SARI PIETILÄ

Late Effects in Pediatric Brain Tumor Survivors

A study on renal, skeletal and metabolic sequelae and neurological outcome

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ACADEMIC DISSERTATION
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Contents

List of original publications

This thesis is based on the following four original publications, which are referred to in the text by their roman numerals I–IV. Some additional unpublished data are also presented.

I Pietilä S, Ala-Houhala M, Lenko HL, Harmoinen AP, Turjanmaa V, Mäkipernaa A. Renal impairment and hypertension in brain tumor patients treated in childhood are mainly associated with cisplatin treatment. Pediatr Blood Cancer 2005;44:363–369.

II Pietilä S, Sievänen H, Ala-Houhala M, Koivisto AM, Lenko HL, Mäkipernaa A. Bone mineral density is reduced in brain tumour patients treated in childhood. Acta Paediatr 2006;95:1291–1297.

III Pietilä S, Mäkipernaa A, Sievänen H, Koivisto AM, Wigren T, Lenko HL. Obesity and metabolic changes are common in young childhood brain tumor survivors. Pediatr Blood Cancer 2009;52:853–859.

IV Pietilä S, Korpela R, Lenko HL, Haapasalo H, Alalantela R, Nieminen P, Koivisto AM, Mäkipernaa A. Neurological outcome of childhood brain tumor survivors. J Neurooncol 2012;108:153–161.

Abbreviations

$1,25(OH)_2D$	1,25-dihydroxyvitamin D, 1,25-dihydroxycholecalciferol
"8 in 1"	eight drugs in one day
25(OH)D	25-hydroxyvitamin D, 25-hydroxycholecalciferol
ACTH	adrenocorticotropin hormone
ADH	antidiuretic hormone
ALL	acute lymphoblastic leukemia
ANCOVA	analysis of covariance
ANOVA	analysis of variance
ARA-C	cytarabine
BCNU	carmustine
BMC	bone mineral content
BMD	bone mineral density
BMI	body mass index
BP	blood pressure
BT	brain tumor
CAP	the College of American Pathologists
CCNU	lomustine
CCSS	the Childhood Cancer Survivor Study
CNS	central nervous system
CSF	cerebrospinal fluid
DXA	dual-energy X-ray absorptiometry
FM	fat mass
FSH	follicle-stimulating hormone
GFR	glomerular filtration rate
GH	growth hormone
GHD	growth hormone deficiency
Gy	Gray
HDL-C	high-density lipoprotein cholesterol
HPA	hypothalamic-pituitary axis
IARC	the International Agency for Research on Cancer
ICCC	the International Classification of Childhood Cancer
ICD-O	the International Classification of Diseases for Oncology
ICD-10	the International Statistical Classification of Diseases, Injuries and Causes of Death
ICF	the International Classification of Functioning, Disability and Health

IDF	the International Diabetes Federation
IGF-1	insulin-like growth factor-1
IQ	intelligence quotient
ISCD	the International Society for Clinical Densitometry
LBM	lean body mass
LDL-C	low-density lipoprotein cholesterol
LH	luteinizing hormone
NF1	neurofibromatosis 1
NIH	the National Institutes of Health
PBM	peak bone mass
PNET	primitive neuroectodermal tumor
PTH	parathyroid hormone
SD	standard deviation
SDS	standard deviation score
SNOMED	the Systematized Nomenclature of Medicine
T4	thyroxine
TBBMD	total body bone mineral density
TC	total cholesterol
TSH	thyroid-stimulating hormone
VM-26	teniposide
VMH	ventromedial hypothalamus
VP	ventriculoperitoneal
VP-16	etoposide
WHO	the World Health Organization

Abstract

Background: Brain tumors are the most common solid tumors in children and the second most common form of cancer occurring in childhood. In Finland about 40–50 childhood brain tumors are diagnosed yearly. Treatment modalities include surgery, radiotherapy and chemotherapy. As a result of improvements in diagnosis and treatment, the number of long-term survivors has increased. These survivors are at high risk of chronic health conditions later in life. Adverse late effects may be due to the tumor itself or consequences of the treatment.

Aims: The aim of this study was to assess the renal consequences of treatment, the risk of hypertension, bone health, prevalence of obesity and metabolic changes, and neurological outcome, and to identify factors associated with problems discovered in childhood brain tumor survivors.

Subjects and Methods: A total of 104 primary brain tumor patients diagnosed at under 17 years of age between 1983–1997 were treated in Tampere University Hospital. When the study began in summer 1998, 24 of them had died. Of the 80 survivors 75 potentially eligible patients were invited to attend this cross-sectional study. Fifty-two (69%) participated in the study and were examined at a mean age of 14.2 years (range 3.8–28.7 years) after a mean follow-up time of 7.5 years (1.5–15.1 years). Diagnosed brain tumors included both benign and malignant tumors. The most common single tumor type was pilocytic astrocytoma. All 52 participants had undergone one or more surgical procedures. Twenty (38%) were treated with radiotherapy and 17 (33%) with chemotherapy; 14 (27%) received both. Thirteen (25%) had a residive or residual tumor upon evaluation. Thirty (58 %) had had hydrocephalus; all except one had been shunted. One third of all patients had needed shunt revisions, 10 (19% of all) more than one.

Results: Five out of 14 patients treated with cisplatin had renal glomerular dysfunction (GFR<87 ml/min/1.73m^2) immediately after treatment. They had received high cumulative doses of cisplatin. During the study recovery from renal glomerular dysfunction was observed in one case; 4/14 (29%) thus had abnormal GFR at the time of study. There were several signs of tubular dysfunction in the cisplatin group. Hypomagnesemia was found in 71%. In addition, low plasma phosphate and potassium, hyperuricemia, metabolic alkalosis and tubular proteinuria were more common in patients who had received cisplatin. After cisplatin treatment renal glomerular dysfunction appeared overall to be permanent, and persistent and even progressive changes in renal tubular function were seen.

Approximately every fifth patient had elevated blood pressure. This was associated with cisplatin treatment, cranial irradiation, renal glomerular dysfunction and hypomagnesemia. The risk of elevated blood pressure was higher if the patients had been exposed to both cisplatin and cranial irradiation.

Fifteen out of 46 (33%) had low total body bone mineral density (Z-score < -2.0). Craniospinal irradiation was significantly associated with low Z-score.

Ten (19%) were overweight and four (8%) were obese. Dual-energy X-ray absorptiometry showed 16/46 (35%) to be obese. Central obesity was found in 11 (21%). Thirteen (25%) had hypercholesterolemia, 14 (27%) had raised low-density lipoprotein cholesterol, nine (17%) reduced high-density lipoprotein cholesterol, five (10%) raised triglycerides, four (8%) metabolic syndrome, two (4%) hyperinsulinemia and five (10%) hyperuricemia. Cranial irradiation, hypothalamic/hypophyseal damage, growth hormone deficiency and/or impaired mobility were associated with a higher risk of obesity and metabolic changes. Growth hormone supplementation alleviated adverse metabolic outcomes among brain tumor survivors with growth hormone deficiency.

The neurological status was abnormal in 36/52 (69%) cases. While all were ambulatory, only 50% showed normal motor function. Twenty-nine percent showed clumsiness/mild asymmetry, 21% hemiparesis. The median full-scale IQ was 85 (39–110) in 21 of the 30 participants between 6 and 16 years of age; in 29% IQ was <70. Thirty of the 44 school-aged subjects attended school with normal syllabus, 32% needed special education. Six of the 16 patients over 18 years of age were working. According to structured interview 87% coped normally in daily living. Regarding quality of life, 71% lived an active life with minor disabilities, while 29% had major neurological, cognitive and social disabilities, 8% being incapable of self-care. Supratentorial/hemispheric tumor location, tumor reoperations, shunt revisions and chemotherapy were associated with neurological, cognitive and social disabilities.

