



Rhabdomyosarcoma of the extremities in adults

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Rhabdomyosarcomas are uncommon in adults and literature regarding their management is limited. Eight patients with an average age of 32.6 years (range: 21 to 75) who were treated for rhabdomyosarcomas on the extremities between 1991 and 2002 in a regional centre for the treatment of soft tissue sarcomas were studied retrospectively. Treatment consisted of en bloc resection of the primary tumour in all the patients, combined with radiotherapy or chemotherapy or both.

The tumour size ranged from 5.5 cm to 15 cm (average 9.3 cm). Histologically there were four alveolar, two pleomorphic, one embryonal and one anaplastic subtype. Seven of the eight patients developed metastasis and died after an average period of 15.3 months (range 4-28 months). At the final follow-up, only one patient was disease free and alive 48 months after surgery.

Extremity rhabdomyosarcoma is a highly malignant tumour and our results are poor compared to the reported results in children. Metastatic recurrence is high in adult rhabdomyosarcomas even with local control of the disease and therefore development of effective systemic therapy is an urgent priority.

Keywords : rhabdomyosarcoma ; adult ; extremity ; soft tissue sarcoma.

INTRODUCTION

Rhabdomyosarcoma (RMS) is an aggressive malignant tumour constituting 4-8% of all childhood malignancies (14, 20). They are uncommon in adults and the literature regarding their manage-

ment is limited. Five-year-survival for childhood RMS is improved from 15% to 60% as a result of introduction of a multimodality approach (1, 3, 19, 20). Despite the use of a similar approach in adults, the 5-year survival rate remains poor, in the range of 35%-45% (2, 6, 10). These tumours can arise from any mesenchymal tissues but they are commonly encountered in the head and neck region and the genitourinary tract (10, 15, 16). Extremity RMS constitutes less than one third of all patients with RMS (6, 10). Increasing age (11), tumour size more than 5 cm (12, 13) and extremity locations are associated with poor prognosis (8, 16, 22).

Extremity RMS can pose some of the most difficult therapeutic challenges. Formulating a comprehensive treatment plan for adult RMS is difficult because of the paucity of the literature concerning the specific therapeutic modalities in adults. Our knowledge is mainly derived from childhood RMS, but the applicability in adults is controversial.

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Table I. — Clinical details of patients in this study

Case No	Age (Years)	Sex	Primary site	Metastasis at presentation	Biopsy type	Tumour size (cm)	Subtype
1	75	M	Shoulder	No	Excision*	15	Pleomorphic
2	24	F	Leg	Pulmonary	Incision	6	Alveolar
3	27	F	Thigh	No	Incision	13	Alveolar
4	24	F	Thigh	No	CT guided	8	Embryonal
5	40	M	Thigh	No	Incision	7	Undifferentiated
6	26	F	Thigh	No	Excision*	5.5	Alveolar
7	21	F	Leg	No	Incision	9.5	Alveolar
8	25	M	Axilla	No	Trucut	10.5	Pleomorphic

* Performed elsewhere.

Table II. — Outcome Summary

Case No	Local recurrence	Metastasis	Tumour free survival (months)	Total Survival (months)	Result
1	Yes	Pulmonary	3	10	DOD
2	No	Pulmonary	–	13	DOD
3	No	Pulmonary	10	19	DOD
4	Yes	Pelvis, Mediastinum	2	4	DOD
5	No	No	48	48	NED
6	Yes	Pulmonary	7	28	DOD
7	No	Pelvic nodes, IVC obstruction	9	10	DOD
8	No	Pulmonary & Cerebral	13	23	DOD

DOD : Died of disease.

NED : No evidence of disease.

Another option is to include the adult rhabdomyosarcomas also in the general classification of adult soft tissue sarcomas and to treat accordingly. The purpose of the present study is to report the results of multimodality management of adult RMS on the extremities, treated over a period of ten years.

MATERIALS AND METHODS

Eight adults with extremity RMS who were treated in our regional soft tissue sarcoma unit (table I) between 1992 and 2003 were studied retrospectively. The age of these patients at primary resection was 21 years to 75 years (mean age of 33 years). There were 3 men and 5 women. Six patients were referred to us without a primary diagnosis. Two patients had excision biopsy performed elsewhere for a mistaken benign lesion. Four patients had primary tumours in the thigh, two in the leg

and two in the upper limbs. One patient had pulmonary metastasis and one had regional lymphadenopathy at the time of first presentation.

