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Malignant extracranial germ cell tumors in the Netherlands between 1990 and 2018: Stable incidence and improved survival

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ABSTRACT

Background: Population-based studies assessing long-term patterns of incidence and disease characteristics of germ cell tumors (GCTs) in children are scarce. We investigated incidence and survival trends of malignant extracranial GCTs in children using population-based nationwide data from the Netherlands.
Methods: All malignant extracranial GCTs diagnosed in patients aged 0–18 years between 1990 and 2018 were selected from the Netherlands Cancer Registry. Incidence rates were calculated as the average annual number of cases per 1 million person-years. Five-year overall survival (OS) was calculated.
Results: A total of 815 cases were identified. Gonadal GCTs (n=665, testis n=485, ovarian n=180) were more common than extragonadal GCTs (n=149). Stage distribution for testicular and extragonadal GCTs shifted between 1990 and 2004 and 2005–2018 towards more localized disease. The overall incidence remained stable over time, but a significant increase was noted for extragonadal GCTs in the 0–9 years age group. Survival of extragonadal GCTs (5-year OS 84.1%, 95% CI 77.1–89.1), in particular mediastinal GCTs (5-year OS 66.7%, 95% CI 45.7–81.1), was lower than that of gonadal GCTs (5-year OS testis 95.0%, 95% CI 92.7–96.7;ovary 97.8%, 95% CI 94.2–99.2). The 5-year OS of our entire cohort was 93.6% (95% CI 91.7–95.1). Five-year OS significantly increased from 89.5% (95% CI 86.1–92.2) in 1990–2004–97.4% (95% CI 95.3–98.5) in 2005–2018.
Conclusions: Although the incidence of all malignant pediatric extracranial GCTs remained stable during 1990–2018, an increase was observed for extragonadal GCTs in younger children (0–9 years). There was a shift towards more localized disease for testicular and extragonadal GCTs. Five-year OS increased over time exceeding 90% (91.4%, 95% CI 82.7–95.8) in the most recent diagnostic period. Mediastinal GCTs had the lowest OS, supporting the need for future research.

1. Introduction

Germ cell tumors (GCTs) comprise a diverse group of neoplasms derived from embryonic stem- and primordial germ cells (PGCs) and derivatives, arising due to disturbance of normal germ cell maturation during embryogenesis [1–4]. GCTs are mostly located in the gonads, but can also occur at extragonadal sites along the midline of the body, consistent with the migratory path of PGCs [5,6]. Malignant GCTs are rare and represent approximately 3–5% of childhood neoplasms [7–10].

In young adults, an increasing incidence of malignant testicular GCTs has been reported in many, mainly Northern European countries [10–12]. In contrast, both increasing and decreasing incidence trends have been reported for ovarian GCTs [10,12,13]. The evidence on extragonadal adult GCTs remains limited. In pediatric and adolescent patients, epidemiologic data for malignant GCTs based on large population-based cohorts of patients are scarce [7,10,14]. Survival of

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GCTs has dramatically improved over the past three decades coincident with, among others, more aggressive surgical staging, improved histopathological reporting, and combination chemotherapy including platinum-based agents [13,15].

Epidemiologic measures such as age patterns, incidence, and survival trends could improve our understanding of pediatric GCTs and may provide clues to differences in GCT diagnosis and registration when comparing with other countries. Furthermore, care for pediatric patients with GCTs in the Netherlands has been concentrated in the Princess Máxima Center for Pediatric Oncology in Utrecht since January 2015, which has led to a centralized multidisciplinary diagnostic and treatment approach. To enable future evaluations of the impact of this concentration of care, insight into the prior situation is vital.

We assessed the progress made in the treatment of malignant extracranial GCTs in children and adolescents (0–18 years) in the Netherlands by examining trends in incidence and survival during the period 1990–2018 using population-based data from the Netherlands Cancer Registry (NCR). Detailed trend analyses were performed for the total group of GCTs and by localization (i.e., ovarian, testis and extragonadal), age, and stage at diagnosis.

2. Methods

2.1. Data collection

The NCR is a population-based cancer registry, with an overall coverage exceeding 96% of all diagnosed malignancies in the Netherlands since 1989. Case notification primarily occurs through the Dutch Nationwide Pathology Databank (Palga) and the National Registry of Hospital Discharges. After notification, data managers of the NCR routinely collect relevant information on patient, tumor, and treatment by medical records review. Information on vital status is annually updated via linkage with the nationwide Personal Records Database (BRP, last linkage: February 1, 2023) [16,17].

For this analysis, we retrieved data from the NCR concerning all children and adolescents, aged 0–18 years, who were diagnosed with a malignant extracranial GCT in the Netherlands between 1990 and 2018. Patients were selected using the International Classification of Childhood Cancer, 3rd edition (ICCC-3), diagnostic groups Xb "Malignant extracranial and extragonadal germ cell tumors" and Xc "Malignant gonadal germ cell tumors" [18] (accessed May 2023). Mature teratomas were excluded from this analysis and only immature teratomas were analyzed and labelled as "Teratoma". Information on grade of immaturity for teratomas could not be extracted. "Pure" histology subtype indicated tissue containing 100% of that particular tissue subtype and not containing any other tissue subtype. Histology was considered as "mixed forms" when it contained more than one histology subtype (regardless of percentage). Based on the International Classification of Diseases for Oncology, 3rd edition (ICD-O-3), topography code, tumors were categorized as testis, ovary, extragonadal (mediastinal, abdominal, pelvis, other), or unknown localization (C80.9, N=3, Supplementary Table S1). Sacrococcygeal tumors were labelled "pelvis". Individual histopathology reports from Palga were consulted for the three patients with unknown tumor localization according to the NCR, and for two patients the localization could be changed to "testis" and "pelvis" respectively [19]. Stage was classified using the TNM staging system for testicular tumors (in accordance with the Toronto Paediatric Cancer Stage guidelines [20,21]), the International Federation of Gynecology and Obstetrics (FIGO) system for ovarian tumors [22], and Extent of Disease for extragonadal tumors [23]. The study period was divided into two diagnostic periods, i.e., 1990–2004 and 2005–2018, considering the introduction of the MAKEI 05 treatment protocol for extracranial GCT in 2005 [24].

