HK J Paediatr (new series) 2019;**24**:192-202

Original Article

Long-term Therapy Related Side Effect on Endocrine System Among Paediatric Survivors with Brain Tumour and Acute Lymphoblastic Leukaemia

SSW ***Chan***, JYL ***Tung***, DKL ***Cheuk***, WHS ***Wong***, GCF ***Chan***

Abstract ***Purpose:*** Treatments for childhood acute lymphoblastic leukaemia (ALL) and brain tumours could cause endocrine sequelae after completion of treatment. Yet, the local incidence and pattern are not known. This study aims to evaluate the frequency and nature of endocrine complications among Hong Kong Chinese childhood brain tumours and ALL survivors. ***Methods:*** It is a retrospective cross-sectional review on paediatric ALL and brain tumour patients treated in a tertiary hospital from January 2000 to August 2015. Children survived for more than 2 years were included. ***Findings:*** Overall 233 patients were included in the study (ALL=138; brain tumours=95). The mean duration of follow-up was 10.3 years. Seventy-eight patients (33.5%) had at least one endocrine complication, and 57 (25.4%) had more than one endocrine complication. Hypothyroidism (n=45) was the commonest complication, followed by hypogonadism (n=40). Cranial radiotherapy was a major risk factor of endocrinopathy. ***Conclusions:*** Radiotherapy appeared to be the most significant risk factor. Updated regular surveillance program, together with proper patients' educations are mandatory.

Key words ALL; Brain tumours; Childhood cancers; Endocrine complications

Introduction

With improved effectiveness of childhood cancer treatments, the survival rate continues to increase worldwide. Both UK[1] and USA[2] registry have recorded over 80% of five-year survival rate. However, long-term survivors might develop at least one medical complication after specific therapeutic exposures.[3]

Endocrine complications are frequently reported in childhood cancer survivors.[4] These include problems of growth, puberty and impairment of gonadal, thyroid and adrenal function.[5]

Similar to other ethnic groups, acute lymphoblastic leukaemia (ALL) and brain tumours are the two most common forms of childhood malignancies in Hong Kong, with five-year survival rate comparable to other developed countries (Hong Kong Paediatric Haematology Oncology Study Group Annual Workshop 2017). However, the impacts of cancer and cancer treatments on endocrine dysfunction among Hong Kong Chinese children with these two conditions had not been comprehensively reviewed previously. With this knowledge gap, this study aims to evaluate the frequency and nature of endocrine complications among Hong Kong Chinese childhood brain tumour and ALL survivors.

Department of Paediatrics and Adolescent Medicine, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Queen Mary Hospital, 102 Pokfulam Road, Pokfulam, Hong Kong SAR

SSW **Chan** (陳舒穎) *M.Med.Sc*
FYL **Tung** (童月玲) *MBBS (HK)*
DKL **Cheuk** (卓家良) *MBBS (HK)*
WHS **Wong** (黃慶生) *PhD*
GCF **Chan** (陳志峰) *MD*

Correspondence to: Prof GCF **Chan**
Email: gcfchan@hku.hk

Received June 18, 2019

Patients and Methods

Study Design

This is a retrospective cross-sectional cohort study. Clinical information was obtained by retrospective review of patients' medical records.

Subjects

Medical records of all patients who were less than 18 years of age Chinese paediatric patients with ALL, medulloblastoma, intracranial germ cell tumour (GCT), ependymoma or craniopharyngiomas, who received treatment and follow-up in the Department of Paediatrics and Adolescent Medicine, Queen Mary Hospital and the University of Hong Kong, between January 2000 and August 2015 were reviewed. Patients who completed all treatments for at least two years on or before 31 August 2015 were included for this study.

Subjects were excluded if they: 1) received incomplete treatment, 2) passed away during treatment or within two years of completion of treatment, 3) lost to follow-up, or 4) are non-Chinese patients.

Methods

Basic demographics, cancer diagnosis, disease-related and treatment-related information and duration of follow-up for all eligible patients were assessed. Treatment details on surgery, chemotherapy, haematopoietic stem cell transplant and radiotherapy (including total dose, fractions and radiation fields), details and time of onset of any endocrine complications were also recorded.

Data were analysed using SPSS Statistics version 24.0 (IBM Corp., Armonk, NY, USA). Cox regression or Fisher's exact test (2x2 table) were used to analyse the differences between groups for discrete variables. A p-value of ≤ 0.05 was considered statistically significant. Hazard ratios (HR) were calculated and reported with 95% confidence intervals (CI) for the prediction of different endocrine disorders. Patients with incomplete medical records were excluded from calculation.

Ethics Approval

The study was approved by the Institutional Review Board of the University of Hong Kong/ Hospital Authority Hong Kong West Cluster (HKU/HA HKW IRB).

Results

Three hundred and fifty-nine patients were identified in this retrospective review: 233 patients were included for analysis while 126 patients were excluded. The main reasons of exclusion were 1) still undergoing active treatment at the time of assessment (n=42); 2) incomplete treatment (n=1); 3) passed away during treatment (n=42); 4) incomplete follow-up (n=23); and 5) non-Chinese patients (n=19). The mean duration of follow-up was 10.3 years.