Each patient was evaluated by a multidisciplinary team with full history, physical examination, routine haematological and biochemical tests, and a chest radiography. Staging studies included MRI scan of the tumour and a CT scan of the chest in all cases. Incisional biopsy was performed in 4 patients, one patient had trucut biopsy and one patient had CT guided biopsy. Another two patients had excision biopsy performed elsewhere. Histological examination was performed by a senior pathologist (table I). Immunohistochemical studies were used in all the cases to confirm the diagnosis. Tumours were staged using Enneking's sarcoma staging system as advocated by the Muskuloskeletal Tumour Society (4). Size of the tumour was determined by the preoperative MRI scan and it was based on the largest dimension of the mass.

All except one patient had limb-sparing surgeries. One patient had hip disarticulation for an advanced primary tumour located in the thigh. Our current protocol for surgical resection of soft tissue sarcomas does not include routine lymph node dissection. All patients received postoperative external beam radiotherapy with a dose of 40 Gy to 60 Gy. Seven patients received chemotherapy consisting of doxorubicin or ifosfamide based regimens. One patient did not receive any systemic chemotherapy because she was randomised to a non-chemotherapy group in an ongoing trial (Case 5). No patients received preoperative chemotherapy or radiotherapy. All patients were followed up in a specialised soft tissue sarcoma clinic, at 6 weeks to 3 months during the first postoperative year and at 3-6 months thereafter. Imaging studies were repeated at least once in every year or earlier if clinically indicated.

RESULTS

Histologically there were four alveolar, two pleomorphic, one embryonal and one anaplastic subtype of RMS. There were 5 patients with stage IIA disease, two IIB and one IIIA. The size of the tumour ranged from 5.5 cm to 15 cm with an average size of 9.18 cm (median 9.15 cm).

Histological clearance of the resection margin was achieved in 6 patients. Two patients with incomplete resections had previous excision biopsies performed elsewhere for mistaken benign lesions. One of these patients had stage IIB pleomorphic rhabdomyosarcoma in the suprascapular region. A radical resection with scapulectomy was performed, but histologically a clear margin could not be achieved. The second patient also had excision biopsy performed elsewhere for a mistaken lipoma. Histologically clear margins could not be achieved during the re-excision because the tumour was encroaching upon the sciatic nerve.

Two patients developed local recurrences. Local recurrence occurred in the first patient, in three months after the primary resection. His primary resection was incomplete histologically. Another patient developed locoregional recurrence two months after the primary resection, although he had histologically clear primary resection. Two patients developed pelvic metastasis from the lower limbs resulting in inferior vena cava obstruction in one

and ureteric obstruction leading to hydronephrosis in another. Six patients developed pulmonary metastasis. One patient had developed cerebral metastasis in addition to his pulmonary metastasis.

Complications of treatment included iliofemoral deep vein thrombosis in one case and febrile neutropenia while undergoing chemotherapy in another. One patient required a primary skin graft to close the skin defect.

Seven out of eight patients died of the disease. Only one patient is disease free and alive at last follow-up. There is no 5-year survival in this series. Average tumour free survival was 11.5 months. The average period of survival was 19.37 months after the surgical resection.

DISCUSSION

The Intergroup Rhabdomyosarcoma Study Group (IRSG) was founded in 1977 to formulate an effective treatment protocol for childhood rhabdomyosarcomas (16). With its recommendations in IRS I, IRS II and IRS III trials, the survival rate is improved significantly in children (1, 3, 16, 17, 19, 24). Based on these studies, generally accepted guidelines for treatment of childhood RMS include gross total resection with preservation of function, systemic chemotherapy using a combination of Vincristin, Actinomycin D and Cyclophosphamide and local radiation to all except completely resected embryonal sub type. Although these experiences in childhood RMS are widely used in the adults also, long-term success rate remains poor. Applicability of childhood studies in adults remained controversial and some authors consider adult and childhood forms of RMS as two separate entities (6, 10, 15, 18).

