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Psychosocial well-being of long-term survivors of pediatric head–neck rhabdomyosarcoma

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Abstract

Background: Head and neck rhabdomyosarcoma (HNRMS) survivors are at risk to develop adverse events (AEs). The impact of these AEs on psychosocial well-being is unclear. We aimed to assess psychosocial well-being of HNRMS survivors and examine whether psychosocial outcomes were associated with burden of therapy.

Procedure: Sixty-five HNRMS survivors (median follow-up: 11.5 years), treated in the Netherlands and the United Kingdom between 1990 and 2010 and alive ≥2 years after treatment visited the outpatient multidisciplinary follow-up clinic once, in which AEs were scored based on a

Abbreviations: AMORE treatment, Ablative surgery, MOuld technique after loading brachytherapy, and surgical REconstruction; CTC AE, Common Terminology Criteria for Adverse Events; EKZ-AMC, Emma Children's Hospital-Academic Medical Centre; GOSH, Great Ormond Street Hospital; HNRMS, head–neck rhabdomyosarcoma; HRQoL, health-related quality of life; NL, The Netherlands; PedsQL, Pediatric Quality of Life Inventory; RMH, The Royal Marsden Hospital; SWA, Satisfaction with appearances; UK, The United Kingdom; YQOL-FD, Youth Quality of Life Instrument—Facial Differences Module

predefined list according to the Common Terminology Criteria for Adverse Events. Survivors were asked to complete questionnaires on health-related quality of life (HRQoL; PedsQL and YQOL-FD), self-perception (KIDSCREEN), and satisfaction with appearances (SWA). HRQoL and self-perception scores were compared with reference values, and the correlation between physician-assessed AEs and psychosocial well-being was assessed.

Results: HNRMS survivors showed significantly lower scores on PedsQL school/work domain ($P \leq 0.01$, $P = 0.02$, respectively), YQOL-FD domains negative self-image and positive consequences ($P \leq 0.01$, $P = 0.04$, respectively) compared with norm data; scores on negative consequences domain were significantly higher ($P = 0.03$). Over 50% of survivors negatively rated their appearances on three or more items. Burden of AEs was not associated with generic HRQoL and self-perception scores, but was associated with disease-specific QoL (YQOL-FD).

Conclusion: In general, HRQoL in HNRMS survivors was comparable to reference groups; however, survivors did report disease-specific consequences. We therefore recommend including specific questionnaires related to difficulties with facial appearance in a systematic monitoring program to determine the necessity for tailored care.

KEYWORDS

brachytherapy, Head and neck, pediatric oncology, psychosocial well-being, quality of life, radiotherapy, rhabdomyosarcoma

1 | INTRODUCTION

Pediatric rhabdomyosarcoma (RMS) accounts for 3% to 5% of all pediatric malignancies, and 40% of the cases arise in the head and neck area (HNRMS).[1] Overall survival for patients with localized RMS has increased to around 80% nowadays,[2,3] and the treatment for HNRMS usually consists of chemotherapy followed by local therapy. Microscopically free surgical margins are often difficult to achieve in the head and neck area; therefore, external beam radiotherapy is often the therapy of choice.

RMS generally occurs in young children, and radiotherapy at young age leads to abnormal growth and function of musculoskeletal tissues; therefore, many HNRMS survivors suffer from facial disfigurements (incidence rate, 35–77%).[4–6] Furthermore, other adverse events, such as growth hormone deficiency and cataract, are frequently reported.[4–7] The impact of these adverse events on psychosocial well-being is unclear. Multiple studies showed that, in general, health-related quality of life (HRQoL) in survivors of childhood cancer is comparable with normative values of healthy individuals; however, specific subgroups are at risk for impaired psychosocial well-being.[8–11] Identifying these subgroups at risk is important to develop adequate interventions to improve psychosocial well-being. Kinahan et al showed that in childhood cancer survivors, facial disfigurement negatively affected general health, mental health, and emotional well-being.[12] Previous studies also showed that HRQoL in children with facial deformities, such as cleft lip patients, is impaired.[13,14]

Therefore, psychosocial well-being of HNRMS survivors needs proper attention. Schoot et al previously showed that HRQoL among HNRMS survivors was comparable with normative values.[6] However, this study only described rather general HRQoL measurements. A more comprehensive understanding of the psychosocial well-being of HNRMS survivors is lacking.

