Abstract

Rhabdomyosarcoma is the most common soft tissue sarcoma in childhood, accounting for approximately 6% of paediatric tumours. These tumours arise in various different locations, at all age groups in childhood and adolescence, and with various different histologic subtypes. As a result, there are a number of important considerations that affect the choice of local control measures. Our aim here is to explore these issues. Local control of rhabdomyosarcoma can rarely be achieved by chemotherapy and so local treatment in the form of surgery and/or radiotherapy is essential in most circumstances. Risk stratification which incorporates clinical group stage, TNM stage, histology and tumour location is an important consideration in determining the modality of local control. Other important considerations include resectability and age of the patient. The timing of local treatment is dependant on the tumour location, feasibility of complete resection without unacceptable loss of function or cosmesis, and the presence of an acute emergency such as spinal cord compression.

Rhabdomyosarcoma is a chemotherapy-responsive tumour, and all patients are treated with chemotherapy because this is a systemic disease.\(^1\) The principle North American chemotherapy regimen is vincristine, actinomycin-D and cyclophosphamide (VAC). In European studies, ifosfamide has been substituted for cyclophosphamide (IVA). The role of anthracycline drugs remains controversial; in randomised studies, the addition of doxorubicin or epirubicin did not lead to improved outcomes. However, these drugs do have activity against rhabdomyosarcoma, and some units routinely incorporate them into treatment protocols. A current European study is re-examining the role of doxorubicin, while a recent rhabdomyosarcoma trial within the Children’s Oncology Group for patients with ‘high risk disease’ incorporated doxorubicin in a single arm trial. This latter trial also added irinotecan, ifosfamide and etoposide; early outcome data appear promising.\(^2\) Irinotecan had earlier been shown to be active in a phase II trial given with vincristine,\(^3\) and is being studied in randomised fashion within an ongoing Children’s Oncology Group trial. Other active agents include carboplatin, topotecan, and melphalan.

The use of irinotecan as a radio-sensitiser to improve local control in patients with intermediate risk disease is being evaluated in the most recent Children’s Oncology Group study. Doxorubicin is a potent radiosensitiser, however anthracyclines are usually used only at the beginning of a radiotherapy regimen. The administration of anthracyclines concurrent with radiotherapy, or in the immediate post-radiation period, should be avoided as it often results in unacceptable augmentation of normal tissue radiation toxicity and a radiation recall phenomenon. Other novel radiosensitising agents, including idoxuridine, razoxane and ifosfamide have also been evaluated.\(^4\)

Within North American studies, local therapy, comprising surgery and/or radiation therapy, has been applied systematically. A different philosophy was adopted in European trials. Because of the long-term morbidities often associated with local therapies, a strategy of evaluating chemotherapy response prior to local therapy was adopted. Those patients, who responded promptly, and completely, did not undergo radiation therapy. The expectation was that there would be patients who had a recurrence, but that a second course of treatment, including a local therapy, might be able to achieve a durable second remission. Indeed, this is what the data showed, and so these European trials have lower event free survival than the North American trials, but equivalent overall survival rates confirmed that certain relapsing patients were indeed salvaged.\(^5\)

It is clear that local treatment is essential for local control at least in certain settings.

Initial surgery and work up

Patients with rhabdomyosarcoma are allocated a pre-treatment clinical stage and a post surgical clinical group, both of which carry prognostic significance. Staging is a modification of the UICC-TNM staging system and is based on site, size, clinical regional nodal status and distance spread. ‘Staging’ is clinical and should be performed by the responsible surgeon based on pre-operative imaging and physical findings (table 1). Intraoperative and/or pathologic results do not affect the stage. Site designation alters stage, with certain sites considered favourable and others unfavourable. Careful evaluation of clinical and/or imaging finding should precede multi-disciplinary site assignment.

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Bhavna HarilalChawla,\(^1\) Verity Ahern,\(^2\) Jonathan Karpelowsky\(^3\) and Geoffrey B McCowage\(^1\)
1. Departments of Oncology and Surgery, The Children’s Hospital at Westmead, New South Wales.
2. Department of Radiotherapy, Westmead Hospital, New South Wales.
3. Department of Radiation Oncology, Westmead Hospital, New South Wales.
Email: geoffm@chw.edu.au
The surgical-pathologic (clinical) ‘group’ is based on intraoperative findings and postoperative pathologic status, and includes final pathologic verification of margins, residual tumour, node involvement, and cytological examination of pleural, peritoneal and cerebrospinal fluid when applicable.