2.2. Statistical analysis

Characteristics of the study population were described for all malignant GCT, testicular tumors, ovarian tumors and extragonadal tumors, overall and by diagnostic period. Statistical significance of differences between the diagnostic periods was assessed using Pearson's X^2 tests or Fisher's exact tests ($N \leq 5$ in one or more categories).

Incidence rates were calculated as the average annual number of cases per 1 million person-years and were age-standardized using the weights of the World Standard Population. In the Figures, incidence rates are displayed as 3-year moving averages, which were calculated by taking the average of the rates of each given year and the rates either side of it. Estimated annual percentage change (EAPC) were used to assess potential changes in incidence during the period 1990–2018. EAPC were determined from a regression line that was fitted to the natural logarithm of the rates using the calendar year as the regressor [25].

The traditional actuarial method was used to estimate 5-year observed overall survival (OS) with 95% confidence intervals (95% CI). OS was used instead of relative survival because competing risks of death can be considered negligible in children and adolescents with cancer in developed countries [26]. The survival probabilities of subgroups were characterized using Kaplan-Meier curves and compared with log-rank tests trimmed at 5 years after diagnosis. Patients contributed to the survival analysis from diagnosis until death (i.e., event), emigration or last follow-up (i.e., February 1, 2023), whichever occurred first. Patients first diagnosed at autopsy were excluded from the survival analysis (N=4).

The incidence analyses were performed using SAS (SAS system 9.4, SAS Institute, Cary, North Carolina, USA), whereas Stata/IC 16.1 (StataCorp LLC, College Station, Texas, USA) was used to conduct the survival analyses.

3. Results

3.1. Patient and treatment characteristics

During the study period 1990–2018, 815 pediatric patients (aged 0–18 years) were diagnosed with a malignant extracranial GCT in the Netherlands. The majority of patients had a gonadal tumor (n=665 (82%), testicular: n=485, ovarian: n=180), whereas 149 (18%) patients had an extragonadal tumor. For extragonadal tumors, the male:female ratio was 0.7:1.

The distribution of GCTs over the age categories varied by disease localization. A bimodal age distribution was observed for testicular and extragonadal tumors with peaks occurring in the 0–4 years age group and from 10 years onwards (Table 1, Fig. 1A). The incidence of ovarian GCTs increased from 5 to 9 years onwards. In the extragonadal localization, pelvis tumors occurred solely in the 0–4 years age group, whereas mediastinal tumors were predominant among teenagers (Fig. 1B). No extragonadal GCTs were seen in the 5–9 years age group. Regarding histology, pure yolk sac tumor (YST) histology and teratomas were prevailing in the 0–4 years age group, whereas seminomas/dysgerminomas, choriocarcinomas, embryonal carcinomas (EC), and mixed forms became more frequent in the older age groups (Fig. 1C).

For gonadal tumors, an increase in the proportion of seminomas/dysgerminomas and mixed forms was observed between the diagnostic periods 1990–2004 and 2005–2018, whereas the proportion of teratoma and YST histology decreased (Table 1). Furthermore, patients with testicular and extragonadal GCTs presented more commonly with stage I disease as opposed to higher-stage disease in 2005–2018. On the other hand, this time trend in stage at diagnosis was not reported for ovarian GCTs. Also, there was an increase in the proportion of patients treated in an academic setting as opposed to a non-academic setting in the most recent diagnostic period (58% vs 70%, $p<0.001$). Patients with testicular tumors presented at an older age in the most recent time period

Table 1
Characteristics of children and adolescents (0–18 years) diagnosed with malignant extracranial germ cell tumors in the Netherlands between 1990 and 2018.