Subjects' Demographic and Clinical Characteristics

Among the 233 patients, 156 (67%) were male and 77 (33%) were female. One hundred and thirty-eight (59.2%) were ALL survivors while ninety-five (40.8%) were brain tumour survivors [(medulloblastoma: n=33 (14.2%), GCT: n=46 (19.7%), ependymoma: n=6 (2.6%), craniopharyngioma: n=10 (4.3%)]. Among the 46 GCT cases, 32 were germinoma and 14 were non-germinomatous germ cell tumour (NGGCT).

The mean age at diagnosis for ALL was 6.5±4.8 years (range: 2-17 years) while the mean age for patients with medulloblastoma, craniopharyngioma and GCT were 7.5±4.5 years (range: 1-17 years), 9.8±3.9 years old (range: 3-17 years) and 10.9±3.6 years (range: 0.17-17 years) respectively. Ependymoma patients were the youngest, with a mean age of 5.8±3.8 years (range: 3-14 years).

The majority of brain tumour patients received combined treatment modalities including chemotherapy and radiation therapy. Six ALL patients with central nervous system involvement received cranial radiotherapy at relapse. The information was summarised in Table 1.

Endocrine Complications

A total of 78 patients (33.5%) were found to have at least one endocrine complication, and 57 (25.4%) had more than one endocrine complication. Endocrine complication was observed to be more common among the brain tumour patients (n=60, 63.2%) than ALL patients (n=18; 13%).

Among all the brain tumours patients, craniopharyngioma patients (n=10, 100% of all craniopharyngioma patients) had the highest incidence and earliest onset of endocrine complication, while ependymoma patients (n=1, 16.7% of all ependymoma cases) had the least endocrine dysfunction in this study.

Table 1 Demographics and treatment characteristics of ALL and brain tumour patients

Disease	No. of patients	Sex ratio (F:M)	Mean age at diagnosis (Years old)	Median follow-up (Years)	Mean age of analysis (Years old)	Treatment modality	Frequency and percentage of endocrinioathies
ALL	138	47:91	6.5±4.8	11.1	24.5	Chemotherapy only: n=91 Chemotherapy + BMT + TBI: n=8 Chemotherapy + BMT + TBI + Testicular RT: n=1 Chemotherapy + Cranial RT: n=26 Chemotherapy + Testicular RT: n=5 Chemotherapy + BMT: n=7	Hypogonadism: n=13 (9.4%) GHD: n=2 (1.5%) Hypothyroidism: n=3 (2.2%) Hypoadrenalism: n=1 (0.7%) Precocious puberty: n=1 (0.7%) T2DM: n=3 (2.2%)
Medulloblastoma	33	13:20	7.5±4.5	10.2	24.3	Surgery + Chemotherapy + Craniospinal RT: n=21 Surgery + Chemotherapy + Craniospinal RT + autologous BMT: n=4 Chemotherapy + Craniospinal RT + Autologous BMT: n=3 Chemotherapy + Craniospinal RT: n=3 Surgery + Chemotherapy: n=2	Hypogonadism: n=10 (30.3%) GHD: n=14 (42.4%) Hypothyroidism: n=14 (42.4%) Precocious puberty: n=1 (3%)
GCT	46	10:36	10.9±3.6	8	23.1	Chemotherapy only: n=8 Chemotherapy + Cranial RT: n=37 Chemotherapy + autologous BMT: n=1	Hypogonadism: n=12 (26.1%) GHD: n=6 (13%) Hypothyroidism: n=19 (41.3%) Hypoadrenalism: n=13 (28.3%) DI: n=19 (41.3%) Precocious puberty: n=6 (13%) T2DM: n=1 (2.2%)
Craniopharyngioma	10	5:5	9.8±3.9	8.7	20.5	Surgery only: n=2 Surgery + Cranial RT: n=8	Hypogonadism: n=4 (40%) GHD: n=6 (60%) Hypothyroidism: n=9 (90%) Hypoadrenalism: n=9 (90%) DI: n=10 (100%)
Ependymoma	6	2:4	5.8±3.8	7.8	16.8	Surgery + Cranial RT: n=3 Surgery + Chemotherapy: n=1 Surgery + Chemotherapy + Cranial RT: n=1 Chemotherapy + autologous BMT + Cranial RT: n=1	Hypogonadism: n=1 (16.7%) T2DM: n=1 (16.7%)

ALL: acute lymphoblastic leukaemia; BMT: bone marrow transplantation; TBI: total body irradiation; RT: radiotherapy; GHD: growth hormone deficiency; GCT: germ cell tumour; T2DM: type 2 diabetes mellitus; DI: diabetes insipidus

There was no difference in the prevalence of endocrine complications between germinomatous GCT and NGGCT either; despite NGGCT patients require two extra courses of chemotherapy.

Forty-five patients had hypothyroidism; 40 had hypogonadism; 28 had growth hormone deficiency (GHD). There were 23 patients with hypoadrenalism and 29 patients with central diabetes insipitus (DI). Other complications included precocious puberty (n=8) and type 2 diabetes mellitus (T2DM) (n=5). Table 2 summarised these endocrine complications and their corresponding primary diagnosis.

Hypogonadism

Hypogonadism was diagnosed in 13 ALL and 27 brain tumours patients. One GCT patient was excluded from analysis as the medical record was incomplete.