Conclusions: Most of the childhood brain tumor survivors lived an active life with minor disabilities, but a wide range of adverse renal, vascular, metabolic, skeletal and neurological late effects with multifactorial etiology were observed. Neurological and neurocognitive impairment had the most notable impact on their daily life. The significance of the other observed late effects might be emphasized as the survivors age. With regular follow-up and early intervention it might be possible to improve the quality of life and diminish morbidity in later years. All survivors need life-long, tailor-made multiprofessional support and follow-up.

Tiivistelmä

Lapsena sairastetun aivokasvaimen myöhäisvaikutukset

Taustaa: Aivokasvaimet ovat lasten tavallisimpia kiinteitä kasvaimia ja toiseksi yleisin lapsuudessa esiintyvä syövän muoto. Suomessa diagnosoidaan lapsilla vuosittain noin 40–50 aivokasvainta. Hoitomuotoja ovat leikkaushoito, sädehoito ja solunsalpaajalääkehoito. Parantuneen diagnostiikan ja hoidon myötä pitkäaikaisselviytyneiden osuus on kasvanut. Aivokasvaimen sairastaneilla on suuri riski kroonisiin terveysongelmiin myöhemmässä elämässä. Aivokasvaimiin liittyvät haitalliset myöhäisvaikutukset voivat johtua kasvaimesta tai olla hoitojen seurausta.

Tutkimuksen tarkoitus: Tarkoitus oli selvittää lapsuudessa aivokasvaimeen sairastuneiden pitkäaikaisselviytyjien hoitojen munuaisvaikutuksia, kohonneen verenpaineen riskiä, luustovaikutuksia, lihavuuden ja aineenvaihdunnan muutosten esiintyvyyttä sekä neurologista selviytymistä, ja löytää havaittuihin ongelmiin yhteydessä olevat tekijät.

Aineisto ja menetelmät: Vuosina 1983–1997 alle 17-vuotiaana diagnosoituja Tampereen yliopistollisessa sairaalassa hoidettuja aivokasvainpotilaita oli yhteensä 104. Heistä 24 oli kuollut tutkimuksen alkaessa kesällä 1998. Elossa olevista 80 potilaasta tähän poikkileikkaustutkimukseen kutsuttiin 75 tutkimukseen soveltuvaa potilasta. Heistä 52 (69%) osallistui tutkimukseen. Osallistujien keski-ikä oli 14.2 (vaihteluväli 3.8–28.7) vuotta ja keskimääräinen seuranta-aika 7.5 (1.5–15.1) vuotta. Diagnosoituihin aivokasvaimiin kuului sekä hyvän- että pahanlaatuisia kasvaimia. Tavallisin yksittäinen kasvaintyyppi oli pilosyyttinen astrosytooma. Jokaiselle 52 tutkimukseen osallistuneelle oli tehty yksi tai useampia kirurgisia toimenpiteitä kasvaimen takia. Sädehoitoa oli saanut 20 (38%), sytostaattihoitoa 17 (33%) ja molempia hoitoja 14 (27%). Arviointihetkellä 13:lla (25%) oli joko jäännöskasvainta tai uusiutunut kasvain. Kolmellakymmenellä (58%) oli ollut hydrokefalus, joka yhtä lukuun ottamatta oli hoidettu shuntilla. Kaikista potilaista 1/3 oli tarvinnut shunttirevision, 10 (19% kaikista) useamman kuin yhden kerran.

Tulokset: Viidellä 14:stä sisplatiinilla hoidetuista potilaasta oli munuaisten vajaatoiminta (GFR<87 ml/min/1.73 m^2) heti hoidon jälkeen. Sisplatiinin kokonaisannos oli heillä kaikilla korkea. Tutkimuksen yhteydessä huomattiin heistä yhden munuaisten vajaatoiminnan korjautuneen, ja lievä munuaisten vajaatoiminta todettiin 4/14 (29%) sisplatiiniryhmässä. Sisplatiinia saaneilla oli useita merkkejä tubulusvauriosta. Hypomagnesemiaa oli 71%:lla. Lisäksi fosfaatin ja kaliumin matalat plasmapitoisuudet, hyperurikemia, metabolinen alkaloosi ja tubulaarinen

proteinuria olivat tavallisempia sisplatiinihoitoa saaneilla. Sisplatiinihoidon jälkeinen munuaisten vajaatoiminta vaikuttaa olevan pääosin pysyvä ja pysyviä, jopa eteneviä muutoksia oli havaittavissa munuaisten tubulustoiminnassa.

Noin joka viidennellä potilaalla oli kohonnut verenpaine. Kohonnut verenpainetaso oli yhteydessä pään sädehoitoon, sisplatiinihoitoon, munuaisten vajaatoimintaan ja hypomagnesemiaan, ja riski siihen lisääntyi, jos potilas oli saanut sekä sisplatiinihoitoa että pään sädehoitoa.

Viidellätoista 46:sta (33%) oli pieni koko kehon luun mineraalitiheys (Z-arvo < -2.0). Pään ja spinaalikanavan sädehoito oli yhteydessä matalaan Z-arvoon.

Ylipainoisia oli 10 (19%) ja lihavia neljä (8%). Kaksienergiaisella röntgenabsorptiometrialla arvioiden 16/46 (35%) oli lihavia. Keskivartalolihavuutta oli 11:llä (21%). Hyperkolesterolemia oli 13:lla (25%), kohonnut LDL-kolesteroliarvo 14:llä (27%), matala HDL-kolesteroliarvo yhdeksällä (17%), korkea triglyseridiarvo viidellä (10%), metabolinen oireyhtymä neljällä (8%), hyperinsulinemia kahdella (4%) ja hyperurikemia viidellä (10%). Pään sädehoito, hypotalamuksen/hypofyysin vaurio, kasvuhormonin vajaaeritys ja/tai heikentynyt liikuntakyky olivat yhteydessä lisääntyneeseen lihavuuden ja metabolisten muutosten riskiin. Kasvuhormonihoito vähensi niiden aivokasvaimesta selvinneiden metabolisia ongelmia, joilla oli ollut todettavissa kasvuhormonin vajaaeritys.

Neurologinen status oli poikkeava 36/52 (69%) tutkituista. Kaikki pystyivät kävelemään, mutta vain 50%:lla motorinen toiminta oli normaalia. Kömpelyyttä tai pientä puolieroa havaittiin 29%:lla ja hemipareesi oli 21%:lla. Psykologisiin tutkimuksiin osallistui 21 (70%) 30:stä 6–16-vuotiaasta: mediaani ÄO oli 85 (39–110), 29%:lla ÄO oli < 70. Kouluikäisistä 30/44 oli normaaliopetuksessa, 32% tarvitsi erityisopetusta. Yli 18-vuotiaista työssä oli 6/16. Strukturoidun haastattelun perusteella arvioiden 87% selvisi normaalisti jokapäiväisessä elämässään. Elämänlaatua arvioitaessa 71% eli aktiivista elämää kärsien vain vähäisistä haitoista, 29%:lla oli merkittäviä neurologisia, kognitiivisia ja sosiaalisia ongelmia, 8% ei tullut toimeen itsenäisesti. Kasvaimen sijainti supratentoriaalisesti tai isoaivohemisfäärillä, uusintaleikkaukset, shunttirevisiot ja kemoterapia olivat yhteydessä neurologisiin, kognitiivisiin ja sosiaalisiin ongelmiin.

Johtopäätökset: Useimmat lapsena aivokasvaimen sairastaneet elivät aktiivista elämää, vaikka heillä oli todettavissa hyvin monenlaisia munuaisten toimintaan, verenkiertoon, aineenvaihduntaan, luustoon ja neurologiseen selviytymiseen liittyviä myöhäisvaikutuksia. Eniten päivittäiseen elämään vaikuttivat neurologiset ja neurokognitiiviset myöhäisvaikutukset. Muiden myöhäisvaikutusten merkitys saattaa korostua pitkäaikaisselviytyjien vanhentuessa. Säännöllisellä seurannalla ja varhaisella ongelmiin puuttumisella voi olla mahdollista parantaa elämänlaatua ja vähentää sairastuvuutta myöhemmässä elämässä. Kaikki aivokasvaimesta selvinneet tarvitsevat yksilöllisesti suunniteltua, elinikäistä moniammatillista tukea ja seurantaa.