In this study, psychosocial well-being was assessed by measuring HRQoL, self-perception, and satisfaction with appearances, in HNRMS survivors treated in three large pediatric oncology centers (Great Ormond Street Hospital [GOSH], London, The Royal Marsden Hospital [RMH], Sutton and Emma Children's Hospital-Academic Medical Centre [EKZ-AMC], Amsterdam). Furthermore, we examined whether physician-assessed adverse events were associated with psychosocial well-being.

2 | METHODS

2.1 | HNRMS survivors

All patients (aged 0–18 years) treated for HNRMS in GOSH, RMH, or EKZ-AMC, between 1990 and 2010 and alive ≥2 years after end of therapy were invited to the outpatient multidisciplinary clinic ($n = 113$).

In this cross-sectional study, all survivors were evaluated once at the outpatient multidisciplinary clinics to evaluate the occurrence of adverse events.[6] Survivors ≥ 8 years of age were asked to complete questionnaires regarding their psychosocial well-being. Written informed consent was obtained from all survivors (>12 years) and their guardians treated in GOSH/RMH. For Amsterdam, the local institutional review board decided that the Act on Medical Research Involving Human Subjects did not apply, because data were collected during a regular follow-up clinic.

2.2 | Rhabdomyosarcoma treatment

Treatment details for this cohort have been described previously[6]; in general, all patients received multidrug chemotherapy and decisions on local therapy were made after two or three courses of

chemotherapy. If local therapy was indicated, the patients from the United Kingdom (UK) received external beam radiotherapy and the EKZ-AMC patients received AMORE (Ablative surgery, MOuld technique after loading brachytherapy, and surgical REconstruction) treatment if feasible and otherwise external beam radiotherapy.[6,7,15–17] AMORE treatment was considered feasible if a macroscopic radical resection and adequate mould placement seemed possible.

2.3 | Instruments

HNRMS survivors were asked to complete the *Pediatric Quality of Life Inventory (PedsQL) Generic Core Scales*, self-perception domain of the *KIDSCREEN*, *Youth Quality of Life Instrument—Facial Differences Module (YQOL-FD)*, and the *Satisfaction with appearances (SWA)* questionnaire. The questionnaires are described in detail below. All HNRMS survivors were asked to complete respective questionnaires, unless explicit age groups are specified below.

2.4 | PedsQL

This questionnaire consists of 23 items assessing HRQoL on four subscales: physical functioning, emotional functioning, social functioning, and school/work functioning.[18] Each item states a problem, for example "I have trouble keeping up with school/work" or "I have trouble sleeping." Each item was scored on a five-point Likert scale. Total score (all subscales) and psychosocial health (emotional, social, and school/work) were calculated by summing up scores of the corresponding subscales. Scores ranged 0 to 100, with higher scores indicating better HRQoL. We used weighted reference data, adjusted for sex, for Dutch (NL) survivors and for survivors < 18 years from the United Kingdom.[19–21] We used NL ≥18 years sex-adjusted reference data for UK survivors ≥18 years because no UK reference data were available for adults. We considered this legitimate because reference data for UK and Dutch children aged 11 to 18 years were comparable, and we assumed that reference data in ≥18 years old would also be comparable. Cronbach's alphas for both NL and UK survivors were moderate to good (α: 0.73–0.96).