The use of alkylating agents was associated with hypogonadism in both male and female (p=0.035) with HR of 3.96 (95% CI: 1.63 to 9.62). Testicular radiotherapy at <30 Gy (n=6, p=0.0001) and total body irradiation (TBI) at 12 Gy in six fractions (n=5, p=0.0051) were found to be associated with primary hypogonadism, with at least 3.98 times (HR: 34.64, 95% CI: 3.98 to 301.81) and 2.02 times higher risk (HR: 9.06, 95% CI: 2.02 to 40.50) respectively in male patients as compared to those without irradiation. However, these associations were not observed in female patients (Table 3). The cumulative incidence of hypogonadism in brain tumour patients is shown in Figure 1a.

Growth Hormone Deficiency (GHD)

Although no patient was documented to have GHD before treatment, twenty-eight patients were diagnosed after treatment. The majority were brain tumour patients [medulloblastoma patients (n=14), GCT (n=6) and craniopharyngioma (n=6)] while there were only two ALL patients (Table 2). Both cranial radiotherapy and surgery were significantly associated with the development of GHD (p<0.0001). Patients who had cranial radiotherapy were at least 2.42 times (HR: 7.24, 95% CI: 2.42 to 21.62) or neurosurgery in particularly at the suprasellar region were at least 3.31 times (HR7.68, 95% CI: 3.31 to 17.85) more likely to develop GHD (Table 3). The cumulative incidence of GHD in brain tumour patients is shown in Figure 1b.

Table 2 Summary of cases with endocrine complications and their respective primary diagnosis

Hypogonadism (n=40)	ALL: 13/138 (9.4%)
Primary: 27	GCT: 12/46 (26.1%)
Secondary: 13	Medulloblastoma: 10/33 (30.3%)
	Craniopharyngioma: 4/10 (40%)
	Ependymoma: 1/6 (16.7%)
Growth hormone deficiency (n=28)	Medulloblastoma: 14/33 (42.4%)
	Craniopharyngioma: 6/10 (60%)
	GCT: 6/46 (13%)
	ALL: 2/138 (1.5%)
Hypothyroidism (n=45)	GCT: 19/46 (41.3%)
Primary: 33	Medulloblastoma: 14/33 (42.4%)
Central: 12	Craniopharyngioma: 9/10 (90%)
	ALL: 3/138 (2.2%)
Hypoadrenalism (n=23)	GCT: 13/46 (28.3%)
Primary: 19	Craniopharyngioma: 9/10 (90%)
Secondary: 4	ALL: 1/138 (0.7%)
Central diabetes insipidus (n=29)	GCT: 19/46 (41.3%)
	Craniopharyngioma: 10/10 (100%)
Present at diagnosis: 22	
Post-operation: 7	
Precocious puberty (n=8)	GCT: 6/46 (13%)
	Medulloblastoma: 1/33 (3%)
	ALL: 1/138 (0.7%)
Type 2 diabetes mellitus (n=5)	ALL: 3/138 (2.2%)
	GCT: 1/46 (2.2%)
	Ependymoma: 1/6 (16.7%)

ALL: acute lymphoblastic leukaemia; GCT: germ cell tumour

Table 3 Summary of endocrine complications and their significant treatment-related risk

Endocrine complications	Risk factors	p-value	Hazard ratio	95% CI
Primary hypogonadism	Alkylating agent	p=0.0035	3.96	1.63 to 9.62
	Testicular RT (males only)	p=0.0001	34.64	3.98 to 301.81
	TBI (males only)	p=0.0051	9.06	2.02 to 40.50
Growth hormone deficiency	Cranial RT	p<0.0001	7.24	2.42 to 21.62
	Brain surgery	p<0.0001	7.68	3.31 to 17.85
Hypothyroidism	Cranial irradiation >40 Gy	p<0.0001	9.44	4.41 to 20.22
Hypoadrenalism	Cranial irradiation >40 Gy	p=0.0002	7.94	2.96 to 21.33

CI: confidence intervals; RT: radiotherapy; TBI: total body irradiation

Hypothyroidism

Hypothyroidism was the most common form of endocrine complication in our study. Among the 45 patients, 33 had primary and 12 had central hypothyroidism. Nineteen were GCT patients, fourteen were medulloblastoma patients, nine were craniopharyngioma patients and three were ALL patients.

Fifteen patients developed hypothyroidism within one year after completing all treatments. Yet, one GCT patient developed hypothyroidism 13 years after treatments. The only identified risk factor for the development of hypothyroidism was cranial irradiation >40 Gy ($p<0.0001$) and the risk was at least 4.41 times (HR: 9.44, 95% CI: 4.41 to 20.22) higher (Table 3). The cumulative incidence of hypothyroidism in brain tumour patients is shown in Figure 1c.

Hypoadrenalism

Of these 23 hypoadrenalism patients, 13 were primarily diagnosed with GCT, nine were craniopharyngioma and one was ALL. Nineteen cases were primary and four were secondary hypoadrenalism (Table 2).

There was a strong dose-dependent relationship between cranial irradiation (>40 Gy) and development of hypoadrenalism ($p=0.0002$) with a HR of 7.94 (95% CI: 2.96 to 21.33) (Table 3).

Hypoadrenalism was commonly observed in patients with craniopharyngioma patients and they had a much earlier onset when compared with GCT patients (Figure 1d).

