours and are much more likely to present with, or to develop, metastatic disease.

Other prognostic influences include tumour size and patient age. Data from most of the recent collaborative group studies suggest that patient age >10 years is unfavourable. Tumour size has also emerged as a prognostic factor in recent analyses, and age $\geq$ 10 years and/or tumour size $\geq$ 5 cm will contribute to the definition of high-risk patients in future paediatric studies.

Designing treatment stratifications in response to the possible different combinations of these factors adds considerable complexity to the construction of treatment strategies and clinical trials. All current clinical trials utilise some combination of the best-known prognostic factors to stratify treatment intensity for patients with good or poor predicted outcomes. The

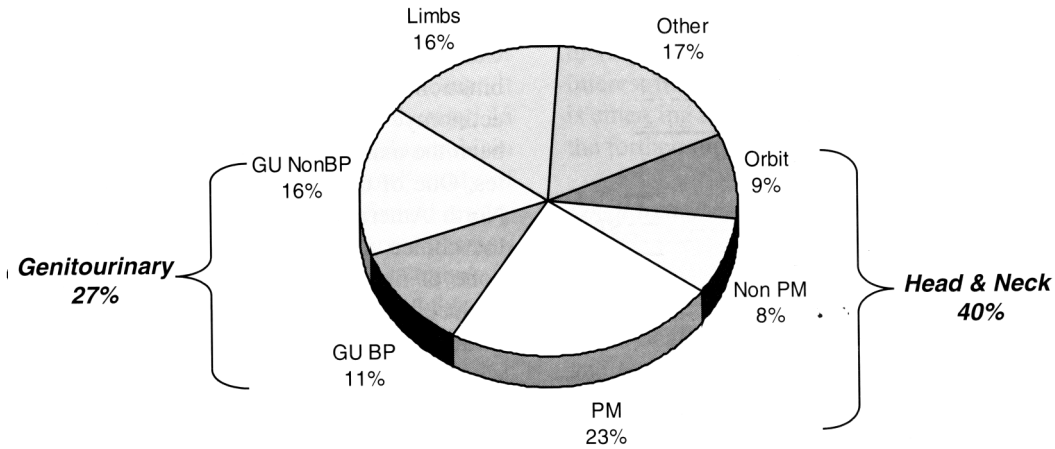


Fig. 4. Rhabdomyosarcoma: distribution of sites of primary tumour. GU non-BP = genitourinary, non-bladder/prostate; GU BP = Genitourinary, bladder prostate; PM = parameningeal; non-PM = non-parameningeal.

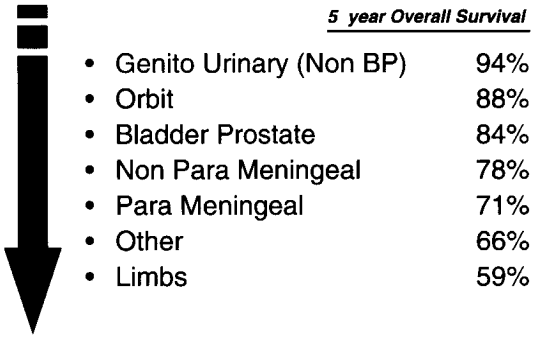


Fig. 5. Rhabdomyosarcoma: site of disease and prognosis.

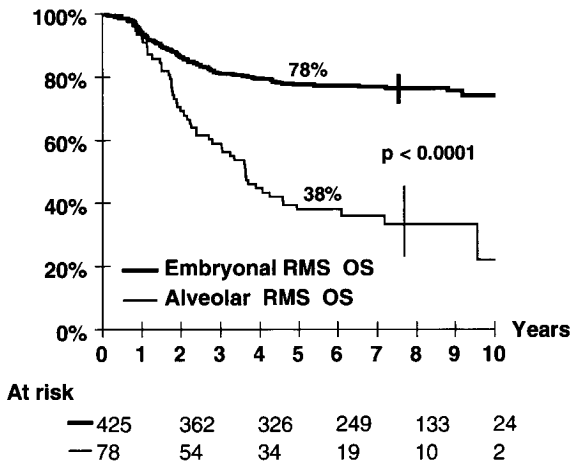


Fig. 6. Impact of alveolar pathology on overall survival.