	All malignant GCT							Testis							Ovary							Extragonadal						
	1990–2018			1990–2004		2005–2018		1990–2018			1990–2004		2005–2018		1990–2018			1990–2004		2005–2018		1990–2018			1990–2004		2005–2018	
Characteristics	N	%	average per year	N	%	N	%	p-value[a]	N	%	average per year	N	%	N	%	p-value[a]	N	%	average per year	N	%	N	%	p-value[a]	N	%	average per year	N	%	N	%	p-value[a]
Overall	815		28	395		420			485		17	240		245			180		6	88		92			149		5	66		83		
Sex								0.30								NA								NA							0.18
Male	547	67.1	19	272	68.9	275	65.5		485	100	17	240	100	245	100		0	0.0	0	0	0.0	0	0.0		61	40.9	2	31	47.0	30	36.1	
Female	268	32.9	9	123	31.1	145	34.5		0	0.0	0	0	0.0	0	0.0		180	100	6	88	100	92	100		88	59.1	3	35	53.0	53	63.9	
Age at diagnosis (years)								0.28								**0.01**								0.63							**0.01**
0–4	183	22.5	6	84	21.3	99	23.6		53	10.9	2	33	13.8	20	8.2		4	2.2	0	1	1.1	3	3.3		126	84.6	4	50	75.8	76	91.6	
5–9	28	3.4	1	16	4.1	12	2.9		2	0.4	0	2	0.8	0	0.0		26	14.4	1	14	15.9	12	13.0		0	0.0	0	0	0.0	0	0.0	
10–14	102	12.5	4	57	14.4	45	10.7		22	4.5	1	15	6.3	7	2.9		75	41.7	3	39	44.3	36	39.1		4	2.7	0	2	3.0	2	2.4	
15–18	502	61.6	17	238	60.3	264	62.9		408	84.1	14	190	79.2	218	89.0		75	41.7	3	34	38.6	41	44.6		19	12.8	1	14	21.2	5	6.0	
Microscopically verified	801	98.3	28	393	99.5	408	97.1	**0.01**	480	99.0	17	239	99.6	241	98.4	0.37	176	97.8	6	88	100	88	95.7	0.12	144	96.6	5	65	98.5	79	95.2	0.38
Histology								**<0.001**								**<0.001**								**0.01**							0.15
Seminomas/ dysgerminomas	111	13.6	4	38	9.6	73	17.4		41	8.5	1	12	5.0	29	11.8		57	31.7	2	21	23.9	36	39.1		13	8.7	0	5	7.6	8	9.6	
Teratomas	278	34.1	10	158	40.0	120	28.6		136	28.0	5	88	36.7	48	19.6		76	42.2	3	44	50.0	32	34.8		66	44.3	2	26	39.4	40	48.2	
Embryonal carcinomas	88	10.8	3	42	10.6	46	11.0		86	17.7	3	41	17.1	45	18.4		0	0.0	0	0	0.0	0	0.0		2	1.3	0	1	1.5	1	1.2	
Yolk sac tumors	121	14.9	4	77	19.5	44	10.5		54	11.1	2	38	15.8	16	6.5		22	12.2	1	14	15.9	8	8.7		45	30.2	2	25	37.9	20	24.1	
Choriocarcinomas	60	7.4	2	38	9.6	22	5.2		49	10.1	2	29	12.1	20	8.2		5	2.8	0	4	4.6	1	1.1		5	3.4	0	4	6.1	1	1.2	
Mixed forms	157	19.3	5	42	10.6	115	27.4		119	24.5	4	32	13.3	87	35.5		20	11.1	1	5	5.7	15	16.3		18	12.1	1	5	7.6	13	15.7	
Stage gonadal[b,c]																**0.003**								0.15							
I									294	60.6	10	127	52.9	167	68.2		99	55.0	3	49	55.7	50	54.4									
II									95	19.6	3	57	23.8	38	15.5		21	11.7	1	9	10.2	12	13.0									
III									96	19.8	3	56	23.3	40	16.3		36	20.0	1	16	18.2	20	21.7									
IV									NA			NA		NA			8	4.4	0	2	2.3	6	6.5									
Unknown									0	0.0	0	0	0.0	0	0.0		16	8.9	1	12	13.6	4	4.4									
Stage extragonadal[d]																															**<0.001**
Localized																									72	48.3	2	18	27.3	54	65.1	
Locoregional																									29	19.5	1	18	27.3	11	13.3	
Metastatic																									30	20.1	1	19	28.8	11	13.3	
Unknown																									18	12.1	1	11	16.7	7	8.4	
Extragonadal localizations																															0.21
Mediastinal																									27	18.1	1	15	22.7	12	14.5	
Abdominal																									31	20.8	1	16	24.2	15	18.1	
Pelvis																									66	44.3	2	23	34.9	43	51.8	
Other																									25	16.8	1	12	18.2	13	15.7	
Site of treatment								**<0.001**								0.16								**0.001**							**<0.001**
Non-academic	294	36.1	10	168	42.5	126	30.0		241	49.7	8	127	52.9	114	46.5		39	21.7	1	28	31.8	11	12.0		14	9.4	0	13	19.7	1	1.2	

(*continued on next page*)

Table 1 (*continued*)

Characteristics	All malignant GCT								Testis					Ovary					Extragonadal				
	1990–2018			1990–2004		2005–2018		p-value[a]	1990–2018			1990–2004	2005–2018	1990–2018			1990–2004	2005–2018	1990–2018			1990–2004	2005–2018	p-value[a]
	N	%	average per year	N	%	N	%		N	%	average per year	N	%	N	%	average per year	N	%	N	%	average per year	N	%	N	%	
Academic	521	63.9	18	227	57.5	294	70.0		244	50.3	8	113	47.1	131	53.5		141	78.3	5	60	68.2	81	88.0		135	90.6	5	53	80.3	82	98.8	
Primary treatment								**<0.001**								**0.04**								0.94						**<0.001**
Surgery only[e]	371	45.5	13	159	40.3	212	50.5		241	49.7	8	107	44.6	134	54.7		80	44.4	3	40	45.5	40	43.5		50	33.6	2	12	18.2	38	45.8	
CT only[f]	32	3.9	1	25	6.3	7	1.7		4	0.8	0	3	1.3	1	0.4		2	1.1	0	1	1.1	1	1.1		25	16.8	1	20	30.3	5	6.0	
Surgery & CT[g]	402	49.3	14	207	52.4	195	46.4		239	49.3	8	130	54.2	109	44.5		98	54.4	3	47	53.4	51	55.4		65	43.6	2	30	45.5	35	42.2	
No/other/ unknown	10	1.2	0	4	1.0	6	1.4		1	0.2	0	0	0.0	1	0.4		0	0.0	0	0	0.0	0	0.0		9	6.0	0	4	6.1	5	6.0	

Abbreviations: GCT, germ cell tumors; CT, chemotherapy.
NA: not applicable.
[a] P-values of differences between the diagnostic periods 1990–2004 and 2005–2018. Pearson's X^2 tests or Fisher's Exact tests (N≤5 in one or more categories) were used for categorical variables.
[b] Testicular tumors: TNM stage according to Toronto Paediatric Cancer Stage guidelines; Ovarian tumors: FIGO stage.
[c] For testicular tumors: stage I corresponds with tumors confined to the testis, stage II with tumor extension to the regional lymph nodes, and stage III with distant metastasis.
[d] Extent of Disease.
[e] Numbers of patients who also received radiotherapy were 13 for all malignant GCT, 13 for testicular tumors, 0 for ovarian tumors, and 0 for extragonadal tumors.
[f] Numbers of patients who also received radiotherapy were 4 for all malignant GCT, 0 for testicular tumors, 0 for ovarian tumors, and 4 for extragonadal tumors.
[g] Numbers of patients who also received radiotherapy were 3 for all malignant GCT, 0 for testicular tumors, 1 for ovarian tumors, and 2 for extragonadal tumors.

