Adult Pleomorphic Rhabdomyosarcoma: A Multicentre Retrospective Study

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Abstract. *Background: Pleomorphic rhabdomyosarcoma (RMS) is a rare sub-type of RMS. Optimal treatment remains undefined. Patients and Methods: Between 1995 and 2014, 45 patients were diagnosed and treated in three tertiary sarcoma Centers (United Kingdom, Switzerland and Germany). Treatment characteristics and outcomes were analyzed. Results: The median age at diagnosis was 71.5 years (range=28.4-92.8 years). Median survival for those with localised (n=32, 71.1%) and metastatic disease (n=13, 28.9%) were 12.8 months (95% confidence interval=8.2-34.4) and 7.1 months (95% confidence interval=3.8-11.3) respectively. The relapse rate was 53.8% (four local and 10 distant relapses). In total, 14 (31.1%) patients received first line palliative chemotherapy including multi-agent paediatric chemotherapy schedules (n=3), ifosfamide-doxorubicin (n=4) and single-agent doxorubicin (n=7). Response to chemotherapy was poor (one partial remission with vincristine-actinomycin D-cyclophosphamide and six cases with stable disease). Median progression-free survival was 2.3 (range=1.2-7.3) months. Conclusion: Pleomorphic RMS is an aggressive neoplasm mainly affecting older patients, associated with a high relapse rate, a poor and short-lived response to standard chemotherapy and an overall poor prognosis for both localised and metastatic disease.*

Rhabdomyosarcomas (RMS) are mainly paediatric neoplasms, although cases can be infrequently diagnosed in adults (1). The current WHO classification sub-divides RMS into four different sub-types: embryonal, alveolar, pleomorphic and spindle cell/sclerosing (2). Pleomorphic RMS, first described by Stout and colleagues in 1946 (3), remains a very rare entity with limited data to guide treatment (4). It is currently defined as a high-grade sarcoma composed of undifferentiated round and spindle cells that display skeletal-muscle differentiation without embryonal or alveolar components (2). Typically, it is an aggressive lesion arising in the deep soft tissues of the extremities with a high propensity for metastasis. Because of its biological and genomic complexity, its clinical behaviour and responsiveness to chemotherapy is more similar to adult high-grade soft-tissue sarcomas than to paediatric RMS (5, 6).

For localised disease, wide surgical resection is the mainstay of treatment. For advanced disease, there is no standard systemic therapy; patients are treated with a variety of chemotherapy regimens, ranging from multi-agent paediatric chemotherapy schedules to single-agent doxorubicin (7-11). Because most retrospective studies have grouped different RMS sub-types together, there is no clear consensus on the optimal systemic treatment for pleomorphic RMS. The chemosensitivity of pleomorphic RMS remains to be defined, although it is generally regarded as chemoresistant.

The aim of the present study was to report on the clinical characteristics, treatment and outcome of patients with pleomorphic RMS, and to document the response to palliative chemotherapy for patients with metastatic disease in order to provide a baseline for future studies and to guide physicians and patients regarding treatment selection.

Patients and Methods

We searched the prospectively maintained databases of the Royal Marsden Hospital (United Kingdom), the University Hospital of Bern (Switzerland) and the University Hospital of Mannheim

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Key Words: Pleomorphic rhabdomyosarcoma, multicenter study, chemotherapy, prognosis.

Table I. *Baseline clinical characteristics at diagnosis of localised or metastatic disease.*

	Localised disease (N=32)		Metastatic disease (N=13)	
Median age (range), years	72.5	(28.4-92.8)	68.0	(45.0-85.4)
Gender, n (%)				
Male	20	(62.5)	9	(69.2)
Female	12	(37.5)	4	(30.8)
Site of primary tumour, n (%)				
Upper extremity	6	(18.8)	2	(15.4)
Lower extremity	11	(34.4)	4	(30.8)
Head and neck	1	(3.1)	0	(0.0)
Thoracic	2	(6.3)	2	(15.4)
Abdominal	4	(12.5)	3	(23.1)
Pelvis	8	(25.0)	0	(0.0)
Other	0	(0.0)	1	(7.7)
Unknown	0	(0.0)	1	(7.7)
Median tumour size (range), cm	11.0	(2.8-20.0)	11.0	(4-27.9)
Tumour depth, n (%)				
Superficial	5	(16.7)	0	(0.0)
Deep	22	(73.3)	10	(76.9)
Unknown	4	(13.3)	3	(23.1)
Metastatic sites, n (%)				
Lung	0	(0.0)	10	(76.9)
Liver	0	(0.0)	1	(7.7)
Bone	0	(0.0)	2	(15.4)
Lymph nodes	3	(9.4)	0	(0.0)
Other	0	(0.0)	5	(30.8)