impetus for this approach derives as much from the wish to avoid over-treatment of patients with a good prospect for cure, as from a desire to improve cure rates for patients with less favourable disease. Current North American IRSG, now COG (Children's Oncology Group) soft tissue sarcoma group, studies

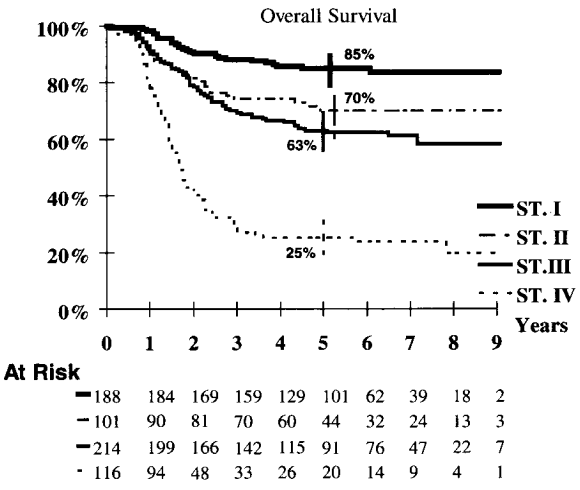


Fig. 7. Rhabdomyosarcoma: overall survival by IRSG stage.

Table 3
IRS clinical staging system

| Stage | Sites | Size | Nodes | Metastases |
|---|---|---|---|---|
| 1 | Orbit<br>H&N non-PM | any | any | no |
| 2 | BP<br>Limb<br>PM<br>Other | ≤5 cm | no | no |
| 3 | BP<br>Limb<br>PM<br>Other | ≤5 cm<br>>5 cm | yes<br>any | no<br>no |
| 4 | All | any | any | yes |

H&N = head and neck; non-PM = non-parameningeal; PM = parameningeal; BP = bladder/prostate.

utilise both Clinical Group (Table 2) as well as a pre-treatment clinical staging system which integrates several prognostic variables including site, stage and tumour size (Table 3) and provides a useful model for stratifying risk (Fig. 7).

*What is the optimal chemotherapy strategy for RMS?*

The importance of multi-agent chemotherapy, as part of co-ordinated multi-modality treatment, has been clearly demonstrated for RMS over many years. Cure rates have improved from approximately 25% in the early 1970s when combination chemotherapy was first implemented, and 5-year overall survival rates of more than 70% are now generally achieved [7].

RMS is a chemosensitive tumour — single agent responses to a wide range of drugs are recognised including vincristine, cyclophosphamide, doxorubicin, actinomycin D, cisplatin, carboplatin, etoposide, ifosfamide, and melphalan. More recent data suggest the value of topotecan, irinotecan, and vinorelbine. Controversies relate to choice of the optimal combination of agents — combinations of vincristine, actinomycin D and cyclophosphamide (VAC) have been the mainstay of chemotherapy in all IRSG studies. One of the most significant differences between North American and European studies has been in the choice of alkylating agent to use as the backbone of first-line chemotherapy. Ifosfamide was introduced into clinical practice earlier in Europe than in the United States, and phase II data are available which support its efficacy in RMS. The IRS-IV study attempted to answer the question of comparative efficacy by randomising VAC (using an intensified cyclophosphamide dose of 2.2 g/m$^2$ per course with G-CSF (granulocyte colony-stimulating factor) sup-

port) against two ifosfamide-containing combinations (using ifosfamide at a dose of 9 $g/m^2$ per course in combination with vincristine and either actinomycin D or etoposide) [8]. No difference was identified between the cyclophosphamide- and the ifosfamide-containing schedules. VAC remains the combination of choice for current COG studies in which the lesser cost and easier (shorter) duration of administration of cyclophosphamide is preferred. There is also concern about the nephrotoxicity of ifosfamide, although recent experience suggests that the risk is small if cumulative ifosfamide dose is $<60$ $g/m^2$ [9] — this is the current threshold for European studies. There is also some suggestion (yet to be confirmed with certainty) that the gonadal toxicity of ifosfamide may be less than that of cyclophosphamide.