Central Diabetes Insipitus (DI)

Central DI was present in 12.4% of our patients and was solely diagnosed in brain tumour patients. Nineteen cases were observed in GCT patients while 10 cases were reported in craniopharyngioma patients. The majority of craniopharyngioma patients (n=7) acquired DI after surgery, while three had DI at diagnosis prior to any form of treatment. It was observed that GCT is significantly associated with central DI before treatment ($p<0.0001$)

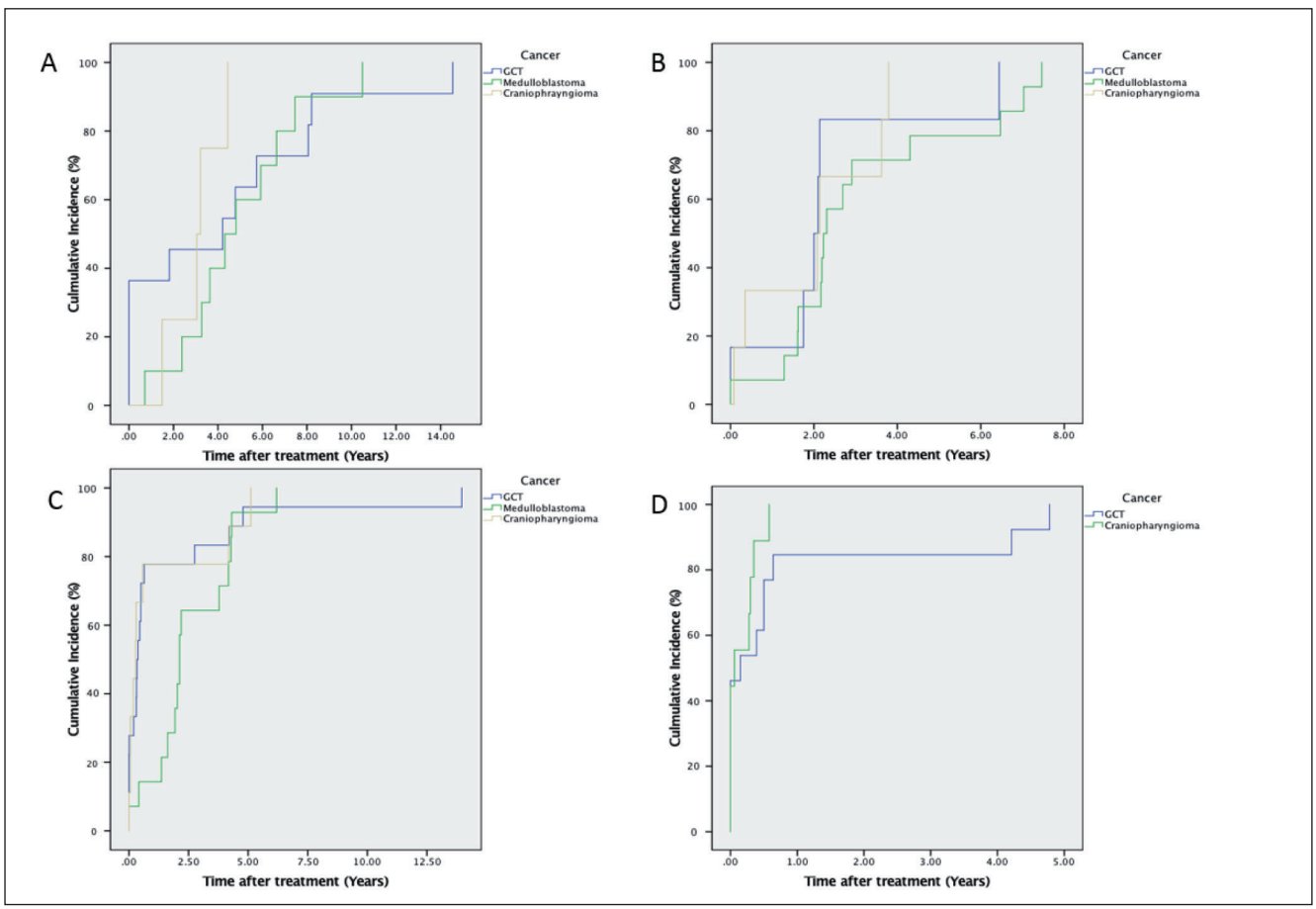

Figure 1 Cumulative incidence of (A) hypogonadism, (B) growth hormone deficiency, (C) hypothyroidism, and (D) hypoadrenalism.

and craniopharyngioma patients are at greater risk for developing DI after surgery (P<0.0001) compared with other brain tumour patients.

Other Endocrine Complications

Four GCT patients presented with central precocious puberty at diagnosis and four (one ALL with Central Nervous System disease, one medulloblastoma and two GCT patients) were diagnosed to have central precocious puberty after treatments. In addition, three ALL, one GCT and one ependymoma patients in our cohort had T2DM.

Discussion

The impacts of tumours and cancer treatments on the endocrine dysfunction among Hong Kong Chinese children had not been comprehensively reviewed previously. This is the first local study to compare the endocrine complications in a cohort of young survivors of ALL and brain tumour patients in Hong Kong. Our results were in line with previous studies on other ethnic groups overseas.

Seventy-eight patients (33.5% of the cohort) were observed to have at least one endocrine complication in our cohort, which is much lower than most reported cohorts of over 40 to 50%.[6,7] This could be related to different surveillance protocol as well as the different definition of endocrinopathies and different follow-up periods.