(Germany) to identify patients who were diagnosed with pleomorphic RMS between 1995 and 2014. All diagnoses of pleomorphic RMS were confirmed by soft-tissue sarcoma pathologists by combining morphological features, immunoprofiling and molecular profiling to exclude alternative diagnoses. All patients with embryonal RMS, alveolar RMS and spindle cell/sclerosing RMS were excluded from the study. Data were collected through a retrospective review of medical records. Approval from the Ethics Committee of each hospital was obtained before commencing the study (SEVAL approval number SE399).

Baseline characteristics including age, gender, primary tumour location, tumour size and anatomic depth, disease stage, and sites of metastatic involvement were recorded. Localised disease was defined by the absence of distant metastases. Primary tumour size was assessed by macroscopic measurement of the surgical specimen when available or by baseline imaging.

Treatment modalities, including surgery, radiation therapy and chemotherapy, used for localised and metastatic disease were analysed. Surgical margins were assessed. An R0 resection was defined by the absence of microscopic tumour involvement of the margins. An R1 resection was defined by the presence of microscopic involvement of margins without evidence of macroscopic disease. An R2 resection was defined by the presence of residual macroscopic disease. Patients who received palliative chemotherapy were re-imaged using computed tomography or magnetic resonance after two or three cycles of chemotherapy according to local hospital guidelines. Response to chemotherapy was assessed via retrospective viewing of radiology reports. A majority of reports used the Response Evaluation Criteria In Solid Tumours (RECIST) criteria (12). Due to the extensive time period covered by this study, it was not possible to re-review radiological response as electronic archiving of imaging was not available for all patients. Final outcome was recorded as of March 2015. Patients were recorded as being either dead or alive.

Statistical analysis. The overall survival (OS) was defined by the time between diagnosis and death or last patient contact. For patients who relapsed, the time to relapse was determined from the time between diagnosis and occurrence of local or distant relapse. For patients receiving palliative chemotherapy, the progression free survival (PFS) was calculated by determining the time between start of treatment and progression of disease according to RECIST criteria or death from any cause. Survival curves were obtained using the Kaplan-Meier method. All statistical analysis was carried out using MedCalc software version 14.8.1 (MedCalc Software, Ostend, Belgium).

Results

Baseline characteristics. A total of 45 patients (39 patients in the UK, 3 in Switzerland and 3 in Germany) were diagnosed between 1995 and 2014 with pleomorphic RMS. Baseline characteristics are summarised in Table I. The overall median age at diagnosis was 71.5 years (range=28.4-92.8 years). Slightly more than two-thirds of patients were diagnosed over the age of 65 years. The male-to-female ratio was 1.8:1.

Table II. *Treatment summary and outcome for patients with localised disease (n=32).*

Treatment modality	N	%
Surgery		
Yes	26	81.3
No	6	18.7
Type of resection		
R0	22	84.6
R1	3	11.5
R2	1	3.9
Radiation therapy		
Preoperative	1	3.1
Postoperative	15	46.9
Palliative	1	3.1
Chemotherapy		
Neoadjuvant	1	3.1
Adjuvant	1	3.1
Outcome		
No relapse	13	50.0
Local relapse	4	15.4
Metastatic relapse	10	38.5
Median time between diagnosis and local relapse (range), months	6.1 (3.6-13.8)	
Median time between diagnosis and distant relapse (range), months	5.3 (1.0-9.5)	
Status at last follow-up		
Alive, no disease	9	28.1
Alive, with disease	1	3.1
Dead, of disease	15	46.9
Dead of other cause	4	12.5
Dead, unknown reason	3	9.4