The role of anthracycline drugs in the treatment of non-metastatic RMS remains uncertain. This is being re-evaluated, particularly as doxorubicin has been a first-line agent for adult soft tissue sarcoma for many years. Data from IRSG studies failed to show that the addition of doxorubicin to VA or VAC (depending on risk group) offered no apparent survival benefit [10]. Despite these results, and the lack of historical phase II data to support the use of doxorubicin in RMS, many paediatric oncologists continue to assume the value of anthracyclines in the treatment of rhabdomyosarcoma. Both the SIOP MMT and the German–Italian cooperative studies continue to treat some patients with chemotherapy combinations which include anthracycline drugs. Current European studies (MMT 95 and CWS-ICG 96) include randomisations between their ifosfamide-based standard chemotherapy options and an intensified 6-drug combination which includes epirubicin (with carboplatin and etoposide). The first results of these studies should be available by late 2003, and although neither of the study designs can specifically address the anthracycline question, the absence of any benefit from the intensified chemotherapy arm would further reinforce the message that patients may not benefit from anthracycline as part of first-line therapy. In contrast, a recent French study explored doxorubicin as a single agent in an "up-front window" study of children with metastatic RMS and confirmed a very high response rate (>70% after two courses of treatment) (C. Bergeron, Centre Leon Berard, Lyon). A randomised evaluation of doxorubicin, in addition to IVA, will form a principal question in the forthcoming European collaborative study (ESSG, European Soft Tissue Sarcoma Group, a new collaboration between the SIOP, German, and Italian soft tissue sarcoma groups). Ultimately the benefit of anthracyclines in the treatment of rhabdomyosarcoma must be sufficient to justify the risk of exposing children to the potential of cardiotoxicity.

Platinum-based combination regimes, such as cisplatin/etoposide and cisplatin/doxorubicin have also been shown to be effective, with response rates ranging from 30–40% in phase II studies [11], although the results of the IRS III study showed that the addition of cisplatin and etoposide to front-line therapy with VAC did not appear to improve the complete response rate or FFS (failure-free survival) in selected patients [12]. Second generation compounds, carboplatin and epirubicin, have been utilised as front-line therapy in newly diagnosed children with metastatic soft tissue sarcomas in the European Intergroup Study MMT-4 and a 53% response rate has been reported with this combination [13].

More recently, the topoisomerase I inhibitors, topotecan and irinotecan, have been identified as promising new agents. The data for topotecan are particularly difficult to evaluate, as the response rate in a phase II window study of topotecan in previously untreated patients with metastatic RMS was significantly better than that seen in a conventional phase II evaluation [14]. The IRS-V protocol is testing the potential value of intensive VAC alternating with VCR, topotecan and cyclophosphamide compared with intensive VAC which remains the "gold standard" therapy for North American studies.

Vinorelbine, a semi-synthetic vinca alkaloid, has also been described to have evidence of activity in patients with heavily pre-treated paediatric sarcomas, particularly in alveolar RMS [15] — a finding which justifies further evaluation.

So far, there is insufficient experience with new agents such as imatinib mesylate (Glivec, Gleevec, STI-571) to define any possible role in RMS.

The optimal duration of adjuvant chemotherapy for patients who attain complete response is still unknown. The recent tendency has been to shorten treatment programmes to a duration of 6–12 months, but interest in the value of "maintenance" chemotherapy is emerging and this will be explored in the context of the forthcoming ESSG.

### *Local treatment for non-metastatic RMS: what and when?*

Achieving and maintaining local control is the major challenge in patients with non-metastatic RMS and local failure is a much more common first event than metastatic relapse. Primary surgical management of RMS is less aggressive in children than that adopted for soft tissue sarcoma in adults and a conservative approach is feasible in many patients,

particularly if tumours which are unresectable at first presentation are reassessed for secondary surgery after initial chemotherapy.