1. Introduction

Brain tumors (BTs) are a heterogeneous group of neoplasms which includes morphologically both malignant and benign variants. They are the most common solid tumors in children, and the second most common form of cancer occurring in childhood (Parkin *et al.* 1998, Smith & Gloecker Ries 2002, Steliarova-Foucher *et al.* 2004). In Finland about 40–50 childhood BTs are diagnosed yearly. Survival rates among childhood BT patients have improved over recent decades, this related to advances in diagnosis and treatment; approximately 2 out of every 3 pediatric patients with BTs will be long-term survivors (Gatta *et al.* 2005). However, these survivors are at high risk of chronic health conditions later in life (Dickerman 2007). The challenge to treatment protocols is to maintain a balance between effective therapy and acceptable toxicity.

This study was initiated to investigate the long-term effects of childhood BTs and their treatment on the health of survivors. The specific aims were to assess the renal consequences of the treatment, the risk of hypertension, the prevalence of low bone mineral density (BMD), obesity and metabolic changes and the neurological outcome in survivors, and to identify factors associated with problems observed.

2. Review of the literature

2.1 Incidence of childhood brain tumors

BTs are a heterogeneous group of neoplasms comprising morphologically both malignant and benign variants. They are the most common solid tumors in children, and the second most common form of cancer occurring in childhood (Parkin *et al.* 1998, Smith & Gloecker Ries 2002, Steliarova-Foucher *et al.* 2004). The Nordic countries have a high incidence of childhood BTs (Parkin *et al.* 1998, Magnani *et al.* 2001, Peris-Bonet *et al.* 2006, Lannering *et al.* 2009). Results from an International Agency for Research on Cancer (IARC) study from the 1980s and 1990s showed central nervous system (CNS) tumor incidence rates ranging from 2.5 to 4.1/100 000 children below 15 years of age; Finland had an incidence of 3.9 and Sweden 4.1/100 000 children (Parkin *et al.* 1998). The mean annual incidence of CNS tumors in children below 15 years of age in 1984–2005 in Sweden was 4.2/100 000, and it has not increased during the study period (Lannering *et al.* 2009). In 2007 the Finnish population of children aged 0–14 years was about 900 000 (Finnish Cancer Registry 2009). In 1978–1997 758 CNS tumors were registered in Finland in children aged 0–14 years (Peris-Bonet *et al.* 2006), which means about 38 CNS tumors per year. Intraspinal tumors, but not intracranial germ cell tumors, were included in the above-mentioned calculations (Peris-Bonet *et al.* 2006, Lannering *et al.* 2009). In 2007 in Finland 41 CNS cancers were diagnosed in children below 15 years of age, 16 in children and adolescents aged 15–19 years. In these figures spinal tumors were included but benign tumors, e.g. craniopharyngiomas, were excluded (Finnish Cancer Registry 2009). Some 40–50 new BTs in children aged 0–16 years can thus be expected in Finland every year, and in the Tampere region, with a current population of approximately 1.2 million (Hospital District of Pirkanmaa 2012) and children aged 0–16 years approximately 220 000, about nine to eleven new childhood BT diagnoses per year.

2.2 Classification and localization

The classification of tumors in children is based on morphological findings (Steliarova-Foucher *et al.* 2005, Lannering *et al.* 2009). The World Health Organization (WHO) proposed a uniform consensus nomenclature for CNS tumors in 1979 (Kleihues *et al.* 1993). The fourth edition of the WHO classification of CNS tumors was published in 2007 (Louis *et al.* 2007a). The International Classification of Diseases for Oncology (ICD-O) has been used since 1976, principally in cancer registries for coding the site (topography) and the histology (morphology) of neoplasms, usually obtained from a pathology report (Louis *et al.* 2007b). The ICD-O histology codes have been adopted by the Systematized Nomenclature of Medicine (SNOMED), issued by the College of American Pathologists (CAP). The ICD-O topography codes largely correspond to those of the tenth edition of the International Statistical Classification of Diseases, Injuries and Causes of Death (ICD-10) of WHO. The WHO classification of CNS tumors contains the morphology (ICD-O) codes. The International Classification of Childhood Cancer (ICCC) is based on the ICD-O classification (Steliarova-Foucher *et al.* 2005, Lannering *et al.* 2009).

In 1993 WHO published a grading system for CNS tumors (Kleihues *et al.* 1993). It is a 'malignancy scale' ranging across a wide variety of neoplasms rather than being a strict histological grading system (Kleihues *et al.* 1993, Louis *et al.* 2007b). The WHO grading system is a means of predicting the biological behavior of a neoplasm (Louis *et al.* 2007b). In the clinical setting, tumor grade is a key factor influencing the choice of therapies, particularly in determining the use of adjuvant radiation and specific chemotherapy protocols. Grade I applies to lesions with low proliferative potential and the possibility of cure following surgical resection alone (Kleihues *et al.* 1993, Louis *et al.* 2007b). Neoplasms designated grade II are generally infiltrative in nature and, despite low-level proliferative activity, often recur. Some type II tumors tend to progress to higher grades of malignancy, for example, low-grade diffuse astrocytomas, which transform to anaplastic astrocytoma and glioblastoma. Similar transformation occurs in oligodendroglioma and oligoastrocytomas. The designation WHO grade III is generally reserved for lesions with histological evidence of malignancy, including nuclear atypia and brisk mitotic activity. In most settings, patients with grade III tumors receive adjuvant radiation and/or chemotherapy. The designation WHO grade IV is assigned to cytologically malignant, mitotically active, necrosis-prone neoplasms typically associated with rapid pre- and postoperative disease evolution and a fatal outcome. Examples of grade IV neoplasms include most embryonal neoplasms. Widespread infiltration of surrounding tissue and a propensity to craniospinal dissemination characterize some grade IV neoplasms.

CNS primitive neuroectodermal tumors (PNETs) were reclassified in the latest WHO classification (Louis *et al.* 2007a). Instead of the term supratentorial PNET, the term CNS PNET is recommended for undifferentiated or poorly differentiated embryonal tumors occurring at any extracerebellar site in the CNS (Louis *et al.* 2007b). Tumors classified as nonmalignant in the second edition of ICD-O (ICD-O-2) may represent up to one-third of intracranial and intraspinal tumors in children, and classification of pilocytic astrocytoma, one of the most common childhood CNS tumors, as nonmalignant would increase this proportion to more than one half (Steliarova-Foucher *et al.* 2005).

Pediatric CNS tumors differ considerably from their adult counterparts by histology and anatomical site. The main diagnostic groups in children are astrocytoma (38–50%, grade I–IV), ependymoma (8–14%, grade I–III), PNET (grade IV), including medulloblastoma (16–25%, grade IV), and other gliomas (4–16%, grade I–III) (Parkin *et al.* 1998). CNS PNETs and medulloblastomas decrease in incidence with age (Kieran *et al.* 2010). The majority of astrocytomas in children are low-grade tumors. In adults, meningiomas, which are rare in children, and high-grade astrocytomas are common (Robertson 1998, Kieran *et al.* 2010). In children, 50–60% of tumors arise below the tentorium, whereas in adults, most arise above it (Robertson 1998).

2.3 Treatment

BTs are treated according to their histology, size and location, with a number of factors such as age, comorbid medical conditions and impact on quality of life, also considered in treatment planning. Treatment may include surgery, radiotherapy and/or chemotherapy.