Among all the brain tumours patients, craniopharyngioma patients had the highest incidence and earliest onset of endocrine complication. This is probably confounded by the location of the tumours and the focal treatment involving or in close proximity to the hypothalamic-pituitary axis. Ependymoma patients had the least endocrine dysfunction in this study, with only one patient suffered from hypogonadism. This might be due to the fact that local RT in ependymoma patients especially at the posterior fossa did not affect pituitary function much. On the whole, brain tumours were significantly more commonly associated with endocrine complications than ALL patients though. One study suggested medulloblastoma had a higher prevalence of hypoadrenalism than the other brain tumours.[7] However, our study did not see any significant difference in this aspect.

Growth failure can be contributed by GHD, secondary hypothyroidism, hypogonadism or a combination of all three, but they can be distinguished by simple laboratory tests. However, detecting these endocrine complications basing on only history and physical examination could be challenging. For example, patients with both GHD and precocious puberty might present with a 'normal growth velocity' for age and these conditions could be missed if the clinician is just looking at the growth data without proper pubertal assessment or biochemical tests, and that appropriate interventions could not be given within the critical time windows. On the other hand, testicular enlargement, which is the first sign of puberty in males, could be masked in patients with hypogonadism and seminiferous tubules dysfunction, in whom testicular sizes are typically smaller than their corresponding pubertal states. Therefore, assessing the timing of puberty in this group of individuals could be challenging. Regular surveillance with growth data and proper pubertal assessment, together with regular blood tests should be done in all these individuals.

Radiotherapy has been reported to have a positive association with precocious puberty,[5] we did not observe any significant association in our study. However, TBI was found to be associated with hypogonadism. Therefore, proper counselling should be offered and the options of fertility preservation should be discussed with patients and their parents. Currently, we are offering the options of cryopreservation for post-pubertal boys at risk of developing hypogonadism in our unit. In view of more complicated procedures involved in fertility preservation in pre-pubertal boys or girls, this service is not routinely offered to these groups at the moment.

In the current Hong Kong Paediatric Haematology Oncology Study Group follow-up protocol for childhood cancer survivors, regular screening with gonadotrophins levels for patients who have previously received alkylating agents or cranial radiotherapy starts at 13 years old. Thyroid function test and lipid profile are performed every five years or yearly if they were exposed to RT greater than 40 Gy. Comparing to similar guidelines overseas (Table 4), the Children's Oncology Group Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers (COG LTFU Guidelines)[8] suggests annual endocrinology evaluation if RT dose ≥30 Gy to hypothalamic-pituitary axis or more frequently during periods of rapid growth. The UK Children's Cancer Study Group (UKCCSG)[9] recommends monitoring all patients every six months during pubertal stage even without

Table 4 Summary of local and overseas surveillance program, and suggested surveillance program for our local childhood cancer survivors

Sequelae	Risk factors	HKPHOSG	US COG LTFU Guidelines	UKCCSG	SIGN	Suggested surveillance protocol/program
Thyroid	RT to the neck, spine or brain after completion of treatment	Every five years or yearly if they were exposed to RT greater than 40 Gy	Yearly or more frequent screening during periods of rapid growth if receive ≥40 Gy to Cranial	If receive RT to field including thyroid (base of skull, cervical spine)	Annually if receive RT to the neck, spine or brain after completion of treatment	Annually if receive RT to field including thyroid
Puberty	Exposure to alkylating agents, cranial RT	LH and FSH at 13 years old, repeat if clinically indicated after received alkylating agents, cranial RT	LH and FSH if patients are clinically indicated and with signs of accelerated pubertal progression and growth	LH and FSH from approximately 10 years of age	Not specify	Annual growth and pubertal assessment LH and FSH from age of 10, or when clinically indicated
Metabolic syndrome	Steroid, cisplatin, and carboplatin exposure Brian tumour survivor Overweight/obese individuals	Lipid profile every 5 years if received cisplatin, carboplatin	Annual BP and BMI in all survivors Fasting blood glucose OR HbA1c, fasting lipid profile every 2 years	Screen for glycosuria Fasting blood glucose, fasting lipids, HbA1c	Annual BP and BMI in all survivors Fasting glucose, insulin, lipid profile: 2-yearly if obese/ overweight; 5-yearly if normal weight	Annual BP and BMI in all survivors Fasting glucose, insulin, lipid profile: 2-yearly if obese/ overweight; 5-yearly if normal weight
Bone health assessment	ALL treatment Glucocorticoids, methotrexate, 6-mercaptopurine exposure TBI/Cranial radiotherapy, Bone marrow transplantation Endocrine dysfunction (GH deficiency, hypogonadism, hypothyroidism)	Baseline DXA, repeat if clinically indicated	Bone density evaluation (DXA or quantitative CT) at baseline at entry into long-term follow-up, repeat as clinically indicated in at risks individuals	Enquire at long term follow up clinic re: 1) Back pain 2) Fractures Consider evaluation of bone mineral density by DXA scan	DXA 2 years post-end of treatment Repeat if abnormal or clinical change	DXA and lateral spine X-ray/vertebral fracture assessment 2 years post-end of treatment Serial measurements if abnormal clinical change