The response evaluated by physical examination and imaging data may differ from the pathological findings obtained during surgical exploration. For example, in IRS-III, 46% of group III patients achieving a clinical partial remission were without evidence of tumour, i.e. found to be in complete remission at surgical exploration, and another 28% were converted to complete remission by excision of tumour residue. The most surprising fact was that 30% of group III patients with no apparent clinical response were shown to be in complete remission at surgical exploration, and another 43% of these patients could be converted to complete remission (i.e. completely resected) by the surgeon. These data underline the importance of secondary surgery in the cases of a residual mass, even when a poor clinical response to chemotherapy has been obtained. The value of histological verification of a complete clinical remission is uncertain and re-biopsy of the previous site of a tumour is generally unhelpful as it may be unrepresentative or falsely reassuring.

Those tumours which remain unresectable or have been incompletely resected by second surgery after initial chemotherapy are usually treated with radiotherapy. In very young children for whom the long-term toxicity of radiotherapy may be considered unacceptable, radical surgical resection may be preferred despite the functional consequences. In any child, if a combination of chemotherapy and radiotherapy has failed to control local disease, radical surgery is indicated if feasible as the aim must then be to achieve complete excision of residual disease. Children with RMS in the head and neck, particularly those with disease at parameningeal sites which almost always involve the base of the skull, present particular surgical challenges.

The role of radiotherapy in the management of childhood RMS is well-known, but controversies relate to the method and timing of local treatment. More specifically, there has been debate about the place of radiotherapy in guaranteeing local control for (a) patients who undergo primary complete resection and (b) those who achieve clinical complete remission with chemotherapy with or without second surgery [16,17].

It is accepted that patients with group I embryonal RMS (at all sites) have an excellent prognosis when treated with chemotherapy alone and do not require irradiation. However, data from several studies have shown that group I tumours with unfavourable (alveolar) histology had an unexpectedly high local regional relapse rate. Radiation therapy is now widely used for such patients.

Clinical complete remission can be achieved in about 35% patients with chemotherapy alone after initial biopsy or after primary incomplete resection. The important question is whether this is sufficient to ensure local control. Experience suggests that this is determined by site, stage, histological subtype, tumour size and patient age. For tumours at certain sites, for example, in patients with parameningeal tumours, the introduction of systematic radiotherapy has increased survival rates and it remains difficult to cure patients with tumours at these difficult sites without this element of treatment [18]. Although the use of RT is clearly important for patients with parameningeal disease, the delivery of such treatment to very young children raises concerns in view of its predicted toxicity. In the SIOP MMT 89 study, children aged <3 years were treated primarily with chemotherapy. RT was utilised according to chemotherapy response. Although the results showed that very few patients aged <3 years with parameningeal disease could be cured without radiotherapy at some point in their treatment, it was nevertheless seen that age at the time of delivery of radiotherapy was extended in some survivors with potential benefit in terms of late effects of therapy and without reduction in overall survival [19].

In contrast, data are emerging which suggest that particular subsets of patients may be treated successfully without the use of radiotherapy and despite incomplete primary excision. For example, data from the SIOP MMT studies suggest that up to 40% of patients with orbital tumours can be cured without RT [20]. A recent collaborative international analysis of children with orbital RMS treated in Europe and the United States showed that a strategic approach which limited the use of RT to those who did not achieve clinical complete remission with initial chemotherapy did not compromise overall survival despite a higher local recurrence rate [21]. It is important to acknowledge, however, that patients treated in this way may require more intensive initial chemotherapy and that those who relapse are exposed to further chemotherapy in addition to radiotherapy. These are important issues which must be considered in the context of the impact of the total burden of therapy borne by survivors (Fig. 8). For the future, methods must be developed which allow the incorporation of some measure of the "cost" of survival, i.e. by taking account of the total burden of therapy experienced by an individual patient and hence of the predicted late sequelae that may result, as well as the overall survival rate.