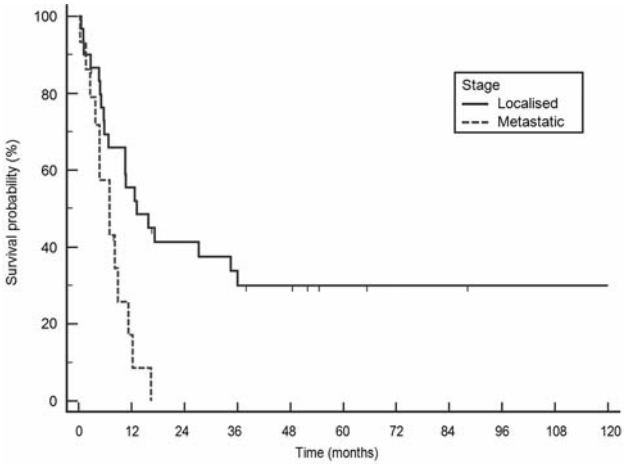

Figure 1. *Overall survival in patients with localised or metastatic disease.*

Table III. *Treatment summary and response for patients treated with palliative chemotherapy.*

First-line chemotherapy	N	Best response
Doxorubicin	7	2 SD, 4 PD, 1 NE
Ifosfamide-doxorubicin	2	1 SD, 1 PD
Multi-agent chemotherapy	3	1 PR, 2 SD
Other	2	1 SD, 1 PD
Second-line chemotherapy and beyond		
Doxorubicin	1	1 PD
Ifosfamide-doxorubicin	1	1 PD
Gemcitabine-docetaxel	2	2 PD
Ifosfamide	1	1 PD
Dacarbazine	1	1 PD
Oral cyclophosphamide	1	1 PD
Trabectedin	1	1 PD
Pazopanib	1	1 PD

SD: Stable disease; PD: progressive disease; PR: partial remission; NE: not evaluable.

The majority of patients (n=32, 71.1%) had localised disease at their initial diagnosis. The primary tumor was more frequently documented in the extremities (n=23, 51.1%). Tumor size was similar in patients with localised and metastatic disease. A minority of patients with localised disease had a superficial primary tumour (n= 5, 16.7%). No superficial primary tumour was identified in the metastatic group. Nodal involvement was uncommon (fewer than 10% of patients with localised disease). Lungs were the most frequent site of distant metastatic involvement (n=10, 76.9%).

Management of localised disease and outcome. Surgical resection of the primary tumour was attempted in 26 patients (81.3%) with localised disease. Positive margins were documented in four patients (12.5%, one pelvic, one intra-abdominal and two lower extremity primary tumours). The majority of patients (57.7%, 15/26 patients) received postoperative radiation therapy. Two patients received neoadjuvant or adjuvant chemotherapy. One patient had progressive disease following two cycles of neo-adjuvant doxorubicin. Another patient had an R1 resection and was treated with two cycles of ifosfamide and etoposide with concomitant radiation therapy followed by three cycles of ifosfamide, etoposide and doxorubicin.

Outcomes are summarised in Table II. During follow-up, a relapse was identified in 14 (53.8%) patients initially operated on for localised disease. There were four (15.4%) local relapses and 10 (38.5%) metastatic relapses. The median time to relapse was 5.3 months (range=1.0-13.8 months). Two out of four patients who had a local relapse did not receive pre- or postoperative radiation therapy. All four patients with positive margins (R1 and R2 resection) experienced relapse (two local and two metastatic relapses).

The median relapse-free survival was 7.3 months [95% confidence interval (CI)=4.9-25.4 months]. At the last follow-up, 9 patients (28.1%) were alive without evidence of disease. The median OS for patients with localised disease was 12.8 months (95% CI=8.2-34.4 months) (Figure 1). Among the 14 patients with identified relapses, 13 died of their disease. One patient re-operated for local relapse was still alive with no evidence of disease at last follow-up.