2.3.1 Surgery

Virtually all pediatric BTs are first treated with surgery if possible, although the prospect of surgical cure is usually limited to low-grade astroglial tumors (Anderson *et al.* 2001, Robertson 2006). Tumor site might prevent operation and even biopsy. For example, diffuse brainstem gliomas are inoperable by reason of their location (Kivivuori *et al.* 2011, Pollack & Jakacki 2011). The two primary goals of surgery in pediatric BTs are diagnosis and cytoreduction (Anderson *et al.* 2001, Pollack & Jakacki 2011). Surgery is normally required to establish a definitive diagnosis. Direct open biopsies are the preferred method of obtaining tissue and often allow a simultaneous reduction of tumor burden. Surgical resection as

extensive as possible improves outcome in most childhood BTs (Anderson *et al.* 2001, Robertson 2006, Pollack & Jakacki 2011). Newer techniques such as the use of operating microscopes, functional magnetic resonance imaging, intraoperative image-guided stereotactic techniques and electrophysiologic monitoring have aided surgeons in reducing late effects (Anderson *et al.* 2001, Hernesniemi *et al.* 2005, Robertson 2006, Pollack & Jakacki 2011).

Patients with intracranial tumors are predisposed to persistent hydrocephalus, often requiring a permanent cerebrospinal fluid (CSF) diversion procedure with shunts (Reddy *et al.* 2011). Implantation of a ventriculoperitoneal (VP) shunt is the most widely used approach in the management of the condition (Piatt & Garton 2008). Although CSF shunting reduces morbidity and mortality in hydrocephalus, it is associated with potential complications which may require multiple surgical procedures or shunt revisions during the patient's lifetime (Stein & Guo 2008, Reddy *et al.* 2011).

2.3.2 Radiotherapy

Children treated for CNS tumors generally receive radiation either specifically to the site of the tumor itself or to the whole brain and spinal cord with a boost at the tumor site (Anderson *et al.* 2001). Radiotherapy for primary CNS tumors in children tends to be higher in dose than is used in other malignancies, typically greater than 30 Gray (Gy) and frequently as high as 50–60 Gy. The threshold dose required to produce tissue damage resulting in late effects is not known. Substantial improvements in radiation therapy for BTs have arisen from the development of technologies maximizing tumor exposure to radiation while minimizing exposure of the normal brain parenchyma (Anderson *et al.* 2001, Robertson 2006, Pollack & Jakacki 2011). These newer technologies include three-dimensional conformal radiation therapy, intensity-modulated radiation therapy, stereotactic radiosurgery (Robertson 2006), and brachytherapy (Anderson *et al.* 2001). In addition to photon-based radiotherapy proton-based treatment facilities have been developed (Pollack & Jakacki 2011). With the improved survival of children with BTs over the last decades, due in part to advances in the delivery of radiation therapy, recognition of its adverse effects on the developing nervous system has increased (Robertson 2006). Radiation-mediated late effects are magnified in younger children (Anderson *et al.* 2001, Robertson 2006). In hopes of reducing neurotoxicity, current treatments limit the dose and volume of radiation or defer radiotherapy while adding chemotherapy (Anderson *et al.* 2001, Duffner 2004, Pollack & Jakacki 2011). Results have not been uniformly positive, however, and in some cases toxicity may be increased (Duffner 2004).

2.3.3 Chemotherapy

Chemotherapy for the treatment of pediatric BTs is driven by the relatively poor prognosis of many of these neoplasms, as well as by concerns for the detrimental adverse effects of radiation therapy on the developing brain (Robertson 2006). With conventional chemotherapeutic agents alone or in combination with radiation therapy, there has been considerable improvement in the outcome of children with BTs, these including medulloblastoma, malignant astrocytoma, low-grade optic pathway glioma, and malignant tumors in infants (Robertson 2006). Different tumors show varying sensitivities to chemotherapy regimens (Anderson *et al.* 2001). Agents commonly used include nitrosureas, cyclophosphamide, procarbazine, vincristine, platinum compounds, etoposide (VP-16) and bleomycin.

2.4 Prognosis

Survival rates among childhood BT patients have improved over recent decades (Magnani *et al.* 2001, Gatta *et al.* 2005, Steliarova-Foucher *et al.* 2004, Peris-Bonet *et al.* 2006), the improvement being related to advances in diagnosis and treatment (Duffner *et al.* 1986, Gatta *et al.* 2005). In the Nordic countries 5-year survival is over 70% (Magnani *et al.* 2001, Gatta *et al.* 2003, Peris-Bonet *et al.* 2006). The overall 10-year survival rate among children with CNS tumors diagnosed in Sweden in 1995–2005 was 74% (Lannering *et al.* 2009). The rates vary considerably depending mainly on age at diagnosis, histology, location and size of the tumor (Duffner *et al.* 1986, Äärimaa *et al.* 1997, Magnani *et al.* 2001, Peris-Bonet *et al.* 2006, Lannering *et al.* 2009, McGuire *et al.* 2009). Survival improves with increasing age, and is poorest in very young children or infants (Duffner *et al.* 1986, Äärimaa *et al.* 1997, Magnani *et al.* 2001, Peris-Bonet *et al.* 2006, Lannering *et al.* 2009, McGuire *et al.* 2009). PNET has a poor prognosis with a 5-year survival of 47–49%, while astrocytoma has a good prognosis with a 5-year survival of 75–84% in Europe (Magnani *et al.* 2001, Peris-Bonet *et al.* 2006, Lannering *et al.* 2009); 'astrocytoma' however includes a variety of tumors with different prognoses. In Sweden in 1984–2005 5-year survival was 93% in low-grade astrocytomas and only 28% in high-grade astrocytomas (Lannering *et al.* 2009). Diffuse brainstem gliomas have an extremely poor prognosis (Kivivuori *et al.* 2011). The extent of surgical resection has been shown to be a strong independent prognostic factor in clinical series (Heideman *et al.* 1997). In spite of increments in survival, childhood BTs are still a leading cause of cancer-related morbidity and mortality in this age group (Smith & Gloecker Ries

2002), and late mortality occurs in a substantial number of long-term survivors of pediatric CNS tumors (Möller *et al.* 2001, Morris *et al.* 2007). Many survivors suffer considerable sequelae which may necessitate lifelong medical surveillance (Anderson *et al.* 2001, Oeffinger *et al.* 2006). Although most nonmalignant tumors carry a favorable prognosis, other factors such as inaccessibility to surgical resection and rarely, malignant transformation during the natural clinical course, make it difficult to predict the biological behavior accurately based on histopathology alone.

2.5 Late effects of childhood brain tumors and their therapy

Childhood BT survivors run a high risk of a variety of late effects, including secondary malignancies and neurological, endocrinological, cardiovascular and pulmonary problems (Anderson *et al.* 2001, Gurney *et al.* 2003a, Duffner 2004, Ellenberg *et al.* 2009, Reimers *et al.* 2009). Anticancer drugs can also cause renal damage in BT patients (Kintzel 2001). There have been only limited data on osteopenia in survivors of childhood BTs (Anderson *et al.* 2001). In the following the renal, vascular, endocrinological, metabolic, including skeletal, and neurological late effects are covered in detail.

2.5.1 Renal late effects

Nephrotoxicity is a known side-effect of certain childhood cancer therapies, including chemotherapeutic drugs and renal radiotherapy (Knijnenburg *et al.* 2011). Chemotherapy-induced renal dysfunction affects pediatric BT patients. It can be caused by damage to the renal structures or vasculature, hemolytic-uremic syndrome, or prerenal perfusion deficits (Kintzel 2001). The drugs which typically cause renal injury in patients with BTs include platinum analogs, ifosfamide and nitrosureas. Methotrexate is also known to be nephrotoxic (Brandis *et al.* 1993, Grönroos *et al.* 2008). Chemotherapy-induced nephrotoxicity can manifest in acute or long-term adverse effects (Brandis *et al.* 1993, Jones & Chesney 1995, Rossi *et al.* 1999a, Kintzel 2001). Both glomerular and/or tubular damage can occur (Cobos & Hall 1993, Kintzel 2001, Bárdi *et al.* 2004, Skinner 2004).