Final risk stratification within recent North American studies has combined group and stage with histological sub-type. Low, intermediate and high-risk groups are therefore defined (table 2). Similarly complex stratification takes place within European trials.

When possible and reasonable, a wide and complete resection of the primary tumour, with a surrounding envelope of normal tissue, should be performed as an initial and/or subsequent operation. This may be possible with extremity or trunk primaries, but is often not possible with head and neck, orbital and some genitourinary sites. Procedures which would lead to an unacceptable loss of function or cosmesis are not recommended.

Approximately half of all patients have unresectable tumours (clinical group 3) at presentation and 15% have metastatic disease (group 4). Microscopically complete (group 1) and

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**Table 1: The distribution of histological types in 142 patients with musculoskeletal tumours – 2002.**

<table>
<thead>
<tr>
<th>Group</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Localised tumour, completely removed with pathologically clear margins and no regional lymph node involvement.</td>
</tr>
<tr>
<td>II</td>
<td>Localised tumour, grossly removed with (a) microscopically involved margins, (b) involved, grossly resected regional lymph nodes, or (c) both</td>
</tr>
<tr>
<td>III</td>
<td>Localised tumour, with gross residual disease after grossly incomplete removal, or biopsy only</td>
</tr>
<tr>
<td>IV</td>
<td>Distant metastases present at diagnosis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stage</th>
<th>Sites of primary tumour</th>
<th>Tumour size (cm)</th>
<th>Regional lymph nodes</th>
<th>Distant metastases</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Orbit, non-PM head/neck; GU non-bladder/prostate; biliary tract</td>
<td>Any size</td>
<td>N0, N1</td>
<td>M0</td>
</tr>
<tr>
<td>2</td>
<td>All other sites</td>
<td>&lt; 5</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>3</td>
<td>All other sites</td>
<td>&lt; 5, &gt; 5</td>
<td>N1, N0 or N1</td>
<td>M0</td>
</tr>
<tr>
<td>4</td>
<td>Any site</td>
<td>Any size</td>
<td>N0 or N1</td>
<td>M1</td>
</tr>
</tbody>
</table>

PM, Parameningeal; GU, genito-urinary; N0, regional nodes not clinically involved by tumour; N1, regional nodes clinically involved by tumour; M0, no distant metastases; M1, distant metastases at diagnosis

**Table 2: RMS risk stratification as per recent North American Studies.**

<table>
<thead>
<tr>
<th>Histology</th>
<th>Clinical Group</th>
<th>Stage</th>
<th>Age</th>
<th>Risk Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Embryonal, with variants</td>
<td>I, II, III</td>
<td>1</td>
<td>All</td>
<td>Low</td>
</tr>
<tr>
<td>Embryonal, with variants</td>
<td>I, II</td>
<td>2, 3</td>
<td>All</td>
<td>Low</td>
</tr>
<tr>
<td>Embryonal, with variants</td>
<td>III</td>
<td>2, 3</td>
<td>All</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Embryonal, with variants</td>
<td>IV</td>
<td>4</td>
<td>&lt; 10 years</td>
<td>Intermediate (moved to high for ARST0431)</td>
</tr>
<tr>
<td>Embryonal, with variants</td>
<td>IV</td>
<td>4</td>
<td>&gt; 10 years</td>
<td>High</td>
</tr>
<tr>
<td>Alveolar</td>
<td>I, II, III</td>
<td>1, 2, 3</td>
<td>All</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Alveolar</td>
<td>IV</td>
<td>4</td>
<td>All</td>
<td>High</td>
</tr>
</tbody>
</table>
incomplete (group 2) resections are achieved at diagnosis in 16% and 20% respectively.

Patients with unresectable tumours undergo biopsy. Adequate tissue needs to be obtained to facilitate immuno-histochemical and molecular studies. Fine needle biopsies are generally inadequate.

Selected sites require further surgical staging. Patients with extremity tumours should have aggressive sampling of relevant lymph nodes. Lymphscintigraphy may guide this nodal sampling, especially in truncal tumours; radical lymph node dissection is not performed. Patients over the age of 10 years with para-testicular rhabdomyosarcoma routinely undergo selective ipsilateral retroperitoneal lymph node dissection in North American trials.

The remainder of the staging studies include a computerised tomography scan of the chest, bone scan or positron emission tomography scan, bilateral bone marrow trephines and lumbar puncture in patients with para-meningeal tumours.