Management of metastatic disease and outcome. Thirteen patients had metastatic disease at presentation. During the course of their management, two patients had a resection of their primary tumor, six received palliative radiation therapy and seven received palliative chemotherapy (see following section for details). Palliative chemotherapy was not given to the other Six patients because of either poor performance status or advanced age. The median OS of patients with initial metastatic disease was 7.1 months (95%CI=3.8-11.3 months) (Figure 1). At last follow-up, 10 (76.9%) patients had died of disease and three (23.0%) patients were alive with evidence of disease.

Response to palliative chemotherapy. A total of 14 (31.1%) patients received palliative chemotherapy (seven patients with initial localised disease and subsequent metastatic relapse and seven patients with initial metastatic disease) (Table III). The number of lines of chemotherapy ranged from 1 to 4 (eight patients treated with one line, four with two lines, one with three lines and one with four lines of chemotherapy). For first-line therapy, single-agent doxorubicin was the most common choice (seven patients). Multi-agent chemotherapy was given to three patients and consisted of vincristine, doxorubicin, cyclophosphamide alternating with carboplatin/etoposide, (vincristine, actinomycin D, cyclophosphamide (VAC) only and carboplatin, epirubicin, vincristine, actinomycin D, ifosfamide and etoposide. Doxorubicin-ifosfamide combination was given to two patients. One patient received carboplatin and paclitaxel because of an erroneous initial diagnosis of adenocarcinoma and another patient received doxorubicin plus palifosfamide or placebo in a clinical trial.

In the first line, clinical activity (partial response and stable disease) was seen in seven (50.0%) patients. Partial response was only seen in one patient treated with a VAC regimen. Stable disease was documented in two patients treated with doxorubicin, in one treated with doxorubicin-ifosfamide combination, in one with doxorubicin-palifosfamide combination and in two with multi-agent chemotherapy. A median of four cycles were administered in responders. The only documented durable response was reached with the VAC regimen (7.3 months at last follow-up). The median PFS was 2.3 months (range=1.2-7.3 months). No patient had documented clinical activity beyond first-line chemotherapy, all had progressive disease.

Discussion

Our case series detailing treatment modalities of pleomorphic RMS is the largest reported cohort to our knowledge (4, 7-9, 11, 13-16). Consistent with previous reports, pleomorphic RMS is a rare disease, mainly of the elderly, associated with an aggressive clinical course.

The genetic landscape of pleomorphic RMS is often characterised by a very complex karyotype and contrasts with the less complex karyotypes observed in alveolar RMS and in embryonal RMS (17, 18). Further supporting pleomorphic RMS as a distinct entity is its morphology, it being composed of markedly atypical spindle and polygonal cells, often with bizarre forms. In comparison, a relatively monotonous population of round and ovoid cells are found in alveolar RMS and ovoid to spindle cells are usually described in embryonal RMS. These unique characteristics of pleomorphic RMS may offer some explanations for its aggressive behaviour and its poor response to conventional chemotherapy.

For localised disease, wide surgical resection with pre- or postoperative radiation therapy remains the standard-of-care and can offer a possibility of cure in a minority of patients. However, despite adequate surgical resection, distant relapses were often documented during follow-up. The relatively small number of patients in our study limited the potential to identify prognostic variables, although positive margins are predictive for relapse.

The older age and poor performance status of this cohort precluded a majority of patients with advanced disease from receiving palliative chemotherapy. Chemotherapy regimens varied greatly and reflect the lack of consensus on a standardised approach to systemic treatment in pleomorphic RMS. In our series, there was only one confirmed partial response with a paediatric-type chemotherapy regimen, however, follow-up was short. This observation contrasts greatly with the known chemosensitivity of alveolar and embryonal RMS, and supports the concept of pleomorphic RMS being a distinct clinical entity with its own unique tumor biology. Although some response to paediatric-type chemotherapy is possible, no conclusions can be drawn because of the small number of treated patients. Furthermore, it is unlikely that this level of chemotherapy intensity can be tolerated in elderly patients, who represent the majority of patients with this disease.

Based on our experience, pleomorphic RMS should be regarded as refractory to standard chemotherapy routinely used in treating soft tissue sarcoma and therefore efforts must be made to better understand the underlying molecular features responsible for its tumourigenesis. Effective novel therapies are urgently needed and our case series provide a baseline for comparison for future studies.

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Received July 14, 2015
Revised September 6, 2015
Accepted September 22, 2015