(p=0.01), whereas patients with extragonadal tumors presented at a younger age (p=0.01). Finally, there was a significant difference in primary treatment modality between the diagnostic periods for testicular and extragonadal tumors, with more patients being treated with surgery only as opposed to chemotherapy only or surgery in combination with chemotherapy in recent years (please refer to Supplementary Figure S1 for information on treatment by stage).

3.2. Incidence

On average, 28 children and adolescents were newly diagnosed with a malignant GCT annually (range 21–42) during 1990–2018. The overall age-standardized incidence rate of malignant GCTs in the age group 0–18 years was 9.1 per million person-years and remained stable over time (EAPC +0.7% per year, 95% CI −0.1–1.4; Fig. 2A). Age-standardized incidence rates of testicular, ovarian and extragonadal GCTs were 10.1, 3.9 and 2.0 per 1 million person-years, respectively, and also remained stable over time (Fig. 2B). However, a significant increase in incidence was noted for extragonadal GCTs in the 0–9 years age group of +2.8% per year (95% CI 0.4–5.2). No increase was noted in the 10–18 years age group for extragonadal GCTs or in any of the age groups for gonadal GCTs (Fig. 2C, Fig. 3).

3.3. Survival

Results of the survival analyses are shown in Table 2 and Fig. 4. Five-year OS of all malignant GCTs diagnosed in children (0–18 years) in the Netherlands between 1990 and 2018 was 93.6% (95% CI 91.7–95.1). Between five and ten years follow-up, only two additional deaths (ovarian n=1, extragonadal n=1) occurred. Best survival was noted for ovarian GCTs at 97.8% (95% CI 94.2–99.2). Five-year OS was 95.0% (95% CI 92.7–96.7) for testicular GCTs and 84.1% (95% CI 77.1–89.1) for extragonadal GCTs. Of the latter group, the mediastinal localization had the worst reported 5-year OS at 66.7% (95% CI 45.7–81.1). Five-year OS was 83.9% (95% CI 65.5–92.9) for the abdominal localization. Extragonadal GCTs at the pelvic localization had the best 5-year OS at 92.2% (95% CI 82.2–96.7). Five-year OS did not differ between the age groups overall and for gonadal GCTs. However, there was a significantly lower survival in teenagers (10–18 years) with extragonadal GCTs compared to the 0–9 years age group (Table 2).

There was a significant increase in 5-year OS of all malignant GCTs between the two diagnostic periods, from 89.5% (95% CI 86.1–92.2) in 1990–2004–97.4% (95% CI 95.3–98.5) in 2005–2018. This increase in survival was seen for testicular, ovarian and extragonadal GCTs, though not significant for the latter category. In 2005–2018, 5-year OS exceeded 90% for extragonadal GCTs (91.4%, 95% CI 82.7–95.8) and was near or at 100% for gonadal GCTs (testis 98.4%, 95% CI 95.7–99.4; ovary 100%).

4. Discussion

This is the first comprehensive population-based study on malignant extracranial GCTs in the pediatric and adolescent population (0–18 years) in the Netherlands. Our study showed a stable incidence for gonadal and extragonadal GCTs in general, but a significant increase in incidence for extragonadal GCTs in the 0–9 years age group. The survival of patients with extragonadal (5-year OS of 84.1%, 95% CI 77.1–89.1) and in particular of patients with mediastinal GCTs (5-year OS of 66.7%, 95% CI 45.7–81.1) was lower than the survival of gonadal GCTs. Five-year OS of increased over time reaching>90% for extragonadal GCTs and (almost) 100% for gonadal GCTs.

Our cohort displayed a clear correlation between age and histology, with 0–4 year-olds displaying histopathology of either pure YST or teratoma, whereas seminomas/dysgerminomas, choriocarcinomas, EC, and mixed forms became more frequent in the older age groups. This is in keeping with the classification of GCTs into Type I and Type II tumors

