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Diagnosis and treatment of lymph node metastases in pediatric rhabdomyosarcoma in the Netherlands
A retrospective analysis

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ABSTRACT

Background: In pediatric rhabdomyosarcoma (RMS), evaluation of lymph node involvement (N1) is an important staging aspect, but difficult to assess. The aim of our study was to evaluate the assessment of lymph node infiltration and impact on outcome in N1 RMS patients.
Methods: We identified 277 non-metastatic RMS patients diagnosed and treated between 1990 and 2008. Patients with recorded N1 disease were evaluated for their diagnostic procedures and outcome.
Results: In 13.7% N1 status was reported. In 19 of 34 N1 patients, lymph node biopsies were performed for histologically confirmation. Different treatment modalities were used to treat lymph node metastases. In total 23 of 31 patients received local treatment of the node (11/23 RT, 4/23 surgery, and 8/23 both). All patients received chemotherapy. Lymph node relapse occurred in 7 of 31 patients who were treated with one or two modalities. Only 1 (14%) of 8 patients treated with three modalities relapsed. In N0 patients 10 (4.2%) of 239 had a regional lymph node relapse, and 9 of 10 died.
Conclusion: Lymph node metastases are an essential part of staging. Node positivity contributes to relapse of disease. Nodal relapse is also associated with a high mortality rate. These data imply that nodal assessment needs to be optimal and standardized for improved staging.

Lymph node status is an important part of pre-treatment staging and directly impacts risk-based treatment strategies in rhabdomyosarcoma (RMS). Positive (tumor infiltrated) lymph node status is an independent poor prognostic factor for both event-free survival and overall survival especially in alveolar RMS but also in embryonal RMS [1,2].

Regional lymph node disease (N1) is present in 23% of all RMS patients, predominantly in primary tumor sites, including the perineum, retroperitoneum, extremity, bladder/prostate, parameningeal and paratesticular [1].

However, the diagnosis of lymph node metastases and effects of local treatment of lymph node metastases are not well studied. The assessment of lymph node involvement is usually based on physical or radiological examination, and confirmed by histological investigation [3]. Different surgical techniques are applied, such as fine needle aspiration cytology (FNAC), core biopsy, node picking or sentinel node biopsy [4–6]. In adult studies, biopsy of suspected lymph nodes has a sensitivity of 79.6% and a specificity of 98.3%. The sensitivity and specificity of histological versus cytological diagnosis are comparable ($p = 0.41$) [7]. In RMS, the correct diagnosis with FNAC can be difficult without clinical history and/or diagnosis of the primary tumor and is therefore not suitable for initial diagnosis [8]. This most advocated logarithm of clinical and radiological (imaging) assessment followed by surgical exploration may not detect the presence of tumor in radiologically unsuspected lymph nodes. We retrospectively evaluated this practice in a cohort of non-metastatic rhabdomyosarcoma with an aim on patients with N1 disease and nodal relapse.

1. Methods

1.1. Patient cohort

All rhabdomyosarcoma patients treated between 1990 and 2008 in four surgical departments of pediatric oncology centers in the

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Netherlands were included in the evaluation. Eligible patients included all non-metastatic RMS patients less than 18 years of age, with histologically confirmed RMS. The charts of these patients were reviewed retrospectively.

1.2. Diagnosis and treatment

Patients were treated according to the protocols of the International Society of Pediatric Oncology (SIOP) for Malignant Mesenchymal Tumors (MMT) used at the time of diagnosis. This included the protocols SIOP-MMT-89, 95, 98, EpSSG2005 [3,9]. According to protocols, lymph nodes were assessed using clinical evaluation, ultrasound, CT scan or MRI scan. The presence of nodal involvement was confirmed by lymph node biopsy (excision or core biopsy) or fine needle aspiration (FNAC) depending on the center of treatment. The EpSSG2005 protocol suggested a standard sentinel node biopsy, but this was not mandatory.

Treatment in these protocols was based on systemic chemotherapy with ifosfamide, vincristin and actinomycin-D (IVA). Local treatment was (delayed) resection of the remaining primary tumor load. Radiotherapy to the primary tumor was applied by external beam varying between 41.1 Gy (23 fractions) and 50.4 Gy (28 fractions) depending on histology and IRS stage. Radiotherapy to regional lymph nodes was only performed when there was clinical or pathological evidence of lymph node involvement. A radiation dose of 41.4 Gy (23 fractions) was given when there were no enlarged nodes after initial therapy. An additional boost of 9 Gy was applied when there was still evidence of tumor load in the lymph nodes after chemotherapy. A selected group of head and neck RMS were treated according to the AMORE protocol, a specific combined surgical and brachy-radiotherapy treatment protocol. [9].