Many of the earlier studies on RMS have in fact included a few patients with other soft tissue tumours who had better prognosis (5, 21). This was because of the difficulty in histological diagnosis and unavailability of modern immunohistochemical methods. Miettinen *et al* (18) in a histological review of 25 cases of previously diagnosed cases of adult RMS found only 2 (8%) cases of true RMS after applying strict criteria. Both patients died within 3 months. None of the tumours affecting an

extremity could be verified as RMS. The comparative rarity of RMS has been ascribed to the fact that skeletal muscles are completely de-differentiated and do not undergo cellular division in postnatal life (2).

There are no published studies evaluating the prognostic factors and treatment methods in adults with extremity RMS. Tabrizi *et al* (23) in a review of 6 patients with childhood RMS on extremities and trunk concluded that complete tumour free excision was a major factor in survival. Median survival from diagnosis was 39 months. LaQuaglia *et al* (12) in a retrospective analysis of 35 paediatric patients (median age 7.75 years) with extremity RMS, concluded that local tumour invasiveness is the most important determinant of clinical stage and predictor of fatal outcome. Even in children, localisation on an extremity has been identified as an unfavourable predictor for overall survival (8, 16). In IRS I study group, tumours arising from extremities and retroperitoneum had the worst prognosis (16).

In our study, the average tumour size was 9.3 cm (range, 5.5 cm-15 cm). Esnaola *et al* (6) in a study of 39 patients with adult RMS treated over a period of 23 years, have reported an overall 5-year survival rate of 31%. Five year survivals for tumours less than 5 cm, 5-10 cm and more than 10 cm were 60%, 14% and 0% respectively. These authors concluded that age, location, nodal status and histological subtypes were not significantly associated with prognosis whereas metastasis at presentation and poor response to chemotherapy was strongly associated with poor prognosis.

A mainstay in the treatment of adult soft tissue sarcomas of extremities is complete local excision of the tumour, often complemented by radiotherapy. Soft tissue sarcomas are well known for their poor sensitivity to chemotherapy. In fact the only surviving patient in our study has not received any chemotherapy. Hawkins *et al* (10) in a retrospective study of adult patients with RMS have found no survival benefit with chemotherapy. On the contrary, Little *et al* (15), Esnaola *et al* (6) and Ferrari *et al* (7) showed that chemosensitivity of adult RMS is good and comparable to that of childhood RMS. Based upon the studies on soft tissue sarcomas of

extremities in general, radiotherapy may be beneficial in improving local control of the disease (25).

The most common pattern of disease recurrence in adults is distant metastasis, most often in lungs (6, 7, 10, 15). A similar trend is noted in the present study also. Six patients developed metastatic recurrence even with local control of the disease. There were two instances (out of 8) of local recurrence, one each in histologically positive and negative resection margins. Previous studies on adult RMS have reported 11% to 14% local recurrence (6, 10, 15).

The average period of survival in the current study was 20.7 months from initial surgical resection. There is no five-year survival in this study. In adult RMS including all anatomical locations, overall five-year survival rates of 31% to 44% were reported previously (6, 7, 10, 15). Poor disease specific survival rate in our study has been the consequence of the larger average size of the tumour (9.3 cm), metastasis at presentation (one) and previous incomplete resection in non-specialised centres (two).

Two patients in our study were referred to us after a primary resection performed in non-specialised centres. In both instances RMS were mistaken for benign swellings by general surgeons. Goodlad *et al* (9) in a histological review of 95 patients with primary resection of soft tissue sarcomas performed in non-specialist centres found 56 (59%) patients had residual tumours. In our study, a histologically clear margin could not be achieved during re-excision in both patients.

The small sample size makes it hard to analyse the data with statistical methods but our observations suggest that these tumours are inherently aggressive and surgical clearance alone is probably not the answer. The higher rate of metastatic recurrence even in absence of local recurrence necessitates development of more effective chemotherapy agents. In absence of prospective randomised trials, which is clearly unfeasible because of the extreme rarity of the disease, it is not possible to recommend a standard protocol for adult RMS on extremities. An approach either similar to paediatric RMS protocol or a standard adult soft tissue sarcoma protocols are followed in different centres.

CONCLUSION

In conclusion, adult RMS is a highly malignant tumour with poor prognosis. Despite the reported good prognosis in children, a similar approach in adult extremities has not yielded better results. Metastatic recurrence is a major occurrence even with local control of the disease, and development of effective systemic therapy is an urgent priority. Excision of these tumours in non-specialist units still poses significant problems. Since salvage therapy after recurrence is unsuccessful, aggressive initial therapy is necessary.

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