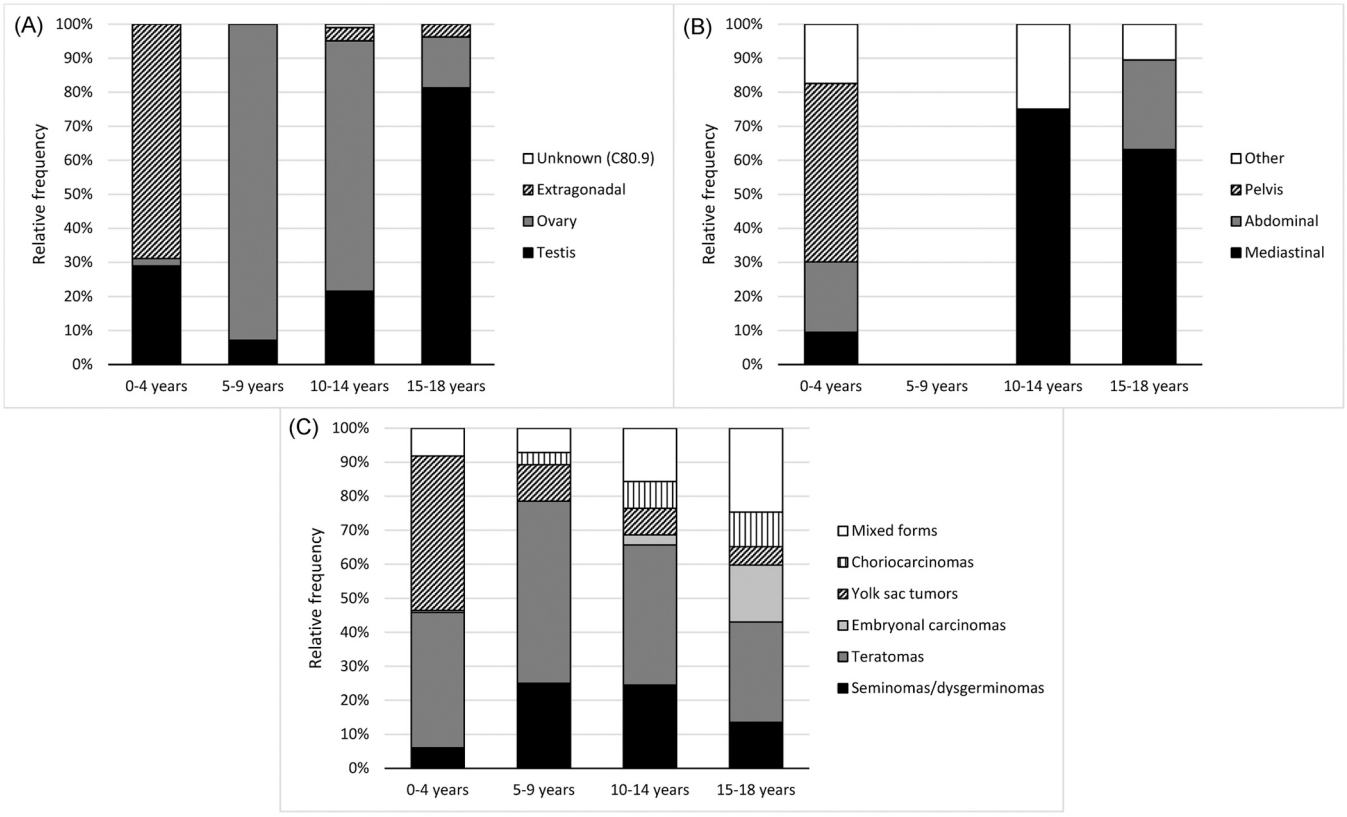

Fig. 1. Age-specific distributions of main localizations (A), extragonadal localizations (B), and histology (C) of malignant extracranial germ cell tumors in children and adolescents (0–18 years) diagnosed in the Netherlands between 1990 and 2018.

as described in the literature [27]. Briefly, GCTs within the pediatric cohort can be divided into two main groups, type I and II, which are separated by age and can be further subdivided into biologically and clinically distinct subgroups. PGCs are specified early in embryogenesis and migrate through the embryo to the developing gonad. Type I GCTs exhibit a limited histologic spectrum, a partial erasure of genomic imprinting, and a propensity for development at extragonadal sites, most frequently the sacrococcygeal region, all suggesting a derivation from early stages of germ cell development. They occur in the 0–4 years age group, with teratomas and YST representing the characteristic histological appearances, and often, both histological subtypes can be appreciated simultaneously in one tumor. In fact, sometimes teratomas with microscopic foci of YST can be seen, which can relapse with pure YST histology after incomplete resection [28–30]. In the 0–4 years age group, there is an equal sex distribution. The female predominance in extragonadal GCTs is counterbalanced by the much higher frequency of testicular compared to ovarian GCTs during childhood [14]. With the onset of puberty, the clinical and histopathologic pattern of GCTs changes. Type II GCTs of the testis frequently contain foci of germ cell neoplasia *in situ* (GCNIS) and exhibit the full range of seminoma and nonseminoma histology, while the frequency of teratomas is low. Together with a more complete erasure of imprinting, these features suggest that the Type II tumors arise at a later stage of germline development [5,27,31–34]. The female predominance in childhood extragonadal GCTs shifts into a male predilection during adolescence [14]. Improved pathology reviews and increased awareness of GCTs being composed of different malignant components in more recent years could have led to the finding that, for gonadal GCTs, the proportion of seminomas/dysgerminomas and mixed malignant forms increased, while the proportion of teratoma and pure YST histology decreased.

The overall incidence of malignant extracranial GCTs in children and adolescents in the Netherlands during 1990–2018 was 9.1 per million person-years. This was considerably higher than the 4 per million person-years reported for the period 1981–2000 in a large population-based cohort study from Germany [14]. The difference may be explained by the fact that the German study only included patients up to 15 years of age, missing out on the 15–18 years age group that, in our cohort, contained 62% of all patients. The incidence in our study, when only 0–14 year-olds are taken into account, amounted to 4.0 per million person-years which is comparable to the German cohort. Our cohort also displayed a higher number of testicular primaries than in this German cohort. This can be explained by the age limit of 15 years in the German study, as the incidence of testicular tumors is increasing from the age of 12 (Fig. 3). In our cohort, 84.1% of testicular tumors (n= 408) occurred in the 15–18 years age group. A French/Belgian study describing intermediate risk (IR) and high risk (HR) disease displayed lower numbers of testicular primaries [35]. However, our cohort included all risk groups and showed that testicular tumors mainly present as low-risk (LR) disease (stage I disease in 294 (60.6%) cases).

