The treatment of soft tissue tumours (STS) in children and adolescents is complex. The commonest STS occurring in childhood is rhabdomyosarcoma (RMS) and we will concentrate on its management in this presentation. However the complexity of other STS that occur more commonly in older children and adolescents, particularly issues of local control will also be reviewed.

The challenges of the treatment of STS in childhood

- STS in childhood are rare. There are many pathologies, although RMS is the commonest in childhood. Even for this tumour, treatment depends many variables, including the age of the child, the site, stage and size (> /< = 5cm) of the tumour as well as the pathological subtype (alveolar, embryonal) and clinical (post operative) IRS grouping.
- There is a need for collaborative, multimodal approach and treatment dependent on many factors. Treatment of the tumour is often complex, depending on good 'local control', i.e. surgery and radiotherapy and appropriate systemic therapy (chemotherapy).

Progress has been made

- The understanding of the biology (cyto- and molecular genetics) of the tumour has improved. The identification of the translocation in alveolar RMS has been important, particularly in the identification of those patients who have tumours with a poorer outlook. The t(2;13) and t(1:13) are known to be associated with alveolar disease the former carrying the poorer prognosis, the latter having a prognosis more like that of embryonal disease. The fusion of the PAX 3 and PAX 7 with FKHR has also been demonstrated to occur as a result of these translocations (Barr, Sorensen), allowing for even more sensitive identification of poor risk tumours.
- Risk stratification for RMS is improving. There is a need to optimise local control and, as overall survival rates improve, there aim is to not to over- or under-treat patients wherever possible. Risk stratification in RMS is complex. Historically there have been different approaches between European and North American countries to both risk stratification and therapy. Understanding these differences and their impact on event free survival, overall survival and late effects improves our understanding of the disease. Whilst the overall survival improves there is still more to learn about which patients are at higher risk, requiring systematic local therapy i.e. radiotherapy (e.g. those with parameningeal rhabdomyosarcoma) and which can potentially be cured without local therapy (e.g. some group II patients and even those with Group III tumours at particularly 'good' sites e.g. the orbit (Oberlin), in addition to many group I patients. It is clear that there are differences in outcome between the recent Intergroup Rhabdomyosarcoma Study (IRS IV) (Crist) and the SIOP study MMT 89 (Stevens), with better EFS and OS for some groups of patients treated within the IRS study, conversely there are some in the MMT study cured without the need for radiotherapy with its late sequelae, particularly important for those who receive therapy at a very young age.
- For patients with non –RMS STS, there is greater understanding of pathological grading with comparisons between the French FNCLCC and POG classification undertaken. It is hoped that further understanding of the molecular and cytogenetics these tumours (e.g. the t(12;22) translocation in clear cell sarcoma) of will soon follow.
Improvements in the delivery of local therapy

The three major risk factors of prognostic significance in soft tissue sarcomas are tumor grade, size and depth (Wunder et al., 2000). In rhabdomyosarcoma (RMS) nodal status is also very important. In this disease regional nodal involvement is not considered metastatic disease while in other soft tissue sarcomas it is. Enneking et al 1980, described a schema for classifying surgical margins which were radical, wide, marginal and intra-lesional. Essentially there are only three types of surgical procedures which are utilized for soft tissue sarcomas. They are: intralesional (R2), marginal (R1) and wide (R0) excisions. The corresponding pathologic margins are gross residual, microscopic residual and no residual (clear) margins. A wide margin (R0) is achieved when the tumor is removed en bloc and the plane of dissection is through a narrow rim of normal tissue surrounding the pseudocapsule and reactive zone of the enclosed tumor. Currently a margin of normal tissue 5mm thick or an intact fascial layer is considered the minimal acceptable wide margin. In a marginal excision (R1), the tumor is removed en bloc but the plane of dissection cuts through the tumor pseudocapsule or reactive area surrounding the tumour leaving microscopic residual disease. For an intralesional margin (R2), the tumour is exposed during surgery and gross macroscopic tumour is left behind.

Types of Surgical Procedures:

<table>
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<tr>
<th>Surgical Procedure</th>
<th>Pathologic Results</th>
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<tr>
<td>Wide Excision</td>
<td>R0 Clear Margin</td>
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<tr>
<td>Marginal Excision</td>
<td>R1 Microscopic Residual</td>
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<tr>
<td>Intralesional Excision</td>
<td>R2 Gross residual</td>
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The adequacy of the margin of resection is the most important variable that is associated with local relapse (Bell et al., 1989; Baldini et al., 1999; Spiro et al., 1997) while tumour size is the major determinant of the risk of systemic disease (Bell et al., 1989). Data from the IRSG (Intergroup Rhabdomyosarcoma Study Group) indicates the most frequent sites of primary tumor to be the genitourinary tract (23%), extremity (17%), parameningeal area (nasopharynx, nasal cavity, paranasal sinuses, middle ear-mastoid area, pterygopalatine, and infra-temporal fossa (16%), other head and neck sites (excluding orbit) (10%) and orbit (8%). The tumor also arises in the trunk (10%). retroperitoneum (11%), and miscellaneous other sites (Maurer et al., 1993).