2.5.1.1 Platinum compounds

Cisplatin (cis-diamminedichloroplatinum) is an inorganic platinum compound. Platinum is a heavy metal. Kidney damage is the most important dose-limiting

side-effect of cisplatin (Krakoff 1979, Townsend *et al.* 2003). Despite the prophylactic use of hyperhydration and forced diuresis, considerable reductions in glomerular filtration rate (GFR) and tubular toxicity have been described in children receiving the drug (Womer *et al.* 1985, Gomez Campdera *et al.* 1986, Brock *et al.* 1991, Skinner *et al.* 1998). Depending on the nature and timing of investigation, the incidence of glomerular toxicity has varied from about 10% to over 80% (Kamalakar *et al.* 1977, Womer *et al.* 1985, Skinner *et al.* 2009). Similarly, the incidence of hypomagnesemia has varied from 12% to 100% (Hayes *et al.* 1981, Brock *et al.* 1991, Stöhr *et al.* 2007). Most children receiving cisplatin suffer some acute loss of renal function, but with wide individual variation in severity (Womer *et al.* 1985). The magnitude of GFR decline has been reported to correlate directly with peak serum or urine platinum concentrations and cisplatin infusion rates (Erdlenbruch *et al.* 2001). After a follow-up of one to two years, moderate or severe glomerular impairment and/or hypomagnesemia due to tubular damage has been reported to be significantly more frequent in children receiving a high cisplatin dose rate (> 40–120 mg/m^2 per day) than in those receiving a low rate (40 mg/m^2 per day) (Skinner *et al.* 1998). A relationship between cumulative cisplatin dose and nephrotoxicity has been suggested (Lam & Adelstein 1986). Also opposite results indicating no relationship between cumulative dose and nephrotoxicity have been published (Brock *et al.* 1991, Skinner *et al.* 1998). Similarly there are conflicting results concerning age and nephrotoxicity, with no association (Womer *et al.* 1985, Brock *et al.* 1991, Skinner *et al.* 1998), but the severity of nephrotoxicity also being found to correlate with older age at treatment (Skinner *et al.* 2009). Treatment with other potential nephrotoxins, including ifosfamide and methotrexate, may increase the risk of renal injury (Preiss *et al.* 1988, Loebstein & Koren 1998).

The mechanism of cisplatin-mediated damage has been extensively studied (Hanigan & Devarajan 2003, Skinner 2004). Platinum is still detectable in the blood up to 20 years after treatment with this drug (Gietema *et al.* 2000), and the chronicity of cisplatin nephrotoxicity is probably related to its retention in renal tissue (Skinner 2004). Histopatological examination of renal specimens from cisplatin-treated patients have shown a variety of tubular lesions but a lack of effect on glomeruli (Gonzales-Vitale *et al.* 1977, Dentino *et al.* 1978). The precise cause of cisplatin nephrotoxicity remains unknown (Skinner 2004). It may be mediated by renal tubular transport and accumulation of the drug or a toxic metabolite (Caterson *et al.* 1983, Townsend *et al.* 2003). Renal damage may also be initiated by renal arterial vasoconstriction (Barros *et al.* 1989, Daugaard & Abildgaard 1989).

Chronic cisplatin glomerular nephrotoxicity can manifest as chronic renal failure with reduced GFR (Brock *et al.* 1991, Skinner *et al.* 1998, Skinner 2004). Magnesuria, leading to hypomagnesemia, is the commonest manifestation of

chronic proximal tubular toxicity (Lam & Adelstein 1986). Cisplatin-induced hypomagnesemia may also result from an injury to a distal tubular site (Lajer & Daugaard 1999). Hypomagnesemia may be symptomatic and cause paresthesia, muscular weakness, tremor, tetany, convulsions and cardiac arrhythmias (Schilsky & Anderson 1979, Pratt *et al.* 1981, Gomez Campdera *et al.* 1986, Bellin & Selim 1988, Skinner *et al.* 2009). The long-term outcome of platinum-induced nephrotoxicity is unknown (Skinner *et al.* 2009). There are reports of some recovery from cisplatin glomerular toxicity (Brock *et al.* 1991). Recent studies have shown that cisplatin toxicity persists during follow-up for even up to 10 years after treatment in childhood, as GFR has been found to be < 90 ml/min/1.73 m^2 in 48% and < 60 ml/min/1.73 m^2 in 11% of patients (Skinner *et al.* 2009). Cisplatin-induced hypomagnesemia tends to be long-lasting; approximately one to two-thirds of patients have been reported to remain hypomagnesemic (Brock *et al.* 1991, Ariceta *et al.* 1997).

Some reports of the effect of carboplatin – a second-generation platinum compound – on renal function in children have indicated little or no impairment in glomerular function (Castello *et al.* 1990, Brandt & Broadbent 1993). On the other hand, high cumulative doses of carboplatin have been associated with significant reductions in GFR (English *et al.* 1999). Hypomagnesemia has been reported (Ettinger *et al.* 1994, English *et al.* 1999). Carboplatin has been surmised to be less nephrotoxic than cisplatin (Bárdi *et al.* 2004, Cobos & Hall 1993, English *et al.* 1999, Jones & Chesney 1995, Rossi *et al.* 1999a, Skinner 2004). However, acute renal failure (Frenkel *et al.* 1995) or chronic renal dysfunction (Tscherning *et al.* 1994) is possible. Carboplatin nephrotoxicity has been reported to correlate with older age at treatment, and at some time points with higher cumulative dose, and to persist during 10 years' follow-up (Skinner *et al.* 2009). It is possible that the risk of renal insufficiency and tubulopathies is higher with carboplatin/ifosfamide than with cisplatin/ifosfamide combination therapy (Hartmann *et al.* 2000, Marina *et al.* 2000).

2.5.1.2 Alkylating agents

Ifosfamide is an alkylating agent. It may cause any combination of chronic glomerular, proximal or distal tubular toxicity, with a particularly wide range of severity (Skinner *et al.* 1993). The most common manifestation of ifosfamide-induced nephrotoxicity is proximal tubular dysfunction, and less often, decreased GFR (Ho *et al.* 1995, Rossi *et al.* 1999b).

Severe failure of proximal tubular reabsorption may lead to the Fanconi syndrome with excessive urinary excretion of glucose, amino acids, phosphate, bicarbonate, potassium and other solutes handled by this nephron segment

(Burk *et al.* 1990, Skinner *et al.* 1990, Jones & Chesney 1995, Jones *et al.* 2008). Affected patients may develop growth failure and hypophosphatemic rickets. Ifosfamide toxicity has been proved to persist for even up to 10 years after treatment (Oberlin *et al.* 2009, Skinner *et al.* 2010). Potentially progressive kidney damage may occur (Rossi *et al.* 1999b, Oberlin *et al.* 2009). Additional toxic effects of ifosfamide include hemorrhagic cystitis, which is effectively prevented by mesna (mercaptoethanesulfonate) (Cobos & Hall 1993). Cyclophosphamide is an alkylating agent with little, if any, late nephrotoxicity (Cobos & Hall 1993, Rossi *et al.* 1999a). One major side-effect of cyclophosphamide is hemorrhagic cystitis, with a reported sequela of hydronephrosis (Rossi *et al.* 1999a).