1.3. Endpoints and statistics

In our study local failure was defined as relapse at the primary tumor site. Regional failure was defined as a relapse in a draining lymph node. Evidence of lymph node involvement beyond the regional lymph nodes was interpreted as distant metastasis.

In the distant failure group were all patients with distant metastases with or without local and/or regional failure.

We used SPSS 20 for our statistical calculations. All statistical tests were two sided and used a significance level of 5%.

The event-free survival (EFS) was calculated from the age of diagnosis to the time of the first event, which was defined as a relapse or death.

Overall survival (OS) was calculated from the age of diagnosis to the time of death.

A Cox proportional hazards regression analysis was performed with the following factors as predictor variables: patient age and sex, tumor size, histology and site, TNM and IRS staging, and EFS and OS as outcome variables. To evaluate lymph node relapse in relation to tumor site we used Fisher exact test.

2. Results

2.1. Patient cohort

We identified 331 RMS patients and 287 had localized (M0) RMS disease (Fig. 1). Ten patients were lost during follow-up and were excluded. The remaining 277 M0 patients included 172 males and 105 females with a median age at diagnosis of 59 months (range 0–214). As expected more than 80% of tumors had embryonal histology and were T1 tumors. The median follow-up of all surviving patients was 142 months (range 36–271). The 5-year event-free survival (EFS) rate of all patients was 61.4%. The 5-year overall survival (OS) was 77.6%. Only size was predictive for EFS and OS ($p = 0.008/0.034$). Four events occurred after 5 years of follow-up. Patient and clinical characteristics are listed in Table 1.

2.2. Failure patterns

The local failure rate was 71 (25.6%) of 277, 24.7% (59/239) in N0 patients, and 31.6% (12/38) in N1 patients. The regional failure rate was 6.5% (18/277) and 4.2% (10/239) in N0 patients and 21.1% (8/38) in N1 patients. Only 2.9% (8/277) developed distant metastases (all N0 patients).

Regional lymph node relapses occurred in N0 patients where the primary tumor was localized in the extremities (3/13), parameningeal (2/65), GU non-bladder/prostate (2/42), GU bladder/prostate (1/23), abdominal (1/22) and thorax (1/6). The mean time between end of therapy and lymph node relapse was 16 months (1–45). In all

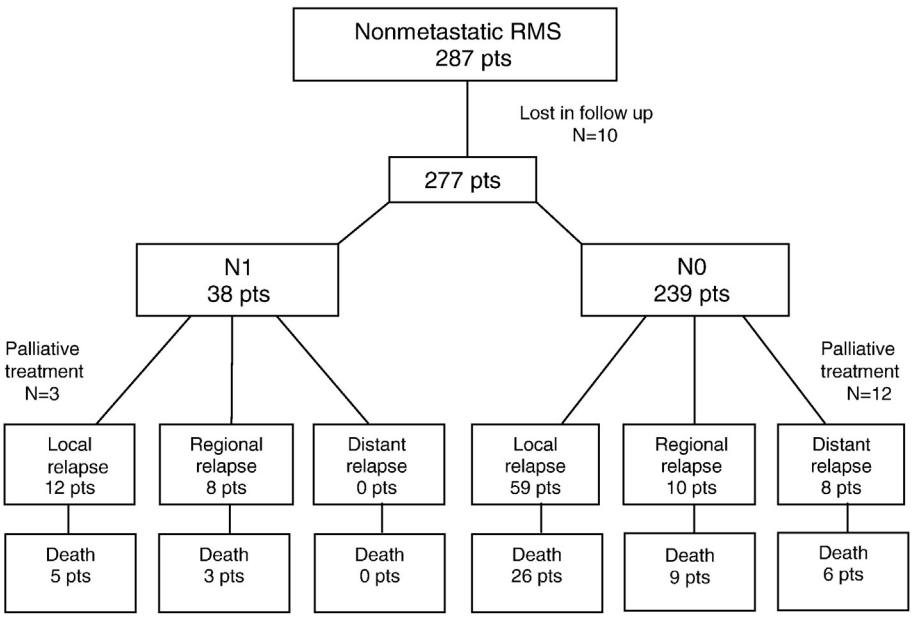

Fig. 1. Patient selection.