We showed that 5-year OS of malignant extracranial GCTs in the Netherlands increased from 89.5% (95% CI 86.1–92.2) in 1990–2004–97.4% (95% CI 95.3–98.5) in 2005–2018. After the introduction of platinum-based chemotherapy regimens for GCTs in the 1980 s, survival increased markedly and was already very good in the 1990 s which marks the onset of data registration for our cohort. However, a pattern of continuing improvement in survival was seen, a pattern similar to that reported in the literature [10,26,36]. Possible explanations are ongoing improvements and availability of clinical trials over the years allowing for ongoing cumulative experience, and improved supportive care [35,37,38]. Furthermore, the rising proportion of patients treated in an academic setting in our cohort over time, reflecting the trend to treat children in specialized pediatric oncology centers, could have contributed to the improved outcomes. Also, patients with testicular and extragonadal GCTs presented more commonly

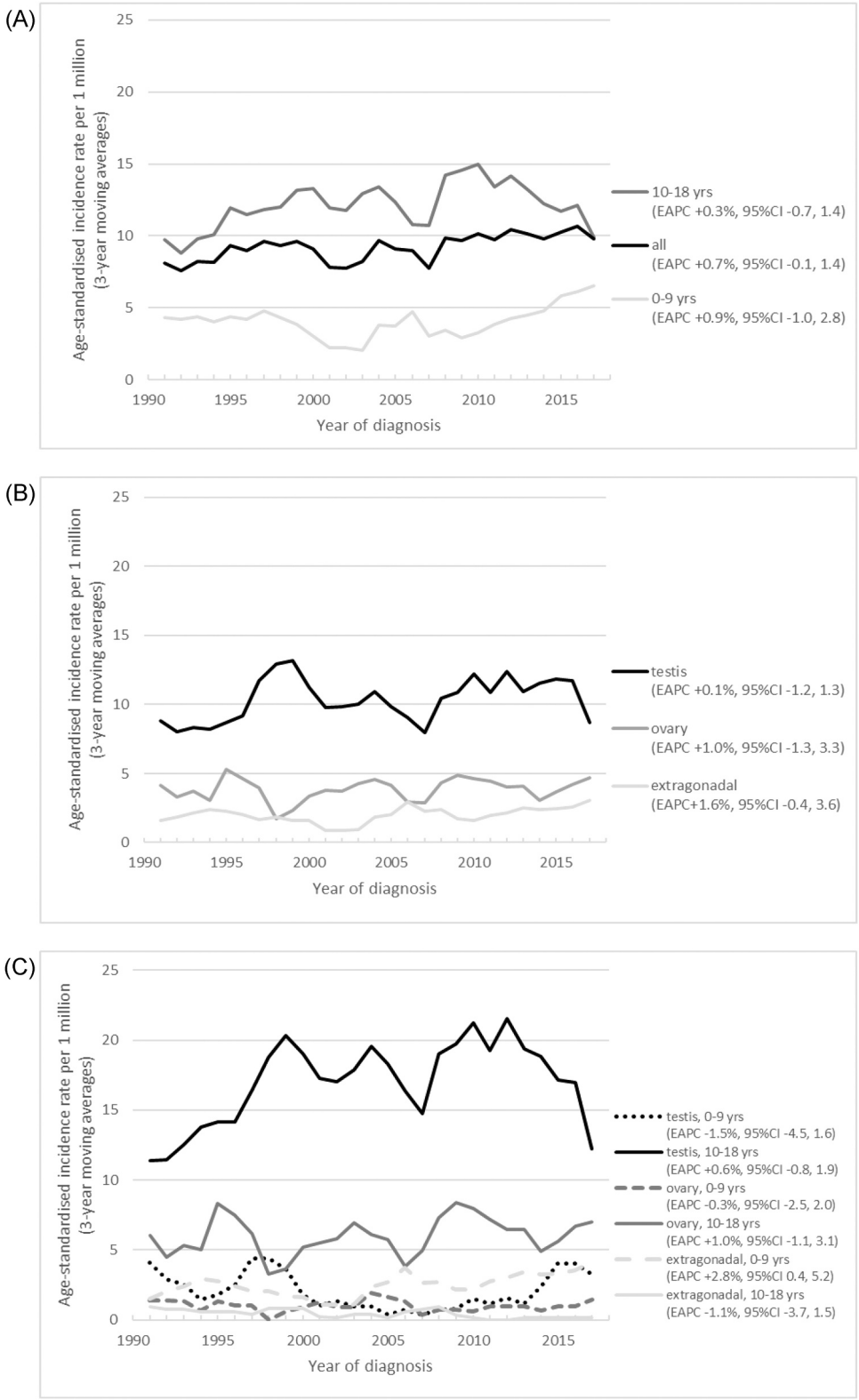

Fig. 2. Time trends in incidence of malignant extracranial germ cell tumors in children and adolescents (0–18 years) diagnosed in the Netherlands between 1990 and 2018 by age (A), main localizations (B), and main localizations and age (C).

with stage I disease in 2005–2018, indicating that earlier detection of disease could have played a role as well. Extragonadal GCTs had lowest five-year OS (84.1%, 95% CI 77.1–89.1) in our cohort. This is similar to outcomes reported for other national cohorts. An Italian cohort describing extracranial GCTs from 1991 to 1996 reported poor outcomes for extragonadal disease, in particular non-sacrococcygeal extragonadal sites [39]. Similar poor outcomes for extragonadal disease were reported in French analyses [35,40]. Patients with a mediastinal localization had the lowest 5-year OS of 66.7% (95% CI 45.7–81.1) in our cohort. The International Germ Cell Cancer Collaborative Group (IGCCCG)

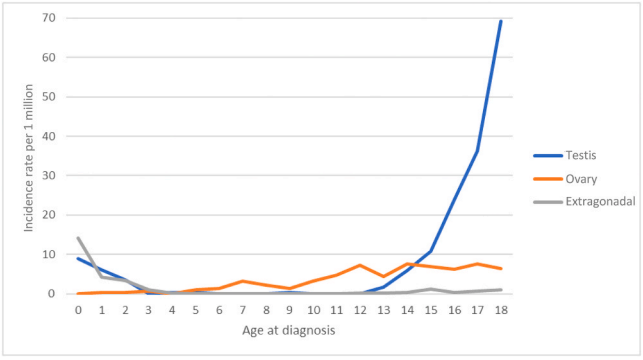

Fig. 3. Incidence of malignant extracranial germ cell tumors in children and adolescents (0–18 years) diagnosed in the Netherlands between 1990 and 2018 by age and localization.