The nitrosureas, carmustine (BCNU), lomustine (CCNU) and semustine (methyl-CCNU), are lipid-soluble alkylating agents. They may all cause chronic irreversible glomerular impairment, which often develops only after the completion of treatment (Skinner 2004). Semustine is more evidently nephrotoxic than carmustine or lomustine. A substantial risk of end-stage renal failure has been reported in children receiving > 1500 mg/m^2 semustine (Weiss *et al.* 1983). Lomustine nephrotoxicity has been reported with cumulative drug doses of more than 1200–1500 mg/m^2 (Schacht *et al.* 1981, Ellis *et al.* 1985), and carmustine nephrotoxicity with cumulative doses of more than 1200 mg/m^2 (Schacht *et al.* 1981). Slowly progressive end-stage renal failure may follow lomustine treatment (Silver & Morton 1979, Schacht *et al.* 1981). Renal histology usually reveals tubular atrophy, interstitial fibrosis and glomerular sclerosis (Harmon *et al.* 1979, Berglund 1980, Schacht *et al.* 1981).

2.5.1.3 Methotrexate

In recent years methotrexate has been used in some treatment protocols for BTs in children (Rutkowski *et al.* 2005, Van Poppel *et al.* 2011, Wolff *et al.* 2011). The drug may cause both glomerular and tubular toxicity (Skinner 2004). There is a lack of information as to chronic nephrotoxicity (Skinner 2004, Grönroos *et al.* 2008, Jones *et al.* 2008). Quite recently it has been reported that high-dose methotrexate treatment significantly reduces GFR and may cause albuminuria in pediatric cancer patients several years after treatment, but no changes in tubular function have been observed (Grönroos *et al.* 2008).

2.5.2 Vascular late effects

The primary role of the kidney in the control of blood pressure (BP) is related to regulation of salt and water excretion in response to changes in extracellular

fluid volume and generation of humoral agents which directly increase peripheral vascular resistance (Jones *et al.* 2008). Hypertension may occur as a sequela of nephrotoxic chemotherapy (Skinner 2004, Jones *et al.* 2008). Case reports of cisplatin-associated transient hypertension have been published (Kletzel & Jaffe 1981, Harrell *et al.* 1982, Brock *et al.* 1991). In a follow-up examination of side-effects 3.5–9 years after chemotherapy for germ cell cancer with cisplatin, vinblastine and bleomycin, 15% of subjects had hypertension and this was not related to renal impairment (Hansen 1992). Renovascular mechanisms have been suggested to cause drug-induced hypertension (Harrell *et al.* 1982).

Childhood BT survivors are at a significantly increased risk of cardiovascular late effects (Heikens *et al.* 2000, Gurney *et al.* 2003a, Oeffinger *et al.* 2006). One of the most common health complications in adult survivors of childhood medulloblastoma is hypertension (Edelstein *et al.* 2011). As part of the Childhood Cancer Survivor Study (CCSS), self-reported late effects were collected from more than 1600 childhood BT patients who survived their disease five or more years (Gurney *et al.* 2003a). A heart or circulatory late effect was reported by 18% of them, the risk being highest among those treated with surgery, radiotherapy and chemotherapy compared to surgery and radiotherapy alone, suggesting a potential additive vascular injury from chemotherapy. In survivors of childhood brain cancer who had received cranial irradiation, the risk of cardiovascular disease has been found to be strongly increased due to elevated systolic BP, central obesity and dyslipidemia, particularly for those with growth hormone deficiency (GHD) (Heikens *et al.* 2000). The first effects of this increased risk of cardiovascular disease were observed in the carotid bulb, as assessed by intima-media thickness measurements. Body mass index (BMI) was the most important risk factor for hypertension following treatment of childhood cancer (Cardous-Ubbink *et al.* 2010). It has been suggested that pediatric patients who receive spinal irradiation for malignancies are at risk of significant cardiac dysfunction (Jakacki *et al.* 1993), but no such relation was clearly revealed by the CCSS (Gurney *et al.* 2003a). Anthracyclines are well known for their cardiotoxicity but they are rarely used in the treatment of childhood BTs (Gurney *et al.* 2003a). Other agents with cardiac effects include cyclophosphamide, ifosfamide, cisplatin, vinca alkaloids, VP-16 and teniposide (VM-26) (Pai & Nahata 2000, Simbre *et al.* 2005), but delayed cardiotoxicity (years after completion of chemotherapy) has been seen only after anthracycline therapy (Pai & Nahata 2000).

Survivors of childhood BTs are at risk of late-occurring cerebrovascular complications (Mitchell *et al.* 1991, Gurney *et al.* 2003a, Bowers *et al.* 2006, Ullrich *et al.* 2007, Morris *et al.* 2009). In one CCSS study 63 (3.4%) of 1871 BT survivors reported a late-occurring stroke (Bowers *et al.* 2006). BT survivors were 29 times more likely than the sibling comparison group to report stroke

occurrence. The rate of stroke was significantly higher among patients treated with cranial radiation therapy than those not so treated, and radiotherapy in doses of ≥ 30 Gy was associated with an increased risk of stroke in a dose-dependent fashion, with the highest risk after doses of ≥ 50 Gy. Alkylating agents appeared to enhance the risk of stroke, while other chemotherapeutic agents did not. Clinically silent white matter lacunar lesions have been reported in children with CNS tumors treated with radiation with or without chemotherapy (Fouladi *et al.* 2000). Common manifestations of radiation-induced cerebrovascular disease include steno-occlusive disease, moyamoya, aneurysm, mineralizing microangiopathy, vascular malformations, and strokelike migrains (Morris *et al.* 2009). In adult patients radiation therapy for head and neck cancer is associated with accelerated atherosclerosis of the carotid arteries (Murros & Toole 1989).

2.5.3 Endocrine and metabolic late effects

Endocrine dysfunction is a common occurrence in children treated for BTs. Endocrine problems can occur at many levels within a hormone axis. A hormonal axis consists of central components including the hypothalamus and pituitary and endocrine organs, which respond to hormones released from the central nervous system. Hypothalamic and pituitary components of hormonal axes are vulnerable to compression or invasion by a tumor, and to intracranial interventions such as surgery and radiation (Meacham *et al.* 1997, Darzy & Shalet 2005). The hypothalamus is the primary site of radiation-induced damage (Shalet 1996, Darzy & Shalet 2005, Darzy & Shalet 2009). The pathophysiology of radiation-induced hypothalamic damage remains poorly understood*;* the current evidence favors direct neuronal rather than vascular injury to the hypothalamus (Darzy & Shalet 2009). In addition, marked differences in the incidence of anterior pituitary hormone deficiencies suggest that selective hypothalamic neuronal and pituitary cell damage occurs by direct radiation. Hypothalamic-pituitary dysfunction secondary to radiation is time-dependent, with both increased incidence and severity of hormonal deficits with longer post-irradiation follow-up. The progressive nature of the hormonal deficits following radiation damage to the hypothalamic-pituitary axis (HPA) can be attributed to secondary pituitary atrophy consequent upon lack of hypothalamic releasing/trophic factors or delayed direct effects of radiotherapy on the axis. There have been reports indicating that chemotherapy potentiates the deleterious effect of radiation on pituitary function (Spoudeas *et al.* 1996, Gleeson *et al.* 2004). Hypothalamic dysfunction has also been reported to occur after chemotherapy alone, and the mechanism involved is not well understood (Rose *et al.* 2004). In a study of 31 childhood cancer

survivors who received chemotherapy but no cranial or total body irradiation and had no CNS tumor, 25 (81%) had GHD, central hypothyroidism, precocious puberty, and/or gonadotropin deficiency. None had adrenocorticotropin hormone (ACTH) or antidiuretic hormone (ADH) deficiency or primary hypothyroidism. Endocrine end organs such as the thyroid gland and gonads can be affected by radiation and chemotherapy required as treatment for the BT (Shalet 1996, Meacham *et al.* 1997, Gleeson & Shalet 2004).