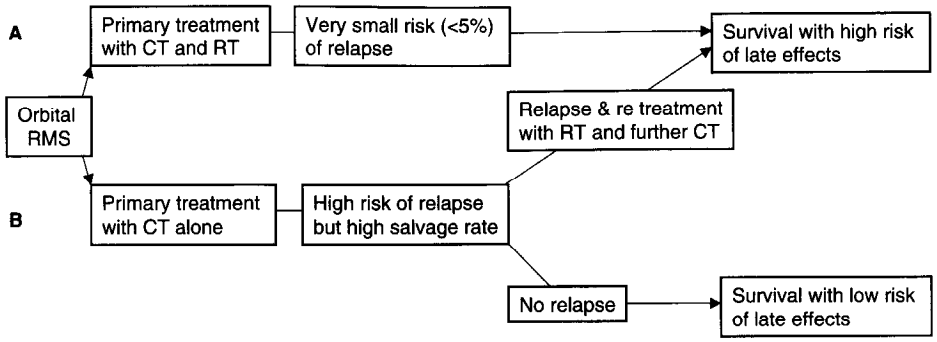


Fig. 8. Orbital rhabdomyosarcoma: outcome of different philosophies of treatment.

Unfortunately, it is not yet possible to reliably identify, at diagnosis, those patients who are most likely to be able to be cured without RT after achieving CR with chemotherapy and conservative surgery. The available data appears to suggest that younger children (aged <10 years) with smaller (<5 cm) primary tumours and favourable (embryonal) histology are most likely to be cured without systematic use of RT.

In selected situations, brachytherapy may be appropriate, for example when the tumour is clinically accessible and limited in volume at sites such as the perineum, bladder, prostate and genital tract. Experience with the late effects of brachytherapy delivered in early childhood is limited, but reasonably reassuring [22].

*Treatment for metastatic RMS*

Cure rates for children with metastatic RMS are very poor (<30% despite initial response to chemotherapy). Recent work using data from all the international collaborative groups has confirmed that two simple prognostic measures (age >10 years and the presence of bone or bone marrow metastases) predict a sub-group of patients with an extremely poor prognosis (<10% survival), whilst a smaller subgroup of patients who are metastatic only by virtue of distant lymph node disease have a much better prognosis. Unfortunately, the majority of patients manifest the poorest risk factors and novel approaches to treatment would seem justified in this setting. In IRS-V, patients at highest risk (stage 4 aRMS or stage 4 eRMS older than 10 years) are being evaluated in an up-front window with irinotecan followed up by VAC and local therapy. High dose chemotherapy followed by haematopoietic stem cell rescue has been explored in patients with metastatic disease in complete remission after conventional therapy as a method of eliminating micro-residual disease. The results of a European Intergroup study (MMT4-91), which evaluated the potential role of high-dose melphalan as consolidation therapy for newly diagnosed children with metastatic disease in first complete remission, showed no benefit in terms of overall survival [23]. Similar results have been obtained with other myeloablative regimens [24].

A new strategy, which utilises repetitive courses of sequential high-dose therapy earlier in the treatment, in an attempt to avoid drug resistance, is currently being evaluated in two studies (conducted by the SIOP and the Italian groups) which are still in progress, and it is not yet clear if this novel approach could be of some benefit for patients with metastatic disease.

## Non-RMS soft tissue sarcoma

Non-rhabdo soft tissue sarcomas (NRSTS) are a heterogeneous group of tumours that are much more common in adults than in children. There are two peaks of incidence in childhood, the first under the age of five years and the second in early adolescence. Primitive neuroectodermal tumour (PNET)/extra-osseous Ewing's sarcoma (EOES), malignant peripheral nerve sheath tumour (MPNST), fibrosarcoma, and synovial sarcoma (SS) are the prevalent entities. Less common types include undifferentiated sarcoma (US), haemangiosarcoma, haemangiopericytoma, epithelioid sarcoma, and alveolar soft part sarcoma (Fig. 9). NRSTS can be found at any anatomical site but most commonly in the extremities, trunk and retroperitoneum (Fig. 10). Involvement of regional lymph nodes is less frequent than that observed in RMS and distant metastases are present at diagnosis in about 10–12% of cases. Survival rates range widely across different histological subtypes (from 30–40% for malignant rhabdoid tumours, epithelioid sarcoma and MPNST, to approaching 80% for synovial sarcoma, leiomyosarcoma).

