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Does aggressive local treatment have an impact on survival in children with metastatic rhabdomyosarcoma? ☆

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Abstract ***Purpose:*** Due to the extensive initial distant tumour spread in metastatic rhabdomyosarcoma, the importance of local treatment is sometimes underestimated. A retrospective study was conducted to identify the prognostic value of aggressive local treatment in paediatric metastatic rhabdomyosarcoma.
Patients: Patients with metastatic rhabdomyosarcoma aged 1–21 years treated in France from 1998 to 2011 according to European protocols MMT-4-89, 4-91, 98 and recent national guidelines were selected. Survival comparison were performed between patients with 'aggressive local treatment' (surgery and radiotherapy) and exclusive surgery or radiotherapy, after exclusion of patients with early progression. End-points were event-free and overall survival (OS).
Results: A total of 101 children, median age 9 years, with majority of primaries in unfavourable sites (73 patients, pts), T2 tumours (66 pts), alveolar subtypes (65 pts) and large tumours

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(>5 cm, 83 pts) received various chemotherapy regimens. On univariate and multivariate analyses, OS was better after 'aggressive local treatment' (49 pts; 44.3 ± 8%), than after exclusive surgery (10 pts; 18.8% ± 15.5%) or exclusive radiotherapy (29 pts; 16.1 ± 7.2%, $P < 0.006$). Moreover, OS was better in the case of surgery with complete resection (41.1 ± 10.2%) or microscopic residue (56.4 ± 14.9%) than macroscopic residue (20.0 ± 12.6%; $P < 0.03$).

Conclusions: In this large retrospective analysis, OS appeared to be better for patients receiving 'aggressive local treatment' even after adjustment for the initial patient and tumour characteristics. Isolated debulking surgery is associated with a very poor outcome and should be avoided. Aggressive local treatment in patients with rhabdomyosarcoma, even with metastasis, should be seriously considered.

1. Introduction

Rhabdomyosarcoma in children accounts for between 5% to 8% of all childhood cancers. It is the most common soft tissue sarcoma in childhood. About 10–20% of patients present metastases at diagnosis [1,2]. The treatment of metastatic rhabdomyosarcoma comprises a multidisciplinary approach with a combination of chemotherapy and adequate local treatment, surgery and/or radiotherapy. However, these patients have not benefited from the therapeutic progress achieved in localised rhabdomyosarcoma, as the 5-year overall survival (5Y-OS) remains between 10% to 35% according to various prognostic [1,2]. Most studies on metastatic rhabdomyosarcoma have evaluated the role of various chemotherapy regimens, focusing on the treatment and prevention of metastatic progression [3–7]. But the precise role of local therapy remains unknown in this situation. Despite indirect evidence, it is still unknown whether or not aggressive local treatment can improve survival of patients with metastatic rhabdomyosarcoma. The aim of this study was to analyse the impact of local treatment on survival in patients with metastatic rhabdomyosarcoma in order to determine whether aggressive local treatment can favourably impact on prognosis.

2. Material and methods

2.1. Patient population

This retrospective analysis of medical charts selected all patients diagnosed with metastatic rhabdomyosarcoma between 1998 and 2011 and treated in the seven large French paediatric centres: Paris, Villejuif, Lyon, Lille, Marseille and Nantes. Inclusion criteria were all patients aged 1–21 years with newly diagnosed metastatic rhabdomyosarcoma, treated according to or in international protocols including European intergroup (MMT 4-89, 4-91), SIOP-MMT 98 and national guidelines for metastatic rhabdomyosarcoma [2–5,7–9].

Unfavourable and favourable sites were defined according to a previous classification for metastatic rhabdomyosarcoma [2]. Unfavourable sites represent extremity and 'other' (thorax, abdomen, pelvis) sites and favourable sites, orbital, head and neck, non-parameningeal, parameningeal or genitourinary sites. Clinical staging was defined according to the SIOP-TNM system [10]. Postsurgical staging was defined by the SIOP TNM staging system, and is presented according to the Intergroup Rhabdomyosarcoma Staging (IRS) grouping system [11]. IRS group IV was defined as the presence of clinical or radiographic evidence of metastases at one or more sites distant from the primary tumour [11]. Metastatic sites in a patient were enumerated according to organ system involvement. Lymph node involvement was evaluated clinically or by imaging and confirmed when necessary by cytological or histological biopsy [12]. Involvement of lymph nodes beyond the primary lymphatic drainage area was staged as group IV disease. At diagnosis, all patients had radiographic assessments comprising chest computed tomography (CT), abdomen CT or ultrasound for lower limbs or abdominopelvic primaries, magnetic resonance imaging (MRI) or CT of the head for head and neck primary, systematic bone CT scan with bone marrow aspirations and biopsies, cerebral spinal fluid (CSF) cytology for parameningeal primaries and optional positron emission tomography-computed tomography (PET-CT). Histological examination of the tumour at diagnosis was performed for all patients and the subtype was classified according to the international classification [13]. As a centralised pathology review was already set up within each international collaborative protocol, diagnoses were not specifically reviewed for this analysis. Somatic tumour biology was not mandatory for this analysis, but was taken into account for diagnosis [13].

2.2. Treatment

Details on medical therapy have already been published: MMT 4-89 MMT4-91 MMT-98 trials and national RMS guidelines [2–5,7–9]. Local treatment, either radiotherapy and/or surgery, was performed, in order to achieve complete remission (CR) prior to starting vincristine-actinomycin D-cyclophosphamide (VAC). Overall, first- or second-look operation (SLO)