2.5.3.1 Obesity

Obesity is a late effect among cancer survivors (Didi *et al.* 1995, Talvensaari *et al.* 1996, Oeffinger *et al.* 2003, Gleeson & Shalet 2004). Increased obesity has been reported especially in acute lymphoblastic leukemia (ALL) survivors and some BT survivors (Diller *et al.* 2009). The CCSS has published results on self-reported BMI in 921 adults aged 20–45 years who were treated for brain cancer as children, and found that the BMI of survivors did not differ appreciably from that of sibling controls, 15% having a BMI greater than 30 kg/m^2 (Gurney *et al.* 2003b). In addition, the CCSS study reports BT survivors to be at an increased risk of being underweight (Meacham *et al.* 2005). In the CCSS studies the overall obesity outcome in BT patients is likely to be underestimated, as non-malignant BTs such as craniopharyngiomas were not included (Diller *et al.* 2009). Survivors of craniopharyngioma are known to be at high risk of obesity (Stahnke *et al.* 1984, Sorva 1988, Sklar 1994, Pinto *et al.* 2000, Müller *et al.* 2004). There is evidence suggesting that up to 50–60% of craniopharyngioma survivors become overweight (Sorva 1988, Hamilton *et al.* 2011).

Hypothalamic damage, due to either the tumor, surgery or radiation, has been identified as the primary cause of obesity in survivors of childhood BTs (Lustig *et al.* 2003). In particular, hypothalamic radiation doses of 50 Gy or higher have been associated with abnormal BMI increase. Young age at diagnosis has also been identified as a risk factor for obesity (Lustig *et al.* 2003), as noted in ALL survivors (Didi *et al.* 1995). In adult survivors of childhood ALL cranial radiotherapy 20 Gy or more was associated with increased prevalence of obesity, especially in females treated at a young age (Oeffinger *et al.* 2003).

Damage particularly to the ventromedial hypothalamus (VMH) is postulated to be responsible for obesity (Schwartz *et al.* 2000). The VMH normally integrates blood-borne information from leptin, ghrelin and insulin, translating the information into regulation of energy balance. Dysfunction of the VMH results in excessive caloric intake and decreased caloric expenditure, which leads to weight gain. It is hypothesized that VMH damage causes either hyperphagia resulting in obesity and compensatory hyperinsulinemia, or disinhibition of

efferent output of the vagus nerve, which acts on the pancreatic β cells to promote excessive insulin secretion (Gleeson & Shalet 2004, Hamilton *et al.* 2011).

In prolonged GHD, affected individuals are at increased risk of obesity (Roemmich *et al.* 2001, Mukherjee *et al.* 2004, Bechtold *et al.* 2011). Thyroid function is associated with body weight (Fox *et al.* 2008). Other factors which may induce obesity in patients with BTs include the use of high-dose glucocorticoids, which could promote obesity by affecting the appetite, regulation of energy intake, alteration in substrate oxidation and/or alteration in energy expenditure (Tataranni *et al.* 1996). Neurological complications associated with intracranial tumors and their treatment may have adverse effects on motor function, which may in turn reduce physical activity and predispose to obesity (Gleeson & Shalet 2004).

2.5.3.2 Growth

Suboptimal growth in BT survivors is multifactorial in etiology (Gleeson & Shalet 2004). The CCSS has published results on self-reported final height in brain cancer survivors and found almost 40% to be below the tenth percentile for height (Gurney *et al.* 2003b). The strongest risk factors for adult short stature were young age at diagnosis and radiation treatment involving the HPA. Growth retardation may be a consequence of hypothyreosis or GHD (Meacham *et al.* 1997). Growth hormone (GH) is the hormone most sensitive to radiation injury (Avizonis *et al.* 1992, Spoudeas *et al.* 1996, Spoudeas *et al.* 2003). It is suggested that nearly 100% of children treated with radiation doses in excess of 30 Gy will have blunted GH responses to an insulin tolerance test, whilst 35% of those receiving less than 30 Gy still show a normal peak GH response to the insulin tolerance test between two and five years after radiotherapy (Clayton & Shalet 1991). The pathophysiology of radiation-induced GH neurosecretory dysfunction is poorly understood (Darzy *et al.* 2007). Data suggest that children who acquire GHD as a result of radiation damage to the HPA, mass lesions or surgical manipulation of the HPA, or a combination of these factors, are likely to remain GHD into adulthood (Nicolson *et al.* 1996).

Spinal irradiation results in a reduction in sitting height, this leading to overall poor adult height (Shalet *et al.* 1987). Adjuvant chemotherapy has been shown to have a deleterious effect on growth in irradiated BT patients (Olshan *et al.* 1992, Ogilvy-Stuart & Shalet 1995). It has been hypothesized that cytotoxic drugs may amplify the damage to the HPA by irradiation, directly affect the production of insulin-like growth factor-1 (IGF-1) by the liver and/or impair the action of IGF-1 on the growth plate (Gleeson & Shalet 2004). GHD has been identified in 48% of childhood cancer survivors, CNS tumors excluded, who were treated

with chemotherapy but did not receive cranial or total body irradiation (Rose *et al.* 2004). Early puberty may contribute to adult short stature (Ogilvy-Stuart & Shalet 1995, Meacham *et al.* 1997). Impaired growth may also be a consequence of poor nutrition or tumor recurrence (Gleeson & Shalet 2004). Slow linear growth in prepuberty and an earlier adolescent growth spurt resulting in reduced final height have been reported in children with shunted hydrocephalus for other reasons than BTs (Löpponen *et al.* 1995).

2.5.3.3 Pubertal development and gonadal function

The gonadal axis abnormalities seen in children treated for BTs include precocious puberty, delay in onset of puberty and hypogonadism. Precocious puberty is frequently seen in association with a variety of intracranial disturbances (Meacham *et al.* 1997). Cranial irradiation is associated with precocious puberty (Leiper *et al.* 1987, Ogilvy-Stuart *et al.* 1994). The mechanism involved in early puberty following irradiation is thought to arise from disinhibition of cortical influences on the hypothalamus. Puberty then proceeds through an increased frequency and amplitude of gonadotrophin-releasing hormone pulsatile secretion by the hypothalamus (Roth *et al.* 2001). Abnormalities in gonadotrophin secretion are dose-dependent. Precocious puberty, predominantly in girls, can occur after a radiation dose less than 30 Gy (Leiper *et al.* 1987, Darzy & Shalet 2005). It occurs in both sexes equally at a radiation dose of 30–50 Gy (Ogilvy-Stuart *et al.* 1994, Darzy & Shalet 2005). There is a linear association between age at irradiation and age at onset of puberty, i.e. the younger the age at irradiation the earlier the onset of puberty (Ogilvy-Stuart *et al.* 1994). Gonadotrophin deficiency occurs infrequently and is usually a long-term complication following a minimum radiation dose of 30 Gy (Darzy & Shalet 2005). When the dose of cranial irradiation exceeds 50 Gy there is a progressive increase in the incidence of the deficiency (Gleeson & Shalet 2004). Gonadotrophin deficiency occurs with a range of severity from subtle (subclinical) abnormalities with low normal sex hormone levels to severe impairment associated with subnormal circulating sex hormone levels. The prevalence of gonadotrophin deficiency also increases with time post-irradiation.

Pubertal abnormalities have been identified in 32% childhood cancer survivors with other than CNS tumors after chemotherapy treatment alone (Rose *et al.* 2004). The abnormalities included precocious puberty, gonadal failure and gonadotropin deficiency. Several reports have indicated that chemotherapeutic agents may cause primary gonadal damage (Ahmed *et al.* 1983, Clayton *et al.* 1989, Wallace *et al.* 1989, Livesey *et al.* 1990). Gonadotoxicity is often dose-dependent (Wallace *et al.* 1989). Chemotherapeutic agents known to be associated

with direct gonadal toxicity include alkylating agents, procarbazine, cisplatin, busulfan and vinblastine (Ahmed *et al.* 1983, Clayton *et al.* 1989, Wallace *et al.* 1989, Livesey *et al.* 1990, Duffner 2004).