3 | KIDSCREEN

The KIDSCREEN self-perception domain consists of five items, for example, "have you been happy with the way you are?" Each item was scored on a five-point Likert scale. Raw domain scores were transformed into T-values, with a mean of 50 and standard deviation of 10 in the reference population. Higher scores indicate better HRQoL. We used age- and sex-adjusted country-specific reference values.[22] Cronbach's alphas for both NL and UK survivors were moderate to good (α: 0.77–0.88).

3.1 | YQOL-FD

The YQOL-FD questionnaire, completed by survivors aged 11 to 18 years, consisted of 30 items assessing quality of life across five domains: stigma, negative self-image, positive consequences, negative consequences, and coping. The instrument is focused on the impact of living with a facial difference, and each item addresses a specific concern, for example, "people stare at me because of how my face looks." Domain scores ranged from 0 to 100. Higher scores on the domains coping and positive consequences indicate *higher* quality of life. Higher scores on the domains negative consequences, negative self-image, and stigma indicate *lower* quality of life. No reference data were available for the YQOL-FD; one study reported data for 307 patients with congenital or acquired facial deformities, in which patients were grouped as mild, moderate, or marked based on self-rated facial deformities.[23] The scores obtained from patients with mild facial deformities ($n = 250$) served as norm data for the functioning of HNRMS survivors. Cronbach's alphas for negative self-image, positive-consequences, negative-consequences, and stigma domain were moderate to good (α: 0.66–0.96). Cronbach's alpha for the coping domain was 0.03 for NL survivors, and we decided to exclude this domain from further analyses.

3.2 | SWA

The SWA, developed by the Psychology Special Interest Group of the Craniofacial Society of Great Britain and Ireland, consists of 18 items (score range, 0–10), with higher scores indicating higher satisfaction with appearance. Each item assesses patients' satisfaction with a specific aspect of the way they look and function in society, for example, "How do you feel about the way you look?" We considered item scores less than 6 as negative. Two items, wearing a hearing aid and braces, were not used in the present study, because the number of survivors with hearing aids or braces was limited. A total mean score was calculated; missing data were imputed by mean scores on the individual item (max two items were imputed). So far, no reference data were published for the SWA. Cronbach's alphas for both NL and UK survivors were good (α: 0.85–0.91).

3.3 | CTC AE

Adverse events were graded according to the Common Terminology Criteria for Adverse Events (CTCAEv4.0, available at http://evs.nci.nih.gov/ftp1/CTCAE/About.html). We used a selection of predefined adverse events as reported previously.[6] For each survivor, we assessed the total number of adverse events, any grade 3/4 adverse event, and total burden of adverse events by using a burden score adapted from Geenen et al.[24]

3.4 | Statistical analyses

Data were analyzed with SPSS version 23.0. Differences between participants and nonparticipants with respect to sex, tumor site and side, histology, treatment protocol, and radiotherapy were analyzed by Fisher exact tests, and difference in age at diagnosis was assessed by the Mann–Whitney test.

One-sample *t* tests were conducted to analyze whether HNRMS survivors' scores on PedsQL, KIDSCREEN, and YQOL-FD differed from reference values.

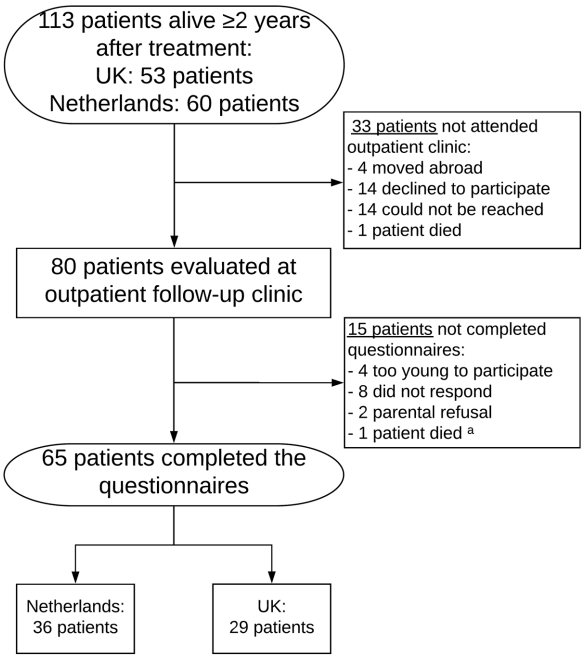

FIGURE 1 Flow diagram: long-term survivors of HNRMS. [a]Patient developed recurrence after follow-up evaluation and did not fill out questionnaire