HKPHOSG: Hong Kong Paediatric Haematology and Oncology Study Group; COG LTFU Guidelines: Children's Oncology Group Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers; UKCCSG: UK Children's Cancer Study Group; SIGN: Scottish Intercollegiate Guidelines Network; ALL=acute lymphoblastic leukaemia; DXA: dual-energy X-ray absorptiometry; BMI: body mass index; BP: blood pressure; GH: growth hormone; CT: computerised tomography; RT: radiotherapy; LH: luteinising hormone; FSH: follicle stimulating hormone; TSH: thyroid stimulating hormone; TBI: total body irradiation

radiotherapy and annual thyroid function test for those who received TBI and radiotherapy to thyroid. As for metabolic syndrome, the Scottish Intercollegiate Guidelines Network (SIGN) suggests to screen metabolic profiles (fasting glucose, insulin and lipids) every five years and every two years for normal weight and overweight survivors respectively.[10] In contrast, we only screen lipid profiles every five years for patients who were treated with cisplatin and carboplatin, while other metabolic profiles are not included. Of note, the prevalence of T2DM and metabolic syndrome were low in our cohort, which is different from other populations. This could also be related to different surveillance protocols on this aspect. With the overseas experience, together with recent findings from both the UK[9] and USA[8] groups showing the association between TBI and central fat accumulation with increased risk of diabetes in young adulthood, our local surveillance protocol should be updated.

Our current osteoporosis surveillance program is also suboptimal. This might potentially prevent the patients from receiving timely and appropriate interventions. In other overseas studies, 13%-21% ALL;[11] 43% of intracranial germ cell tumour survivors[12]; and 47% of survivors of brain tumours[13] were found to have decreased bone mineral density (BMD). If the survivors could not reach optimal bone mass during childhood, it is more likely to develop osteoporosis and fracture in their later life. Therefore, a better surveillance program should be implemented for better care of this group of individuals. Evaluations of BMD with dual-energy X-ray absorptiometry (DXA) or quantitative CT scan are widely recommended in different guidelines. UKCCSG and SIGN recommend it to be done one year after bone marrow transplantation or two years after the end of treatment. In addition to low BMD, the incidental vertebral fracture was reported in up to one-quarter of children with ALL in the 4 years after diagnosis.[14] Therefore, regular vertebral fracture assessment, which could be done simply with a lateral spine X-ray from T4 to L4, should also be included as part of the bone health assessment among these ALL survivors. The overseas surveillance protocols and our proposed recommendations on endocrinopathies screening, together with the classes of chemotherapeutic agents used in our local ALL and brain tumour protocols were summarised in Tables 4 and 5.

With a high percentage of endocrinopathies among ALL and brain tumours survivors, early identifications and timely treatment is needed to optimise physical growth and development, as well as cognitive and psychosocial well-being in this group of patients. This requires multidisciplinary inputs from oncologists, endocrinologists and reproduction specialists, delivering continual care from acute cancer treatment to long-term follow-up of late endocrine effects spanning through childhood to adulthood. Treatments of various endocrinopathies are generally safe and well-tolerated. This mainly consists of supplementation of the deficient hormones, e.g. thyroxine, hydrocortisone and DDAVP replacement for hypothyroidism, adrenal insufficiency and diabetes insipidus respectively. Growth hormone (GH) treatment had been shown to improve the final height of cancer survivors with GHD, especially if it could be initiated at younger bone age[15] and there is no evidence that GH treatment would increase the risk of recurrence.[16] Nevertheless, most guidelines recommend waiting for one year after completion of cancer treatment before initiation of GH treatment.[16]

This study has several limitations. This is a single institution-based review with potential selection bias. In addition, some old medical records contained incomplete data for analysis. Since we have a relatively larger number of brain tumours patients in comparison to ALL patients in our cohort, the prevalence of endocrine complications might be over-estimated among these childhood cancer survivors. Most patients received a combination of treatments; hence it is difficult to conclude on the contribution of individual treatment to endocrinopathy. Finally, some apparent risk factors were not statistically significant which may be due to the relatively small sample size of this study.

Conclusion

Brain tumour patients are more likely to develop endocrine complications than ALL patients. Radiotherapy appeared to be most significant risk factor. An updated surveillance program involving multidisciplinary long-term follow-up by paediatric oncologists and paediatric endocrinologists, together with proper patients' educations should be considered for Hong Kong Chinese patients.

Declaration of Interest

All authors have disclosed no conflicts of interest.

Table 5 SCurrent childhood cancer treatments in Hong Kong, and the corresponding at-risk endocrine issues and suggested surveillance