Sites considered to be parameningeal:
- Middle ear
- Nasal cavity and paranasal sinuses
- Nasopharynx
- Infratemporal fossa/pterygopalatine and parapharyngeal area.

Modalities for local control

Surgery and external beam radiation therapy are the principle modalities. In general, surgery is preferred where wide resection can be obtained without unacceptable loss of function. Radiation therapy is effective for local control, however is generally associated with growth, developmental and cosmetic abnormalities, as well as a small risk of secondary malignant neoplasia, in the order of 2% long term.6

As discussed above, an initial wide resection of the primary tumour at diagnosis is optimal. Primary re-excision of a tumour is defined as a second attempt at complete resection before the initiation of any other forms of therapy. This should be encouraged when an initial excision results in positive margins and further resection can be accomplished without significant functional or cosmetic morbidity. This strategy has been shown to improve survival in selected tumours. In patients with microscopic or macroscopic residual disease, North American investigators have systematically applied external beam radiation therapy following a phase of induction chemotherapy.

More recently, the Children’s Oncology Group studied the role of a delayed, or “second look” operation to resect residual tumour at selected sites after induction chemotherapy, and before radiation therapy. The goals of second look surgery are to remove residual tumour and to determine pathological response. The rationale was that the tumour may become amenable to resection following chemotherapy, and that the second look procedure would improve local control and/or allow the use of a lower dose of radiation therapy. The radiotherapy dose was adjusted according to the completeness of the delayed resection - patients with gross residual disease received 50.4 Gy, microscopic residual received 41.4 Gy and those with a complete resection received 36 Gy. Seventy three patients with tumours at the selected primary sites (bladder/ extremity/trunk) underwent second look surgery and 84% of these achieved removal of all gross disease and were eligible for a reduced dose of radiation therapy. The authors concluded that a second look operation was feasible, and was able to be performed in approximately half of the patients with tumours at the selected sites. A majority of patients who underwent induction chemotherapy and delayed surgery were then eligible for radiotherapy dose reduction. Long-term follow-up of disease control is awaited.7

Radiation treatment, whether definitive or post-operative, may be delivered by external beam or brachytherapy. Brachytherapy involves the insertion of a radioactive source directly into the tumour or tumour bed, concentrating the radiation dose here rather than scattering radiation dose to surrounding structures. This technique is suitable when the area to treat is small and accessible to implantation or is in proximity to a body cavity.

External beam radiation is delivered by a linear accelerator on a daily outpatient basis and may require the use of general anaesthesia to ensure immobilisation of a younger child. Three dimensional conformal radiation and intensity modulated radiation therapy are technologies in current practice designed to conform the radiation treatment to the target volume as concisely as possible.

Tumour location

Rhabdomyosarcomas occur at multiple different locations throughout the body. Typical rhabdomyosarcoma clinical trial protocols give comprehensive recommendations for local control measures at the various sites. Within this review, we will limit discussion to a few general points at key anatomical sites:
- Orbit Surgery - is generally limited to biopsy and treatment is with chemotherapy and radiotherapy.
- Head and neck (non parameningeal) - Wide excision is appropriate when feasible, giving regard to cosmetic and functional outcomes. Otherwise biopsy is followed by chemotherapy, possible second look surgery and radiotherapy.8
- Head and neck (parameningeal) - Sites that are considered parameningeal have been listed previously. In addition to tumour location, tumours are considered parameningeal when there is cranial nerve palsy, skull base bone erosion, or intracranial tumour extension.9 Radical surgery is usually not indicated. Radiotherapy to parameningeal tumours is generally given following a phase of induction chemotherapy. The exception is with those parameningeal tumours where there is intracranial extension demonstrated on magnetic resonance imaging scans. These patients undergo radiotherapy as soon as possible after diagnosis, along with the initiation of chemotherapy.10
Paratesticular - Paratesticular rhabdomyosarcoma should be excised using an inguinal approach. Transcrotal resection will result in contamination of inguinal lymphatics, and North American studies would suggest hemiscrotectomy in these instances. Staging of retroperitoneal nodes in boys over the age of 10 years is discussed above. Radiotherapy to the nodes is not required in group I tumours, but is used in other groups.11

Genitourinary (non bladder-prostate) - Complete gross removal is appropriate if this is possible without a radical procedure. There is no role for initial aggressive resection such as vaginectomy or hysterectomy. The extreme chemosensitivity of the tumours in this location usually precludes the need for radical surgery. For patients with clinical group III tumours of the uterus or cervix that cannot be completely resected, radiation is recommended at week 13; brachytherapy should be considered. However, the European trials SIOP MMT 84 and 89 concluded that local treatment is not necessary in patients who have a complete response to chemotherapy.12