The SWA was analyzed descriptively. Mean, standard deviation, and the proportion of negative scores were calculated for each individual item and for the mean item score.

If appropriate, effect sizes were calculated by dividing differences in mean scores between the HNRMS survivors and reference values by the standard deviation of the reference group. Effect sizes of 0.2 were considered small, 0.5 medium, and 0.8 large.[25]

Pearson product–moment correlation coefficients were calculated to investigate whether adverse events (defined with CTC AE) were associated with psychosocial outcomes. We considered correlation coefficients of 0.1 as small, 0.3 as medium, and 0.5 as large.[25]

4 | RESULTS

4.1 | Survivors

In total, 80 survivors attended the follow-up clinic; 65 individuals (81.3%) also completed the questionnaires (Figure 1). The 15 nonparticipating survivors did not differ significantly from participating survivors with respect to demographic and medical variables (Supporting Information Table S1). Median age at time of questionnaire completion was 19.6 years (range, 8.6–35.7 years) for NL survivors and 16.0 years (range, 8.5–27.9 years) for UK survivors. Survivors' characteristics are further described in Table 1.

4.2 | Health-related quality of life (PedsQL)

In general, subdomain-specific HRQoL of HNRMS survivors did not differ significantly from weighted reference values, except for the school/work domain (Table 2). HRQoL in the school/work domain was significantly lower in both NL and UK survivors compared with the weighted reference for all ages. This was also seen in the NL survivors ≥18 years and in the group of UK survivors 8 to 17 years, but not in other substrata. Effect sizes were moderate to large ($d = 0.58$ to $d = 0.88$). UK survivors also showed significantly lower HRQoL in the psychosocial health domain compared with the weighted reference, with moderate effect size ($d = 0.55$).

TABLE 1 Characteristics ($n = 65$) of HNRMS survivors

		Netherlands $N = 36$	United Kingdom $N = 29$
Age at diagnosis (years)	Median (range)	6.4 (0.5–13.4)	5.1 (1.0–11.9)
Attained age (years)	Median (range)	19.6 (8.6–35.7)	16.0 (8.5–27.9)
Follow-up (years)	Median (IQR)	11.5 (8.5–18.0)	10.9 (6.0–18.5)
Sex, *n* (%)	Male	20 (56%)	22 (76%)
	Female	16 (44%)	7 (24%)
Histology, *n* (%)	ERMS	32 (89%)	21 (72%)
	ARMS	4 (11%)	4 (14%)
	RMS NOS		4 (14%)
Primary site, *n* (%)	PM	15 (42%)	15 (52%)
	ORB	13 (36%)	9 (31%)
	ORB&PM	2 (6%)	2 (7%)
	HNNPM	6 (17%)	3 (10%)
Side	Left	18 (50%)	10 (34%)
	Right	13 (36%)	17 (59%)
	Midline	5 (14%)	2 (7%)
Treatment protocol	MMT 89	11 (31%)	9 (31%)
	MMT 95	19 (53%)	13 (45%)
	MMT 98	0	1 (3%)
	RMS 2005	4 (11%)	6 (21%)
	Other	2 (6%)	0
Initial local Tx	No RT	2 (6%)	2 (7%)
	AMORE	22 (61%)	0
	EBRT	12 (33%)	27 (93%)
Number of RT Tx	0	2 (6%)	2 (7%)
	1	27 (75%)	27 (93%)
	2	5 (14%)	0
	3	2 (6%)	0