Condition	Protocol	Treatments (endocrine issues at risk)	Suggested surveillance for endocrinopathies *(Brain tumour around the pituitary regions could present with panhypopituitarism at diagnosis or after initial surgery – full pituitary hormonal assessment indicated)*
ALL	Before 2002: Hong Kong-Singapore Acute Lymphoblastic Leukaemia 97 2002 to 2007: ALL IC BFM 2002 2008 onwards: CCLG ALL 2008 study	Vincristine Daunorubicin L-asparaginase *(bone health)* Dexamethasone *(bone health)* Methotrexate *(bone health)* Cytarabine Mercaptopurine Thioguanine Cyclophosphamide *(gonadal dysfunction)* Etoposide Craniospinal RT for CNS disease *(growth and pubertal problems,central adrenal insufficiency)*	• DXA and lateral spine X-ray/vertebral fracture assessment 2 years post-end of treatment; serial measurements if abnormal clinical changes • Annual growth and pubertal assessment (monitor for both early and delayed puberty) • LH and FSH monitoring from age of 10, or when clinically indicated • If history of craniospinal RT: - Annual thyroid exam palpation; post-RT 5 years: annual TSH/fT4 and regular USG thyroid every 2-3 years or earlier if clinically indicated - Annual 8am cortisol test
Germ cell tumour	HKPHOSG CNS Germ Cell Tumour Protocol July 2014	Etoposide Carboplatin *(metabolic syndrome)* Ifosfamide *(metabolic syndrome)* Craniospinal RT *(thyroid nodules, growth and pubertal problems, central adrenal insufficiency)*	• Annual blood pressure and BMI measurement • Fasting glucose, insulin, lipid profile: 2-yearly if obese/overweight; 5-yearly if normal weight • Annual thyroid exam palpation; post-RT 5 years: annual TSH/fT4 and regular USG thyroid every 2-3 years or earlier if clinically indicated • Annual growth and pubertal assessment (monitor for both early and delayed puberty); LH and FSH from age of 10, or when clinically indicated • Annual 8am cortisol test
Ependymoma	SIOP Ependymoma 99	Surgical resection *(occurrence of endocrinopathies depends on location of tumour and extent of surgery)* Cyclophosphamide *(gonadal dysfunction)* Vincristine Etoposide RT to tumour bed *(if involves craniospinal region: at risk of thyroid nodules, growth and pubertal problems, central adrenal insufficiency)*	• Annual growth and pubertal assessment (monitor for both early and delayed puberty) • LH and FSH monitoring from age of 10, or when clinically indicated • If any craniospinal RT: - Annual thyroid exam palpation; post-RT 5 years: annual TSH/fT4 and regular USG thyroid every 2-3 years or earlier if clinically indicated - Annual 8 am cortisol test
Medulloblastoma	HKPGOSG-PNET-CNS-2000	Surgical resection *(depends on location of tumour and extent of surgery)* Lomustine Cisplatin *(metabolic syndrome)* Vincristine Craniospinal RT *(thyroid nodules, growth and pubertal problems, central adrenal insufficiency)*	• Annual BP and BMI measurement • Fasting glucose, insulin, lipid profile: 2-yearly if obese/overweight; 5-yearly if normal weight • Annual thyroid exam palpation; post-RT 5 years: annual TSH/fT4 and regular USG thyroid every 2-3 years or earlier if clinically indicated • Annual growth and pubertal assessment (monitor for both early and delayed puberty) • LH and FSH from age of 10, or when clinically indicated • Annual 8 am cortisol test
Craniopharyngioma	No unified protocol in Hong Kong at the moment with individualised treatment	Surgical resection *(depends on tumour locations and extent of surgery - hypothalamic obesity, panhypopituitarism, diabetes insipidus)* Focal RT *(growth and pubertal problems, central adrenal insufficiency)* Intra-cystic interferon	• Annual growth and pubertal assessment (monitor for both early and delayed puberty) • LH and FSH from age of 10, or when clinically indicated • Annual 8 am cortisol test • Annual BP and BMI measurement; if obese, screen for obesity-related morbidity
Children <3 years old with medulloblastoma or ependymoma	Baby brain tumour protocol (HKPHOSG 1994)	Surgical resection (depends on location of tumour and extent of surgery) Cyclophosphamide (gonadal dysfunction) Cisplatin (metabolic syndrome) Etoposide Vincristine	• Annual growth and pubertal assessment (monitor for both early and delayed puberty) • LH and FSH monitoring from age of 10, or when clinically indicated • Annual BP and BMI measurement • Fasting glucose, insulin, lipid profile: 2-yearly if obese/overweight; 5-yearly if normal weight

ALL=acute lymphoblastic leukaemia; DXA: dual energy X-ray absorptiometry; RT: radiotherapy; CNS: central nervous system; USG: ultrasonography; LH: luteinising hormone; FSH: follicle stimulating hormone; BMI: body mass index; BP: blood pressure; GH: growth hormone; TSH: thyroid stimulating hormone; fT4: free thyroxine; CT: computerised tomography