identified the presence of a mediastinal primary site in patients with a non-seminomatous GCT as one of the major adverse factors, possibly representing a clinically and biologically distinct disease entity associated with lower remission rates, higher rates of relapse and failure of salvage chemotherapy [41,42]. Poor outcomes for mediastinal GCTs support the need for future research. The Malignant Germ Cell Tumor International Collaborative (MaGIC) was initiated to create a basis for future international collaborative clinical trials by producing a revised risk classification for pediatric extracranial GCTs by merging data from the Children's Oncology Group (COG, United States) and the Children's Cancer and Leukemia Group (CCLG, United Kingdom) [43]. Age ≥11 years, ovarian stage IV disease, and extragonadal stage III to IV disease were identified as conferring a significantly worse prognosis [43]. In our study, we stratified our analysis by site and age, and by site and stage. We could not stratify our analysis by site, stage and age as numbers at risk were too small to carry out meaningful analyses. Our data confirmed that higher-stage extragonadal disease carried a worse prognosis (5-yr OS 70.0%, 95% CI 50.3–83.1) than localized (5-yr OS 90.2%, 95% CI 80.5–95.2) and locoregional (5-yr OS 89.7%, 95% CI 71.3–96.5) extragonadal disease. Furthermore, extragonadal GCTs in the 10–18years age group had a significantly lower survival (5-yr OS 56.5%, 95% CI 34.3–73.8) than those in the 0–9years age group (5-yr OS 89.3%, 95% CI 82.4–93.7) which concurs with the MaGIC risk classiciation data [43,44].

The data in our study were drawn from an extensive population-based national registry with considerable time-depth covering nearly three decades. It included essentially all cases diagnosed and gave detailed information on this rare group of malignancies. The NCR is known to have well-validated, comprehensive data. GCTs constitute a highly heterogeneous group of neoplasms, and many aspects of the heterogeneity regarding the site of origin and their histological appearance were reflected by the data presented in this analysis. Several factors may have limited our results. Even though data were collected for a cohort spanning nearly three decades, the rare character of these tumors means there is a limited number of cases in our study. This makes the interpretation of certain results (e.g. patterns in histology and localization) challenging. Furthermore, the NCR does not report on clinical information regarding specific chemotherapy regimens administered, clinical course of disease or relapsed or recurrent disease so these data are lacking in our report.

Table 2
Five-year overall survival of children and adolescents (0–18 years) diagnosed with malignant extracranial germ cell tumors in the Netherlands between 1990 and 2018.

	All malignant GCT			Testis			Ovary			Extragonadal		
		1990–2018			1990–2018			1990–2018			1990–2018	
Characteristics	$N_{at\ risk}$	5-yr OS	95% CI	$N_{at\ risk}$	5-yr OS	95% CI	$N_{at\ risk}$	5-yr OS	95% CI	$N_{at\ risk}$	5-yr OS	95% CI
Overall	811	93.6	(91.7–95.1)	485	95.0	(92.7–96.7)	180	97.8	(94.2–99.2)	145	84.1	(77.1–89.1)
Sex												
Male	546	93.2	(90.8–95.0)	485	95.0	(92.7–96.7)	0	NA		60	80.0	(67.5–88.1)
Female	265	94.3	(90.7–96.5)	0	NA		180	97.8	(94.2–99.2)	85	87.0	(77.8–92.6)
Diagnostic period												
1990–2004	393	89.5	(86.1–92.2)	240	91.7	(87.4–94.5)	88	95.4	(88.3–98.3)	64	75.0	(62.5–83.9)
2005–2018	418	97.4	(95.3–98.5)	245	98.4	(95.7–99.4)	92	100.0		81	91.4	(82.7–95.8)
Age at diagnosis (years)												
0–9	207	92.7	(88.2–95.6)	55	96.4	(86.2–99.1)	30	100.0		122	89.3	(82.4–93.7)
10–18	604	93.9	(91.6–95.5)	430	94.9	(92.3–96.6)	150	97.3	(93.0–99.0)	23	56.5	(34.3–73.8)
Stage gonadal[a,b]												
I				294	99.0	(96.9–99.7)	99	97.0	(90.9–99.0)			
II				95	97.9	(91.8–99.5)	21	100.0				
III				96	80.2	(70.7–86.9)	36	97.2	(81.6–99.6)			
IV				NA	NA		8	NA				
Unknown				0	NA		16	100.0				
Stage extragonadal[c]												
Localized										72	90.2	(80.5–95.2)
Locoregional										29	89.7	(71.3–96.5)
Metastatic										30	70.0	(50.3–83.1)
Unknown										14	71.4	(40.6–88.2)
Extragonadal localizations												
Mediastinal										27	66.7	(45.7–81.1)
Abdominal										31	83.9	(65.5–92.9)
Pelvis										64	92.2	(82.2–96.7)
Other										23	82.4	(59.6–93.0)

Abbreviations: GCT, germ cell tumors; 5-yr OS, 5-year overall survival; 95% CI, 95% confidence interval.
NA: Estimation of a reliable survival probability was not possible because of N at risk <10.
[a] Testicular tumors: TNM stage according to Toronto Paediatric Cancer Stage guidelines; Ovarian tumors: FIGO stage.
[b] For testicular tumors: stage I corresponds with tumors confined to the testis, stage II with tumor extension to the regional lymph nodes, and stage III with distant metastasis.
[c] Extent of Disease.