Abbreviations: AMORE, Ablative surgery MOuld brachytherapy and REconstruction; ARMS, alveolar rhabdomyosarcoma; EBRT, external beam radiotherapy; ERMS, embryonal rhabdomyosarcoma; HNNPM, Head and neck nonparameningeal; IQR, interquartile range; MMT, consecutive study of International Society of Paediatric Oncology Malignant Mesenchymal Tumour group; ORB&PM, orbital with parameningeal extension; ORB, orbital; PM, parameningeal; RMS 2005, European *paediatric* Soft-Tissue Sarcoma group RMS 2005 protocol; RMS NOS, rhabdomyosarcoma not otherwise specified; RT, radiotherapy; Tx, treatment.

TABLE 2 HRQOL (PedsQL) of HNRMS survivors

	Netherlands			NL reference	NL cohort vs reference		United Kingdom			UK reference	UK cohort vs reference	
	n	Mean	SD	Mean[a]	Effect size	*P*[b]	N	Mean	SD	Mean	Effect size	*P*[b]
8–17 years	16						17					
Total score		80.3	13.5	82.15	−0.21	0.60		73.1	21.9	82.65	−0.73	0.09
Physical		88.3	13.7	85.39	0.31	0.41		76.2	28.8	86.08[c]	−0.70	0.18
Emotional		70.3	17.8	76.78	−0.46	0.17		74.5	22.4	78.10	−0.20	0.52
Social		87.4	14.0	87.65	−0.02	0.95		77.4	20.4	86.85[c]	−0.56	0.07
School/work		70.6	19.4	76.87	−0.49	0.22		62.4	23.7	77.29[c]	−0.88	0.02
Psychosocial health		76.1	15.4	80.42	−0.42	0.27		71.4	20.0	80.32	−0.64	0.08
18+ years	20						11					
Total score		82.3	12.1	84.81	−0.20	0.36		82.5	13.5	85.73[d]	−0.25	0.45
Physical		86.6	17.3	88.28	−0.11	0.66		88.6	12.7	89.49[d]	−0.06	0.83
Emotional		79.5	15.0	78.69	0.05	0.81		71.8	18.6	80.18[d]	−0.48	0.17
Social		88.0	13.4	87.6	0.03	0.90		87.3	11.5	88.09[d]	−0.06	0.82
School/work		72.5	15.0	82.57	−0.58	0.007		78.9	19.3	82.87[d]	−0.26	0.55
Psychosocial health		80.0	11.2	82.95	−0.22	0.25		78.9	15.2	83.71[d]	−0.35	0.32
All ages	36						28					
Total score		81.4	12.6	83.63	−0.20	0.30		76.8	19.4	83.86	−0.54	0.06
Physical		87.3	15.6	86.86	0.04	0.86		81.1	12.7	87.42[c]	−0.45	0.18
Emotional		75.4	16.7	77.70	−0.14	0.42		73.4	18.6	78.92	−0.31	0.17
Social		87.7	13.5	87.48	0.02	0.91		81.3	11.5	87.34[c]	−0.37	0.08
School/work		71.7	16.9	80.27	−0.58	0.004		68.1	19.3	79.48[c]	−0.70	0.02
Psychosocial health		78.2	13.2	81.83	−0.29	0.11		74.3	15.2	81.97	−0.55	0.04

Pediatric Quality of Life Inventory (PedsQL) scale scores range 0–100, with higher scores indicating better health-related quality of life (HRQoL).
[a]Country-specific weighted reference scores, adjusted for sex and age.
[b]Based on one-sample *t* test.
[c]Not adjusted for sex because there was no sex effect in the reference group.
[d]No country-specific reference scores available; NL norm used for UK patients ≥18 years, adjusted for age and sex distribution.

4.3 | Self-perception (KIDSCREEN)

Self-perception of HNRMS survivors did not differ from the weighted reference values (Supporting Information Table S2).