Genitourinary (bladder/prostate) - Salvage of the bladder and urethral function is an important consideration for tumours arising in this site and can be achieved in at least half the patients. The initial surgical procedure is typically a biopsy usually performed cystoscopically. In the unusual situation of a laparotomy, iliac and para-aortic node sampling should be included, as well as biopsy of any other clinically involved nodes. Martelli et al described conservative surgery with brachytherapy treatment for boys with prostate and/or bladder-neck rhabdomyosarcoma as an alternative to external radiotherapy or radical surgery. It allowed normal continence in nearly all of 24 patients.13 Despite a conservative approach, 30% of patients may still require ablative surgery and those who are able to preserve their bladders may have significant bladder dysfunction. Brachytherapy allows normal growth and function of the unirradiated bladder and bowel as well as normal growth of pelvic bones and the hips.

Extremity - The extremity is an unfavourable site for rhabdomyosarcoma, explained only partly by the higher frequency of alveolar tumours at this location. Regional node evaluation is discussed above. Extremity tumours are often amenable to wide or radical resection while sparing the involved limb. The role of primary re-excision should be employed where feasible, if clear margins were not attained at the initial surgery, as this has been shown to improve survival in tumours less than five centimetres. Surgical margins of two centimetres may not be feasible in children and there is no clear evidence that larger margins decrease the chance of recurrence. Post-operative radiation is required for close surgical margins and for all patients with alveolar histology. Brachytherapy may be considered in this situation as well.

Other sites - These include tumours of the chest wall, paraspinal region, abdominal wall, retroperitoneum, pelvis, biliary tract, perineum, perianal and other locations. As a general principle, complete excision should be performed if feasible and with acceptable morbidity. Radiotherapy is employed if wide resection cannot be obtained.

Timing of local therapy

As discussed above, a wide local resection should be performed at initial diagnosis, or as pre-treatment re-excision following an initial biopsy, if possible with acceptable morbidity. Resection at a second look operation may be performed following induction chemotherapy; post-operative radiotherapy has been employed in this context within American studies.

The timing of radiotherapy varies. It is given at the start of treatment for those patients with parameningeal tumours with intracranial extension, or if there is an acute emergency such as spinal cord compression. Otherwise radiotherapy is generally given following approximately 12 weeks of induction chemotherapy.

A research question within an ongoing trial of the Children’s Oncology Group is whether the delivery of radiotherapy earlier in treatment, at week four of chemotherapy, may improve local control.

When radiotherapy is to be applied to metastatic sites, treatment generally follows a longer phase of chemotherapy, for instance being given at week 20.

Miscellaneous criteria

Special considerations are required for the very young patient, particularly those under the age of 24 months. The long-term sequelae of radiation therapy given to such young patients may make that modality of therapy unacceptable. Clinical trial protocols acknowledge this, and often allow for the clinical team to deviate from those local control guidelines employed in older children.

Very young children with parameningeal tumours and intracranial extension should still undergo radiation therapy early in treatment, as cure cannot be achieved without radiotherapy.

The prognostic significance of tumour histology is well known. Patients with group I embryonal tumours do very well with multi-agent chemotherapy alone, hence radiotherapy is not recommended. However, those with group I alveolar or undifferentiated tumours achieve superior outcomes when radiotherapy is administered.14 Conversely, in group III tumours, histology did not correlate with the risk of relapse.15

Depending on the primary tumour location, consequences of local treatment of rhabdomyosarcoma may include growth disturbances, pituitary failure, cataract formation, hearing loss and dentition malformations. Early referral to a paediatric dentist, endocrinologist, facio-maxillary surgeon or orthopaedic surgeon needs to be co-ordinated through a multidisciplinary clinic.

Failure of local control remains the major cause of treatment failure in rhabdomyosarcoma. Data analysed...
from the Third Intergroup Rhabdomyosarcoma Study for Group III patients showed that the risk of relapse was 33%, and 71% of relapsing patients had local relapse with or without distant relapse. Radiotherapy as a modality for local control was less frequently used in frontline treatment in European trials; in those studies local recurrence accounted for 85% of treatment failures.

Conclusion
Myriad factors impact on decisions regarding local control. These decisions are best made in the context of a multidisciplinary team, incorporating the sarcoma surgeon, radiation oncologist, paediatric oncologist, radiologist and pathologist.

References