Although there are important differences in behaviour between rhabdomyosarcoma and NRSTS, for example in their metastatic potential, chemosensi-

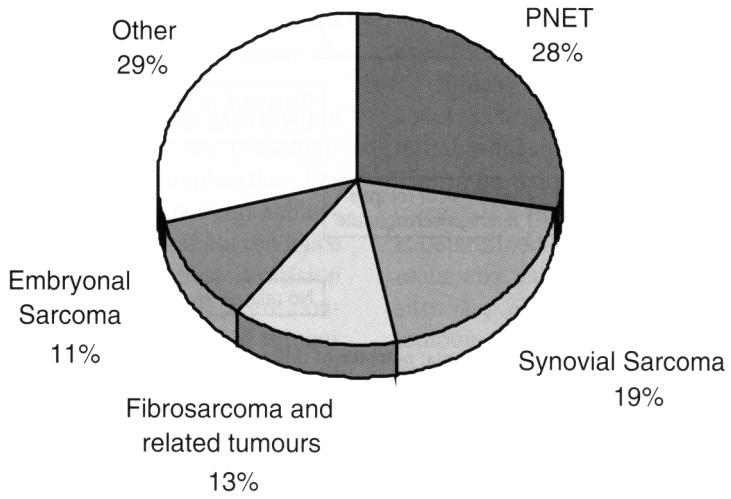


Fig. 9. Frequency of major sub types of NRSTS. The use of the term Embryonal Sarcoma is not entirely accepted internationally, and in IRSG studies, these tumours have been included as undifferentiated RMS, although it has been considered a separate diagnostic entity in the SIOP studies.

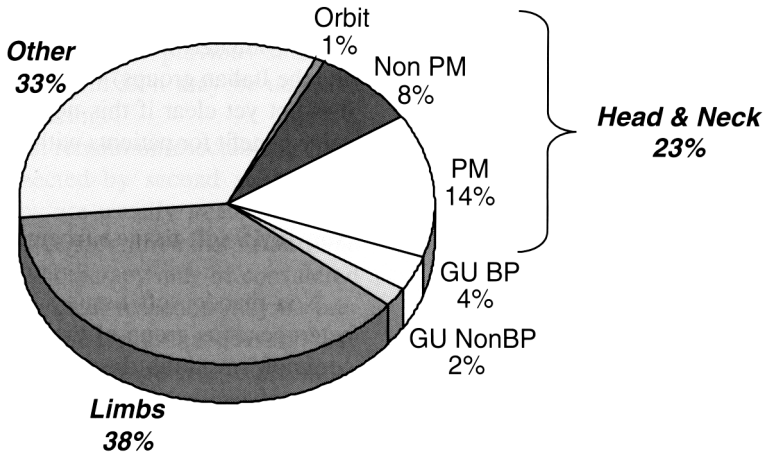


Fig. 10. NRSTS: Distribution of sites of primary tumour. (GU non-BP = genitourinary, non-bladder/prostate; GU BP = genitourinary, bladder/prostate; PM = parameningeal; non-PM = non-parameningeal)

tivity, etc., most of the experience of treatment for NRSTS in childhood derives either from experience of managing the same diagnoses in adult practice or is based on the principles derived from the management of RMS. The two most important questions here are: Is the use of strategies designed to treat RMS appropriate for NRSTS? What evidence is there for altered behaviour or enhanced chemosensitivity when such diagnoses occur in children rather than in adults?