4.4 | YQOL-FD

HNRMS survivors scored significantly lower on negative self-image and positive consequences compared with patients with mild facial deformities described by Patrick et al.[23] HNRMS survivors scored significantly higher on negative consequences (Table 3). Effect sizes ranged from moderate on positive consequences ($d = 0.53$), to large ($d = 0.91$) on negative self-image.

4.5 | Satisfaction with appearances

Over 50% of NL and UK survivors negatively rated their appearances on three or more items. Over one-third of survivors in the NL and the UK scored negative on the items "noticeable to others" and/or "get on with others" (Table 4). Furthermore, over one-third of the UK survivors scored negative on the items "good looking," "overall appearance," and "teeth," whereas one-third of the NL survivors scored negative on the item "face."

4.6 | Association between adverse events and psychosocial well-being

Adverse events were previously described by Schoot et al.[6] In summary, over half of NL and UK survivors experienced any grade 3/4 adverse event and more than five adverse events of any grade. This was also reflected in high burden scores (Supporting Information Figures S1 and S2). Most common adverse events were musculoskeletal deformities of the face in NL and UK survivors, followed by fibrosis and scarring.

There were small negative correlations for CTC AE scores with HRQoL and self-perception (mainly not statistically significant). CTC AE scores (reflected in burden score and any grade 3/4 event) and YQOL-FD domains (except for positive consequences domain) showed medium to large, positive correlations (Table 5). Only small, negative (not significant) correlations between SWA scores and CTC AE scores were observed.

TABLE 3 Quality-of-life facial differences (YQOL-FD) of HNRMS survivors

	HNRMS				Mild facial deformities[a]		Survivors vs mild facial differences	
	n[b]	Mean	SD	95% CI	Mean	SD	*P*[c]	Effect size
Negative self-image								
NL	12	17.1	15.8	7.1–27.1				
UK	11	12	17.4	0.3–23.6				
Total	23	14.6	16.4	7.5–21.7	37.3	25.7	<0.001	−0.91
Positive consequences								
NL	12	55.2	25.7	38.8–71.5				
UK	11	38.5	33.1	16.3–60.7				
Total	23	47.2	30	34.2–60.2	60.7	24.9	0.042	−0.53
Negative consequences								
NL	12	42.7	27.1	25.4–59.9				
UK	11	23.5	31.4	2.3–44.6				
Total	23	33.5	30.2	20.4–46.6	18.4	20.1	0.026	0.72
Stigma								
NL	12	20.6	22.8	6.1–35.1				
UK	11	19.1	29.5	0.0–38.9				
Total	23	19.9	25.6	8.8–31.0	27.3	23.5	0.179	−0.31

YQOL-FD scale scores range 0–100, with higher scores on domain negative consequences, negative self-image, and stigma indicate lower quality of life, whereas higher scores on domain positive consequences indicate higher quality of life.
[a]Values obtained from patient group reported in Patrick et al (23) with self-rated mild facial deformities.
[b]Only patients 11–17 years.
[c]*P* value based on one-sample *t* test.

TABLE 4 SWA of HNRMS survivors

	Netherlands				United Kingdom			
	n	Mean	SD	Negative[a]	*n*	Mean	SD	Negative[a]
Mean score (16 items)	35	7.44	1.35	14%	29	7.48	1.61	24%
How do you feel about the way you look?								
How you face looks?	36	6.81	2.39	33%	29	7.34	2.50	28%
The whole of you appearance?	36	7.44	1.75	14%	29	7.41	2.38	35%
Side view/profile?	36	6.94	2.39	22%	28	7.14	2.55	29%
How good looking do you think you are?	36	6.75	2.35	25%	29	6.17	2.45	45%
How do you feel about these parts of your face?								
Nose	36	7.69	2.32	14%	29	8.00	2.17	17%
Lips	36	7.97	2.01	11%	29	8.10	2.32	10%
Chin	36	7.61	2.62	17%	29	8.17	1.97	14%
Teeth	36	7.03	2.24	22%	29	6.21	2.88	41%
Cheeks	36	7.83	1.89	14%	29	7.69	2.47	24%
Hair	36	8.17	2.01	11%	29	8.83	1.65	3%
Ears	36	8.50	1.52	8%	28	8.04	2.65	18%
Eyes	35	7.74	2.31	19%	29	7.97	2.57	24%
How happy are you with your speech?	36	7.72	2.24	17%	29	7.41	2.68	21%
How happy are you with your hearing?	36	8.22	2.21	14%	29	8.14	2.17	10%
Overall how noticeable do you feel your face is to other people?	36	5.94	2.96	44%	25	6.56	3.42	36%
Does the way you look make a difference to how you get on with other people?	36	6.81	2.03	36%	25	6.48	2.87	52%