Rhabdomyosarcomas are very sensitive to radiotherapy and chemotherapy and in many sites such as the orbit, parameningeal sites and some sites of the genitourinary tract, this is the mainstay of local therapy particularly when the tumour is of embryonal subtype. Some patients with wide excisions (R0) of tumors of non-alveolar histology do not require routine postoperative radiation therapy. Extremities are unfavorable sites for rhabdomyosarcoma partly due to the high (80%) incidence of alveolar histology and the large size >5cm of many of the tumors. Regional nodes are involved in about 17% of tumors arising in an extremity site. Neville et al. (2000) Nodal involvement is a poor prognostic indicator. Recent publications have highlighted the differences in therapy between some European centers and those in North America (Donaldson et al., 2001; Stevens et al., 2005). The North American approach has been to increase the radiation dose and the number of patients receiving radiation therapy to improve local control while in Europe selected patients with local recurrence are given additional therapy to return the patients to a better overall survival. Despite the differences in local relapse, overall survival is surprisingly similar in the two groups. Future collaborative studies may clarify which approach is best (Donaldson, Anderson, 2005; Stevens, 2005).

The therapeutic approach in other types of soft tissue sarcomas is quite different. There is a paucity of good studies in children and most information comes from the abundant adult literature. In non rhabdomyosarcoma soft tissue sarcomas surgery is the mainstay of therapy and radiotherapy forms an adjunctive role. Radiotherapy alone has a poor outcome with only about 1/3 of patients obtaining control of disease (Slater et al., 1986; Tepper, Suit, 1985). A randomized study by Yang et al illustrated the benefits of adjuvant radiotherapy for local control. Twenty two percent of patients with high grade large tumours recurred without
radiotherapy but when a wide margin (R0) was obtained there were no local recurrences (Yang et al., 1998). This demonstrates the necessity of obtaining clear pathologic margins to obtain adequate local control. Radiotherapy can be given either preoperatively or postoperatively. Pre operative radiotherapy has the disadvantage of a higher incidence of wound complications following surgery but has the advantage of treating a smaller volume of tissue and possibly administering a smaller dose. (O’Sullivan et al., 2002). Radiotherapy has the complication of tissue oedema and fibrosis and decreased range of joint motion (Davis et al., 2002; Davis et al., 1999). There is also a risk of development of a radiation induced sarcoma. All of these complications are dose dependant. In children there is the added complication of future limb length discrepancy due to growth arrest of the physeal bone growth at the ends of the bone. The irradiation field size in children may be smaller with preoperative radiotherapy since the postoperative wound does not require treatment. In some cases this may allow growth plate sparing. In the future efforts will be made to diminish late effects while preserving good local control. Modalities such as dose reduction, brachytherapy or Intensity Modulated Radiation Therapy (IMRT) are being investigated in some centres.

Unplanned surgical excisions (UPS procedures) are problematic since there is no preoperative staging imaging to know initial tumour extent or the lesion has been excised without an adequate cuff of normal tissue surrounding the tumour. In these patients there has been an intra-lesional excision (R2) with a wide contamination of the operative field. Further local treatment to treat the problem is more extensive than would have been necessary if the proper staging and surgery was done. This leads to worse functional outcomes and a greater risk of local recurrence. (Davis et al., 1997; Noria et al., 2002)

Where next?

- Whilst the majority of clinical trials have centred around optimising chemotherapy in RMS, little progress has been made. Vincristine (V), Actinomycin D (A) and Cyclophosphamide (Cyclo) remain the gold standard of therapy in the Children’s Oncology Group (COG) studies, whilst therapy VA with Ifosfamide (Ifos) in Europe. The efficacy of Cyclophosphamide and Ifosfamide in RMS appears to be equivalent and the choice of alkylating agent depends on the accepting the different toxicity profile (impairment of fertility with cyclo versus encephalopathy (reversible) and nephrotoxicity with ifos). Costs also differ with drugs costs and the cost of administration being greater for Ifos.

- The role of anthracyclines is debated and although it has not been proved in the phase III setting, a previous IRS II window study and a recent SIOP window study (Bergeron personal communication) have shown excellent partial and complete remission rates. Doxorubicin will be administered in a more dose intensive schedule in the new European non metastatic RMS study, in a randomised setting. Vinorelbine has been demonstrated as active in phase II studies in alveolar rhabdomyosarcoma (Casanova) this agent will also be tested in the phase III setting.

- Positron Emission Tomography (PET), particularly combined with CT or MRI appears to be of value in non- RMS STS. Of particular value is the ability to quantify tumour activity (SUV) and to identify active areas for biopsy. Fusion techniques may also be of value when planning definitive surgical procedures. The role of PET in RMS has yet to be established.

Where are the problems in the management of RMS and other STS?

- The treatment of metastatic disease remains a real challenge with very little improvement in survival for patients with poor risk, metastatic tumours. The relative rarity of this (and other) subgroups has made randomised studies almost impossible. However future strategies evaluating the role of high dose therapy and maintenance chemotherapy are proposed.

- Optimising local control is also critical. Identifying those who can be cured without radiotherapy or major surgery or conversely optimising surgery/ radiotherapy/ brachytherapy for patients who have tumours...
with a high risk of recurrence remains a high priority within current trials. A particular problem is bringing together the appropriate specialists with the skills to manage tumours at difficult sites, often in very young children.

- The lack of new agents over recent years has limited progress although Irinotecan in combination with vincristine will be brought forward into the new phase III COG study (IRS VI) having been demonstrated as highly active in the window setting (Pappo). The role of agents with anti-angiogenesis properties is currently being explored and may also be an exciting way forward in the treatment of these challenging tumours.

References


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