*Non-RMS soft tissue sarcoma: the general approach to treatment in children*

Response to chemotherapy varies from good to very poor and the unpredictability of this presents a major clinical challenge particularly when primary surgical resection is not feasible. By broad consensus, these tumours can be divided into three groups according to potential chemosensitivity:

1. Tumours with proven chemosensitivity. These include PNET/EOE and undifferentiated sarcoma.
2. Tumours with possible chemosensitivity. These include synovial sarcoma (SS), malignant fibrous histiocytoma, liposarcoma, and congenital-infantile fibrosarcoma.
3. Tumours with unproven chemosensitivity. These include "adult-type" fibrosarcoma and malignant peripheral nerve sheath tumour (MPNST).

For most diagnoses, surgery has the major role and the value of chemotherapy in the primary treatment of apparently unresectable tumours is uncertain, but even in those tumours with unpredictable

chemosensitivity, response rates of up to 50% have been reported. It is possible that this is better in children than adults, although no clear evidence exists to support this assertion and it is possible that children with unresectable non-RMS are more likely to be given a trial of chemotherapy. Even when experience suggests that a tumour type demonstrates worthwhile chemosensitivity it remains to be seen how much this contributes to the ultimate outcome. Further details of some of the individually more important diagnoses are given below.

*Primitive neuroectodermal tumour (PNET)/extra-osseous Ewing's sarcoma (EOES)*

There is considerable controversy about the optimal approach to the management of this group of tumours which show variable neural differentiation, yet demonstrate the same cytogenetic abnormalities (t11;22 or, less commonly, t21;22) and presumably share a common histogenesis. They are considered part of the Ewing's sarcoma family and the current debate is whether these soft tissue tumours should be treated like RMS (as they have been in the past) or with current protocols for Ewing's tumours of bone. The distinction largely translates to the importance, or otherwise, of the use of anthracycline drugs in the chemotherapy strategy and to the approach to local therapy. Within previous European studies, overall survival for PNET/EOES has generally been slightly less than that for RMS and the risk of metastatic relapse is greater [25,26]. Although no benefit from the addition of doxorubicin to VAC was noted for these tumours in the IRS III study [27], dose intensity was relatively low and the apparent importance of anthracycline in the treatment of Ewing's tumour of bone has led many paediatric oncologists to prefer to use a strategy such as the current Euro Ewing's study [28]. This has the added advantage that, as it is a trial open to both adult and paediatric patients, some comparative data may be obtained about the chemosensitivity and outcome of this group of tumours at different ages.

*Fibrosarcoma*

Two peaks of age incidence are recognised for this diagnosis: one in infants (<2 years of age) which is defined as infantile fibrosarcoma and the other in young adolescents (10–15 years) which is identified as juvenile or "adult-type" fibrosarcoma. Both forms are histologically identical, but show different biological behaviour. Infantile fibrosarcomas are usually located in the distal region of a limb and usually present as a fast-growing mass. They may be present at birth or appear soon thereafter (congenital fibrosarcoma). Surgery alone (when feasible) is generally able to cure the disease and even if these tumours have a tendency to relapse locally (30–40%), metastases are extremely rare and overall survival is extremely good (85–90%) [29]. There is evidence that primary chemotherapy is valuable in patients with inoperable infantile fibrosarcoma (often a relatively low intensity regimen using drugs such as vincristine and actinomycin may be sufficient) and spontaneous regression is reported, particularly in the congenital form. In contrast to adult-type fibrosarcoma, histological grading is of no value in determining ultimate behaviour and it is of interest that a consistent translocation (t12;15) has recently been recognised in congenital fibrosarcoma which may be of diagnostic value in differentiating from other forms of infantile fibrous proliferation and, ultimately, may provide some clues to its carcinogenesis.

In older children and adolescents, fibrosarcoma has clinical features similar to those found in adults. The most frequent sites are the proximal regions of the extremities and deep in the trunk, where surgical approaches are more limited. The prognosis is less favourable (survival rates <60%) and the role of chemotherapy is limited. The most effective treatment is radical surgery and if a wide excision can be achieved, no further treatment is required. Radiotherapy is important in patients with incomplete or marginal excision.