SWA scale scores range 0–10.
[a]Scores of ≤5 were considered negative.

TABLE 5 Correlations of physician-assessed adverse effects (CTC AE outcome measures) with psychosocial outcomes

	≥5 AEs		Any grade 3/4		Burden score[a]	
	r^b	*P*	r^b	*P*	r^b	*P*
FD-negative self-image[c]	0.073	0.740	**0.553**	**0.006**	**0.531**	**0.009**
FD-positive consequences[c]	−0.302	0.162	0.403	0.057	0.300	0.165
FD-negative consequences[c]	0.007	0.973	**0.463**	**0.026**	**0.434**	**0.038**
FD-stigma[c]	0.066	0.764	**0.476**	**0.022**	**0.465**	**0.025**
SWA (mean score)	−0.127	0.318	−0.223	0.076	−0.231	0.066
PedsQL total	−0.155	0.222	−0.156	0.218	**−0.270**	**0.031**
PedsQL physical	−0.227	0.071	−0.182	0.151	**−0.277**	**0.027**
PedsQL emotional	−0.034	0.792	−0.009	0.941	−0.193	0.126
PedsQL social	−0.209	0.098	−0.179	0.157	**−0.284**	**0.023**
PedsQL school/work	−0.015	0.906	−0.147	0.254	−0.149	0.247
PedsQL psychosocial	−0.090	0.482	−0.122	0.337	−0.233	0.064
Kidscreen self-perception	0.060	0.646	0.016	0.903	0.083	0.520

In bold *P* value < 0.05.

[a]Burden score adapted from Geenen et al, combining number and severity of AE (24).

[b]Pearson correlation coefficient.

[c]YQOL-FD domains only for patients 11–17 years.

Abbreviations: AE, adverse effects; CTC, Common Terminology Criteria; FD, subscale of Youth Quality of Life Instrument–Facial Differences Module; HRQOL, health-related quality of life; PedsQL, Pediatric Quality of Life Inventory; SWA, satisfaction with appearance.

5 | DISCUSSION

In this cross-sectional study, we assessed psychosocial well-being specifically in a cohort of HNRMS survivors. These survivors were evaluated by a standardized protocol at a multidisciplinary outpatient clinic with a median follow-up of >10 years. This study, therefore, provides important insights into the psychosocial well-being of long-term HNRMS survivors and its association with adverse events.

In general, HRQoL and self-perception in HNRMS survivors was comparable to reference groups despite the high prevalence of (musculoskeletal) adverse events. However, survivors did report disease-specific consequences, which emphasize the need for systematic monitoring of psychosocial well-being.

Other studies in childhood cancer survivors (mainly tumors other than HNRMS) also found HRQoL to be comparable to reference values except for specific subgroups such as central nervous system tumor survivors, bone tumor survivors, and survivors who had cranial radiotherapy.[8–11,26,27]

In our cohort, HNRMS survivors showed impaired scores on school/work functioning, which was not shown in previous studies in other groups of childhood cancer survivors, except for survivors of central nervous system tumors.[28–31] We speculated that this finding may be related to specific adverse events experienced by these HNRMS survivors. Over 40% of the survivors had hearing loss, and many survivors suffered from eye conditions potentially causing difficulties to keep up at school/work. However, these conditions were not significantly correlated with school/work domain scores. The scores on school/work functioning could also be impaired because of radiotherapy treatment. Almost all included patients received radiotherapy (61/65 patients) and radiotherapy fields potentially involved parts of the brain. Although this effect might be less in patients treated according to the AMORE principle, this could not be assessed because data on radiotherapy fields were not available.

