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Original Research

Endocrine disorders among long-term survivors of childhood head and neck rhabdomyosarcoma

S.C. Clement [a,b,*], R.A. Schoot [a], O. Slater [c], J.C. Chisholm [d], C. Abela [e], A.J.M. Balm [f,g], M.W. van den Brekel [f,g], W.B. Breunis [a], Y.C. Chang [h], R. Davila Fajardo [i], D. Dunaway [e], E. Gajdosova [j], M.N. Gaze [h], S. Gupta [l], B. Hartley [l], L.C.M. Kremer [a], M. van Lennep [a], G.A. Levitt [c], H.C. Mandeville [m], B.R. Pieters [i], P. Saeed [k], L.E. Smeele [f,g], S.D. Strackee [n], C.M. Ronckers [a], H.N. Caron [a], H.M. van Santen [b,1], J.H.M. Merks [a,1]

[a] *Department of Pediatric Oncology, Emma Children's Hospital Academic Medical Center, Amsterdam, The Netherlands*
[b] *Department of Pediatric Endocrinology, Wilhelmina Children's Hospital University Medical Center Utrecht, Utrecht, The Netherlands*
[c] *Department of Pediatric Oncology, Great Ormond Street Hospital for Children NHS Foundation Trust, London, United Kingdom*
[d] *Children and Young People's Department, Royal Marsden Hospital, Sutton, United Kingdom*
[e] *Craniofacial Unit, Great Ormond Street Hospital for Children NHS Foundation Trust, London, United Kingdom*
[f] *Department of Head and Neck Oncology and Surgery, The Netherlands Cancer Institute, Amsterdam, The Netherlands*
[g] *Department of Oral and Maxillofacial surgery, Academic Medical Center, Amsterdam, The Netherlands*
[h] *Department of Oncology, University College London Hospitals NHS Foundation Trust, London, United Kingdom*
[i] *Department of Radiation Oncology, Academic Medical Center, Amsterdam, The Netherlands*
[j] *Department of Ophthalmology, Great Ormond Street Hospital for Children NHS Foundation Trust, London, United Kingdom*
[k] *Orbital center, Department of Ophthalmology, Academic Medical Center, Amsterdam, The Netherlands*
[l] *Department of Otorhinolaryngology, Great Ormond Street Hospital for Children NHS Foundation Trust, London, United Kingdom*
[m] *Department of Radiotherapy, The Royal Marsden NHS Foundation Trust, Sutton, United Kingdom*
[n] *Department of Plastic, Reconstructive and Hand Surgery, Academic Medical Center, Amsterdam, The Netherlands*

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* *Corresponding author*: Department of Pediatric Oncology, Emma Children's Hospital/Academic Medical Center, PO Box 22660, 1100 DD Amsterdam, The Netherlands. Tel.: +31 20 5668974; fax: +31 20 5669733.
E-mail address: s.c.clement@amc.uva.nl (S.C. Clement).
[1] Both authors contributed equally to this work.

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Abstract ***Purpose:*** Head and neck rhabdomyosarcoma (HNRMS) survivors are at increased risk of developing pituitary dysfunction as an adverse event of radiotherapy. Our aim was to investigate the frequency and risk factors for pituitary dysfunction in these survivors. Secondly, we aimed to compare the prevalence of pituitary dysfunction between survivors treated with external beam radiation therapy (EBRT) and survivors treated with the ablative surgery, moulage technique after loading brachytherapy, and surgical reconstruction (AMORE) procedure.

Methods: Eighty HNRMS survivors treated in London (EBRT based) and Amsterdam (AMORE based: AMORE if feasible, otherwise EBRT) in the period 1990–2010 and alive ≥2 years post-treatment were evaluated. Survivors were evaluated in multidisciplinary late-effects clinics, with measurement of linear growth, determination of thyroid function, and growth hormone parameters. Additional data, such as baseline characteristics, anthropometrics, pubertal stage, and the results of additional laboratory investigations, were retrieved from patient charts.

Results: Pituitary dysfunction was diagnosed in 24 in 80 (30%) survivors, after a median follow-up time of 11 years. Median time to develop pituitary dysfunction after HNRMS diagnosis was 3.0 years. Risk factors were EBRT-based therapy (odds ratio [OR] 2.06; 95% confidence interval [CI] 1.79–2.46), parameningeal tumour site (OR 1.83; 95% CI 1.60–2.17) and embryonal RMS histology (OR 1.49; 95% CI 1.19–1.90).

Conclusions: Radiotherapy used for the treatment of HNRMS confers a significant risk of the development of pituitary dysfunction. AMORE-based treatment in children with HNRMS resulted in less pituitary dysfunction than treatment with conventional EBRT. Our findings underscore the importance of routine early endocrine follow-up in this specific population.

1. Introduction

Rhabdomyosarcoma (RMS) is a highly malignant mesenchymal tumour accounting for 3–5% of all malignancies diagnosed in children [1]. Approximately 40% of RMS arises in the head and neck region (HNRMS) [2]. For the majority of children diagnosed with HNRMS, radiotherapy (RT) and chemotherapy (CT) are essential for effective local control and survival. Survival in children with HNRMS has improved substantially over recent decades with a current expected 5-year overall survival rate of 79–97%, depending on risk category [3–5]. Survivors of HNRMS are at increased risk of late treatment-related side-effects, including both medical and psychosocial sequelae [6–8]. Endocrine disorders are prominent among long-term survivors, with rates as high as 44% [9]. Incidental irradiation of the hypothalamic–pituitary region is often inevitable because of the close anatomical relationship between it and the clinical target volume for RT. This may result in growth hormone deficiency (GHD), thyroid-stimulating hormone (TSH) deficiency, adrenocorticotropic hormone (ACTH) deficiency, and gonadotropin deficiency, and sometimes precocious puberty may be seen [7,10–12]. Radiation therapy to the field including the thyroid gland may result in thyroid dysfunction, nodules or cancer [7]. CT regimens for patients with HNRMS often contain alkylating agents [3,4,13], which may induce gonadal damage in both sexes [14,15].

The aim of this study was to evaluate the frequency and nature of endocrine abnormalities, especially pituitary dysfunction, in childhood HNRMS survivors and to identify possible risk factors for an adverse endocrine outcome among children treated in three large academic centres (Great Ormond Street Hospital [GOSH] London, Royal Marsden Hospital [RMH] Sutton, and the Emma Children's Hospital-Academic Medical Center [EKZ-AMC], Amsterdam). Since the local treatment approach of HNRMS differs between London/Sutton and Amsterdam, a second aim of this study was to compare the prevalence of pituitary dysfunction between survivors treated on protocols including external beam radiation therapy (EBRT) and patients treated in a center choosing, where possible, to use the AMORE procedure [13,16].

2. Methods

2.1. Patients

The study included all patients who were 1) diagnosed and treated for HNRMS in GOSH, RMH or the EKZ-AMC; 2) newly diagnosed from January 1990 to December 2010; 3) aged <18 years at time of diagnosis of a HNRMS; and 4) ≥2 years from end of treatment at the time of follow-up. A total of 80 survivors fulfilled these criteria. Written informed consent was obtained from all survivors (>12 years) and their guardians who were treated in GOSH/