*Synovial sarcoma*

SS is one of the most common NRSTS in adolescents and young adults. Its histology, biology and clinical behaviour are generally identical to that seen in adults.

Wide excision of the primary mass offers the best chance of a favourable outcome in localised forms, but controversy still exists whether adjuvant radiotherapy and chemotherapy is useful after complete excision. Radiotherapy is indicated in the treatment of microscopic residual disease. In inoperable SS, chemotherapy should be given with the aim of improving local treatment with surgery and radiotherapy. Ifosfamide- or cyclophosphamide-based regimens, often with doxorubicin, are the most common and high chemotherapy response rates are reported in most paediatric studies. For example, in the German CWS-81 study, a chemotherapy response rate of 77% (using the VACA combination) was recorded for group III and IV patients [30].

Survival rates are good for patients with non-metastatic disease and seem to be better in some

paediatric studies than reported from the adult experience. In one large retrospective international analysis of 220 children and adolescents treated in different centres between 1966 and 1999, the overall survival at 5 years was 88% for patients with tumours grossly resected at diagnosis (IRS Groups I and II) and 75% for patients with localised but initially unresectable tumours (IRS Group III). Patients with distant metastases fared poorly. The conclusions of this study in relation to the role of chemotherapy suggest that neoadjuvant chemotherapy should be utilised to facilitate delayed surgery, whereas Group I and II patients may not benefit from adjuvant chemotherapy [31]. Ultimately, however, this is a matter than can be resolved only by a randomised clinical trial and a combined adult paediatric study would be of particular interest.

*Malignant peripheral nerve sheath tumour (MPNST)*

These tumours present a considerable challenge to treat. Their pathological features and their association with neurofibromatosis type I is similar to that seen in adults and the most common sites are in the limbs and the trunk. As in adults, surgical excision is the optimal treatment and is the most important prognostic factor for survival. Radiotherapy appears to improve local control in patients with marginal excision, but the role for chemotherapy is not well established. Interestingly, chemotherapy response rates of the order of 45% have been reported in some paediatric series which seem higher than that reported in adult experiences [32]. Whether chemotherapy response substantially improves the prospect of delayed surgical resection, can contribute to local control, or reduce the risk of metastatic disease are all unanswered questions. Overall survival rates are rather poor and are probably worse in children with neurofibromatosis.

*Should non-RMS STS be treated like RMS?*

Apart from a few notable exceptions, for example infantile fibrosarcoma (and infantile haemangiopericytoma), there is little evidence that the pathological or biological characteristics of tumours more frequently encountered in adult practice are significantly different when diagnosed in childhood. Despite this, the strategies for the management of such tumours in children often derive from experience with RMS and children with unresectable tumours usually receive a trial of chemotherapy on a neoadjuvant basis. This is in contrast to the management of the same pathology in an adult which emphasises initial local control with a much more selective use of chemotherapy. Although there is evidence for the chemosensitivity of many NRSTS, it is not clear whether this always contributes to a better survival rate, and there is an urgent need for randomised studies to address this question [33]. Further work on definition of prognostic variables to optimise treatment stratification is also needed; in particular the role of histological grading as a prognostic variable independent of histological sub-type requires evaluation [34]. Finally, drugs such as ET-742, gemcitabine, and imatinib mesylate have all attracted interest in adult sarcoma and need to be evaluated in paediatric tumours, particularly if the appropriate molecular targets are shown to be present [35].

## Summary

Although overall survival rates for children with soft tissue sarcoma have improved, progress for some sub-groups of patients has been less encouraging than might be expected. Priorities for the future include the better identification of patients who can be cured with minimal therapy and better treatment for those who have a poor outcome with current therapy. Improved understanding of the biology of this group of tumours may provide opportunities to utilise some of the more recently designed novel forms of therapy aimed at molecular targets. Although considerable amounts of valuable clinical data have been acquired through clinical trials in patients with RMS, further efforts to systematically explore therapy in children with non-RMS soft tissue sarcoma are now required and there are opportunities for adult–paediatric collaboration in designing new approaches to therapy.

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