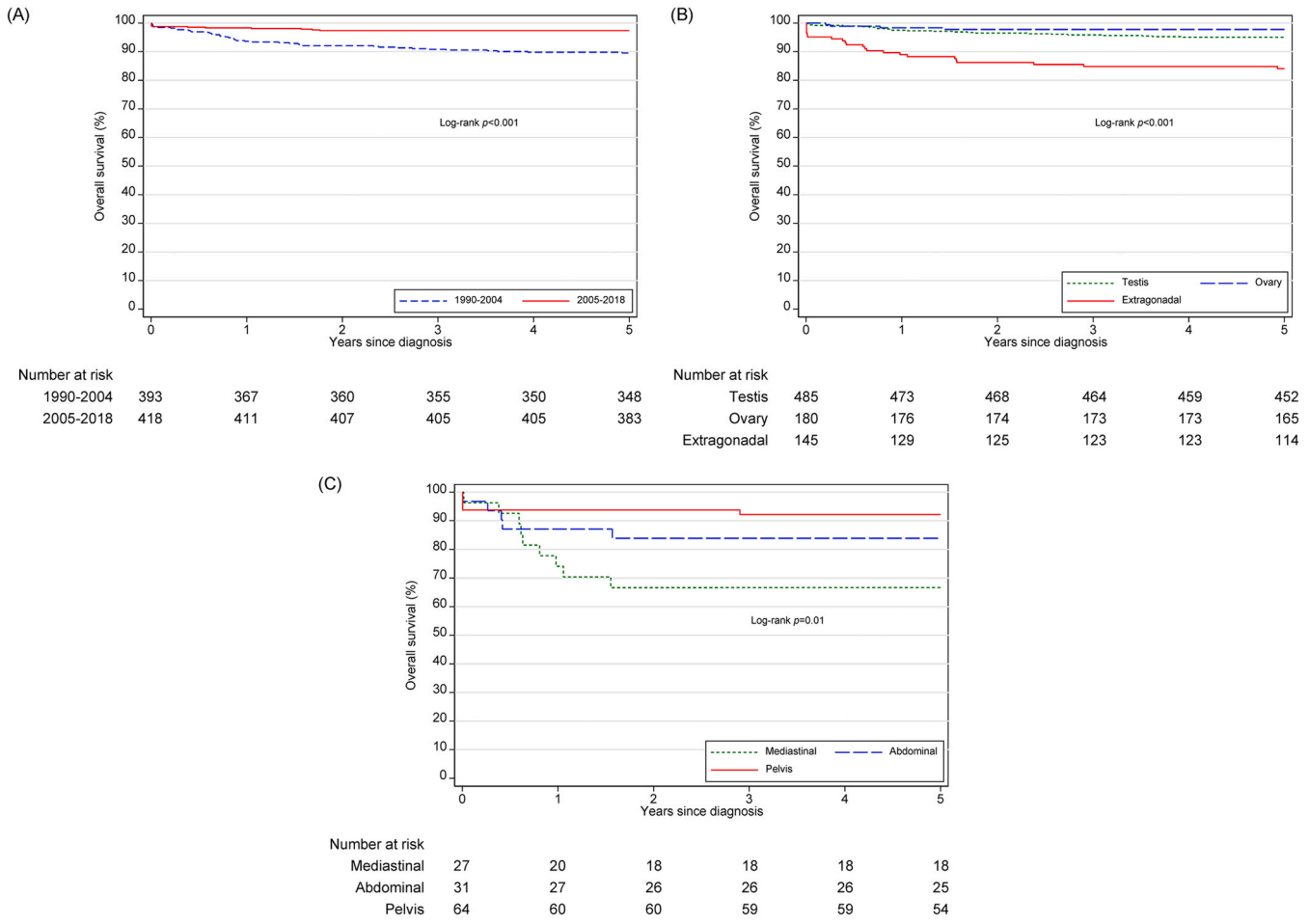

Fig. 4. Overall survival of children and adolescents (0–18 years) diagnosed with malignant extracranial germ cell tumors in the Netherlands between 1990 and 2018 by diagnostic period (A), main localization (B), and extragonadal localization (C).

5. Conclusions

This nationwide study on malignant extracranial GCTs in children and adolescents (0–18 years) in the Netherlands provides detailed information on a rare group of tumors and adds important knowledge to the limited population-based evidence available. Although the incidence of gonadal and extragonadal GCTs was stable overall, a significant increase was observed for extragonadal GCTs in the 0–9 years age group. There were distinct age-specific incidence patterns by anatomical localization, appropriately reflecting the current knowledge of the molecular basis of GCTs in children and adolescents. Stage distribution for testicular and extragonadal GCTs shifted towards more localized disease. Five-year OS of all malignant GCTs increased over time. In 2005–2018, 5-year OS exceeded 90% (91.4%, 95% CI 82.7–95.8) for extragonadal GCTs and was near or at 100% (Testis 98.4%, 95% CI 95.7–99.4. Ovary 100%). for gonadal GCTs. The prognosis of mediastinal GCTs, however, remains moderate and requires attention in future research.

Author contributions

Conceptualization, C.C.C.H., A.F.W.S. and M.H.W.W.; methodology, C.C.C.H., M.S., O.V., A.H.G-B., H.E.K.-K., A.F.W.S.; formal analysis, C.C.C.H., A.M.C.M.-G., A.H.G.-B, M.S., H.E.K.-K. and R.R.de K.; writing—original draft preparation, C.C.C.H., M.S.; writing—review and editing, C.C.C.H., H.E.K.-K., J.Z., A.M.C.M.-G., L.H.J.L, A.F.W.S, M.S. and M.H.W.W. All authors have read and agreed to the published version of the manuscript.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejcped.2024.100148.

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