References

1. Cancer Research UK. Cancer statistics 2014 [accessed Nov 21, 2014]. Available from www.cancerresearchuk.org/cancer-info/cancerstats/childhoodcancer.
2. Howlader N, Noone AM, Krapcho M, et al. Cancer Statistics Review. SEER Cancer Statistics Review, 1975-2014, National Cancer Institute. Available from https://seer.cancer.gov/archive/csr/1975_2014/
3. Oeffinger KC, Mertens AC, Sklar CA, et al. Chronic health conditions in adult survivors of childhood cancer. N Engl J Med 2006;355:1572-82.
4. Diller L, Chow EJ, Gurney JG, et al. Chronic disease in the Childhood Cancer Survivor Study cohort: a review of published findings. J Clin Oncol 2009;27:2339-55.
5. Chemaitilly W, Sklar CA. Endocrine complications in long-term survivors of childhood cancers. Endocr Relat Cancer 2010;17:R141-59.
6. Patterson BC, Wasilewski-Masker K, Ryerson AB, Mertens A, Meacham L. Endocrine health problems detected in 519 patients evaluated in a pediatric cancer survivor program. J Clin Endocrinol Metab 2012;97:810-8.
7. Shalitin S, Gal M, Goshen Y, Cohen I, Yaniv I, Phillip M. Endocrine outcome in long-term survivors of childhood brain tumors. Horm Res Paediatr 2011;76:113-22.
8. Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent and Young Adult Cancers, Version 4.0. Monrovia, CA. Children's Oncology Group October 2013.
9. Skinner R, Wallace WHB, Levitt GA. Therapy based long-term follow-up. The United Kingdom Children's Cancer Study Group (UK CCSG) Late Effects Group 2005; 2nd edition.
10. Scottish Intercollegiate Guidelines Network (SIGN). Long term follow up of survivors of childhood cancer. SIGN 2013;(SIGN publication no. 132): Available from www.sign.ac.uk.
11. van der Sluis IM, van den Heuvel-Eibrink MM, Hahlen K, Krenning EP, de Muinck Keizer-Schrama SM. Altered bone mineral density and body composition, and increased fracture risk in childhood acute lymphoblastic leukemia. J Pediatr 2002;141:204-10.
12. Kang MJ, Kim SM, Lee YA, Shin CH, Yang SW, Lim JS. Risk factors for osteoporosis in long-term survivors of intracranial germ cell tumors. Osteoporos Int 2012;23:1921-9.
13. Wilson CL, Ness KK. Bone mineral density deficits and fractures in survivors of childhood cancer. Curr Osteoporos Rep 2013;11:329-37.
14. Cummings EA, Ma J, Fernandez CV, et al. Incident Vertebral Fractures in Children With Leukemia During the Four Years Following Diagnosis. The Journal of clinical endocrinology and metabolism 2015;100:3408-17.
15. Brownstein CM, Mertens AC, Mitby PA, et al. Factors that affect final height and change in height standard deviation scores in survivors of childhood cancer treated with growth hormone: a report from the childhood cancer survivor study. J Clin Endocrinol Metab 2004;89:4422-7.
16. Raman S, Grimberg A, Waguespack SG, et al. Risk of Neoplasia in Pediatric Patients Receiving Growth Hormone Therapy-A Report From the Pediatric Endocrine Society Drug and Therapeutics Committee. J Clin Endocrinol Metab 2015;100:2192-203.

Appendix 1. Hong Kong childhood cancer treatment protocol

Conditions	Protocol
Acute lymphoblastic leukaemia	Before 2002: Hong Kong-Singapore Acute Lymphoblastic Leukaemia 97 2002 to 2007: ALL IC BFM 2002 2008 onwards: CCLG ALL 2008 study
Germ cell tumour	HKPHOSG CNS Germ Cell Tumour Protocol July 2014
Ependymoma	SIOP Ependymoma 99
Medulloblastoma	HKPGOSG-PNET-CNS-2000
Craniopharyngioma	No unified protocol in Hong Kong at the moment with individualised treatment
Children <3 years old withmedulloblastoma or ependymoma	Baby brain tumour protocol (HKPHOSG 1994)

Appendix 2. Assessment of endocrine function in the Department of Paediatrics and Adolescent Medicine, Queen Mary Hospital, Hong Kong

Gonadal function assessment

Pubertal status was assessed by Tanner staging. Biochemical screening using follicle stimulating hormone (FSH), luteinizing hormone (LH), estradiol, and testosterone would be performed in those received alkylating agents, cranial or pelvic radiotherapy, and ovarian/testicular surgery at the age of 13 years or when they are suspected to have pubertal problems.

Primary hypogonadism is defined as elevated gonadotropins. Secondary hypogonadism is defined as low estradiol or testosterone for age with inappropriately normal or low gonadotropins.

Precocious puberty is defined as onset of breast development before the age of 7 years or onset of menarche before the age of 10 years in girls, and onset of testicular enlargement before the age of 9 years in boys.

Growth assessment

Height was measured regularly during follow up and plotted into the growth chart on every visit. Patients with reduced growth velocity would be tested for growth hormone deficiency by measurement of IGF-1 and growth hormone provocation tests (clonidine test and insulin tolerance tests).

Thyroid function assessment

Thyroid function was assessed by thyroid stimulating hormone (TSH) and free thyroxine (fT4). It would be checked in those who had received cranial or cervical radiotherapy or thyroid surgery. Primary hypothyroidism defined as low fT4 and high TSH. Compensated hypothyroidism defined as normal fT4 and high TSH. Central hypothyroidism defined as low fT4 and low or inappropriately normal TSH.

Adrenal function assessment

Morning cortisol levels used to screen for adrenal insufficiency. If the cortisol level was low then further testing by short synacthen test was carried out.

Glucose metabolism

Fasting glucose (FG), random glucose (RG) and oral glucose tolerance test (OGTT) were used to screen for impaired fasting glucose, impaired glucose tolerance and diabetes mellitus. Impaired fasting glucose was defined as FG 5.6-6.9 mmol/L. Impaired glucose tolerance defined as plasma glucose ≥7.8 and ≤11.1 mmol/L at 2 hours post 75 gram oral glucose. Diabetes mellitus (DM) was defined as FG ≥7 mmol/L or RG ≥11.1 mmol/L or OGTT plasma glucose ≥11.1 mmol/L at 2 hours. These tests were not routinely performed unless patients had special clinical indications e.g. severe obesity, strong family history of diabetes mellitus etc.