The survivors also reported difficulties in more disease-specific domains. Musculoskeletal deformities were noticed in 63% of the patients and over one-third of all survivors considered their facial deformities very noticeable to other people and felt that their facial deformities negatively affected the way they get on with others. This was also reflected in the impact of facial differences on quality of life; HNRMS survivors experienced more negative consequences and fewer positive consequences due to their facial deformities, compared with a group of patients with mild facial deformities. Although the number of patients with musculoskeletal deformity was comparable between patients from the United Kingdom and the Netherlands, this did not reflect the severity of adverse events in both cohorts. Schoot et al previously showed that the severity of facial asymmetry (by clinical assessment) was larger in the UK survivors, compared with NL survivors.[32] Negative self-image, negative consequences, and stigma appeared to be associated with the severity of adverse events and the positive consequences appeared not to be associated with severity of adverse events. This result is in line with the study of Patrick et al, who found no relationship between severity of facial deformities and experienced positive consequences, whereas patients with more severe deformities reported significantly higher scores on negative consequences, negative self-image, and stigma.[23]

We observed important discrepancies in strength of correlation between the psychosocial outcomes and physician-assessed adverse events. Burden of adverse events showed only weak correlations with generic HRQoL and self-perception, whereas burden scores showed moderate/large correlation with experienced negative self-image, negative consequences, and stigma, underlining the necessity to use

disease-appropriate instruments to monitor psychosocial well-being in HNRMS survivors.

There are several limitations to this study. First, we have used disease-related questionnaires (YQOL-FD and SWA) based on the high incidence of facial deformities in this group of HNRMS survivors which were not previously used in childhood cancer survivors. Its applicability as well as our findings should therefore be confirmed in future studies. As for the YQOL-FD questionnaire, we have excluded the coping domain from our analyses because of low Cronbach's alpha. We recommend paying special attention to its reliability in future studies.

Second, this study included survivors treated over a period of 20 years in which treatment protocols have changed significantly and local treatment for patients in this cohort were different between countries. In a previous study, we showed that the local treatment strategy in the EKZ-AMC (i.e., AMORE treatment if feasible) resulted in fewer adverse events compared with standard external beam radiotherapy.[6] Because country-specific reference values were often not comparable or not available, we considered a comparison of psychosocial well-being between patients treated in EKZ-AMC with patients treated in the United Kingdom inappropriate.

Finally, although we have included survivors treated over a long period, total numbers of survivors in our analyses were limited, further complicated by the different age groups and related age-specific questionnaires. Nevertheless, we believe that this study offers important insights as this is the first study assessing psychosocial well-being in HNRMS survivors in depth.

In this study, we did not pay special attention to bullying. However, social interactions are strongly affected by facial appearances[33] and previous studies have shown that children (other than HNRMS survivors) with craniofacial conditions are at higher risk of being bullied compared with healthy peers.[34]

Based on the reported incidences and severity of adverse events in these long-term HNRMS survivors and reported dissatisfaction with appearances and HRQoL, we believe that monitoring of psychosocial well-being of HNRMS survivors should play an important part in standard aftercare. Merely administering generic HRQoL questionnaires is not enough to adequately measure whether long-term HNRMS survivors encounter problems in everyday life, which was also shown in adult head and neck cancer survivors.[35,36] We therefore recommend including disease-appropriate questionnaires in a systematic monitoring program, followed by tailored interventions such as psychosocial care or reconstructive surgery.

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CONFLICTS OF INTEREST

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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