Scattered radiation from spinal irradiation is also known to contribute to gonadal toxicity, particular in females, and may cause ovarian dysfunction in up to 35% of girls (Livesey *et al.* 1990). Lack of puberty may be due to central or primary hypogonadism, or a constitutional delay of puberty, which is a normal variant pattern of growth and is frequently seen in children who have had a severe or chronic illness (Meacham *et al.* 1997). Patients other than BT survivors with hydrocephalus have been shown to experience early puberty (Löppönen *et al.* 1996).

2.5.3.4 Thyroid gland

The late effects on the thyroid seen in BT survivors include hypothyroidism, thyroid nodules, thyroid malignancy and, rarely, hyperthyroidism (Sklar *et al.* 2000). The hypothalamic-pituitary-thyroid axis appears to be the least vulnerable to radiation damage, dysfunction being highly dose-dependent (Littley *et al.* 1989, Constine *et al.* 1993, Darzy & Shalet 2009). The frequency of radiation-induced thyroid-stimulating hormone (TSH) deficiency is also related to time since irradiation (Schmiegelow *et al.* 2003b). The incidence of secondary hypothyroidism remains relatively low (3–19%) in survivors of non-pituitary BTs (Oberfield *et al.* 1986, Livesey *et al.* 1990, Paulino 2002). The thyroid gland in children is among the organs most sensitive to damage by radiation (Sklar *et al.* 2000). Damage can occur in the BT survivor secondary to scattered radiation from craniospinal irradiation as well as from cranial irradiation alone (Schmiegelow *et al.* 2003b). Primary hypothyroidism has been reported in 20–60% of BT survivors, depending on treatment modalities and length of follow-up (Livesey *et al.* 1990, Ogilvy-Stuart *et al.* 1991, Schmiegelow *et al.* 2003b). Chemotherapy has been found to increase the risk of hypothyroidism in patients who have also received radiation therapy (Livesey *et al.* 1990, Paulino 2002). There are also studies which have failed to confirm this finding (Schmiegelow *et al.* 2003b, van Santen *et al.* 2003). On the other hand, central hypothyroidism has been identified in 52% of childhood cancer survivors other than BT survivors treated with chemotherapy and not receiving radiotherapy (Rose *et al.* 2004). In the CCSS hypothyroidism (including both primary and central hypothyroidism) has been reported in 16% of childhood BT survivors (Diller *et al.* 2009).

2.5.3.5 Other endocrine late effects

Elevated serum prolactin levels can be seen after disruption of the HPA and in primary hypothyroidism (Meacham *et al.* 1997). Radiation-induced

hyperprolactinemia, due to a reduction in the inhibitory neurotransmitter dopamine, has been described in both sexes and all age groups, but is most frequently encountered in the adult female with radiation doses in excess of 40 Gy (Littley *et al.* 1989, Constine *et al.* 1993, Agha *et al.* 2005). Radiation-induced hyperprolactinemia is subclinical in the vast majority of patients and a gradual decline in the elevated prolactin level may occur with time and can normalize in some patients (Littley *et al.* 1989, Darzy & Shalet 2009).

Among cases of cranial irradiation for childhood BTs not directly involving the HPA 19% have had abnormalities of the hypothalamic-pituitary-adrenal axis after 15 years of follow-up (Schmiegelow *et al.* 2003a). Previous studies with shorter follow-up have demonstrated only subtle abnormalities (Livesey *et al.* 1990, Constine *et al.* 1993, Spoudeas *et al.* 2003). It is possible that the hypothalamic-pituitary-adrenal axis is affected late by irradiation (Schmiegelow *et al.* 2003a, Gleeson & Shalet 2004).

Radiation-induced damage to the HPA usually presents with anterior pituitary hormone deficiencies. Most cases of diabetes insipidus which are related to BTs arise as a result of surgery at the location of the pituitary or growth of the lesion itself, causing interruption of the neurons supplying the posterior pituitary (De Buyst *et al.* 2007).

Head and neck irradiation in childhood or adolescence has been found to be associated with primary hyperparathyroidism (Rao *et al.* 1980). Radiation exposure of the head and neck can also result in tumors of the parathyroid glands (Ron & Saftlas 1996).

2.5.3.6 Skeletal

During childhood and adolescence the bone mineral mass increases substantially, reaching its peak around the age of 20 years (Haapasalo *et al.* 1996, Baxter-Jones *et al.* 2011). At least 90 % of peak bone mass (PBM) is acquired by 18 years of age, and up to 25 % during the 2-year period surrounding peak height velocity (Matkovic & Heaney 1992, Bailey *et al.* 1999). Complete muscle and bone maturation is reached at a later stage than final height (Boot *et al.* 2009). Adult bone structure and strength are maintained by a continuous process of bone turnover and repair in the bone remodelling cycle, by the coupled activities of bone-resorbing osteoclasts and bone-forming osteoblasts (Waung *et al.* 2011). Genetic factors play a major role in the determination of PBM, accounting for up to 80% of the variance (Slemenda *et al.* 1991). The remaining fraction of the variance in PBM is attributable to environmental factors such as nutrition and physical activity behaviors, but heredity and environment are not distinctly separable (Heaney *et al.* 2000). Normal mineralization of the skeleton is dependent

upon adequate availability of calcium and phosphorus. Extracellular calcium homeostasis is regulated by multiple factors, of which parathyroid hormone (PTH) and the active vitamin D, 1,25-dihydroxyvitamin D ($1,25(OH)_2D$), play a key role (Heaney *et al.* 2000, Sochett & Mäkitie 2005). Exposure to illness or risk factors before and during puberty may result in bone deficits (Heaney *et al.* 2000, Seeman 2002). PBM is regarded as the most important determinant of osteoporosis and fracture risk in older adulthood (Cummings *et al.* 1993). Individuals who fail to achieve optimal PBM and strength during childhood and adolescence are more likely to develop osteoporosis later in life (Heaney *et al.* 2000, Mora & Gilsanz 2003). There is also evidence that bone mass acquisition in early life has no effect on bone mass in adulthood (Gafni & Baron 2007).

Osteoporosis is defined as a skeletal disorder characterized by compromised bone strength predisposing to an increased risk of fracture (NIH consensus statement 2000). Bone strength primarily reflects the integration of bone density and quality. Bone density is expressed as grams of mineral per area or volume. Bone quality refers to architecture, turnover, damage accumulation and mineralization (NIH consensus statement 2000). In adults BMD derived from dual-energy X-ray adsorptiometry (DXA) assessment is used to define osteoporosis. BMD accounts for approximately 70 percent of bone strength. WHO has defined osteoporosis as BMD or bone mineral content (BMC) 2.5 standard deviations (SD) or more below the mean for young adult women (T-score -2.5 or below -2.5), and severe osteoporosis (established osteoporosis) as a value for BMD or BMC more than 2.5 SD below the mean for young adult women (T-score below -2.5) in the presence of one or more fragility fractures (WHO Study Group 1994). Low bone mass (osteopenia) is defined as a value for BMD or BMC more than 1 SD below the mean for young adult women but less than 2.5 SD below this value (T-score between -1 and -2.5).

A widely recognized definition of osteoporosis in pediatrics has been lacking. In 2007 the International Society for Clinical Densitometry (ISCD) presented a definition of osteoporosis in children and adolescents (Rauch *et al.* 2008, Valta & Mäkitie 2011). As distinct from adults, the diagnosis of osteoporosis in children and adolescents should not be made on the basis of densitometric criteria alone; it requires the presence of both low BMC or BMD and a clinically significant fracture history. Low BMC or BMD is defined as lumbar spine or total body BMC or areal BMD Z-score less than or equal to -2.0, adjusted for age and gender, and for body size and/or bone age, when needed. A clinically significant fracture history is one or more of the following: long-bone fracture of the lower extremities, vertebral compression fracture, or two or more long-bone fractures of the upper extremities. In children the term osteopenia should not been used.

Osteoporosis may be associated with many pediatric conditions. Chronically ill children constitute a special risk group (Sochett & Mäkitie 2005, Valta & Mäkitie 2011). In such cases the underlying chronic illness itself, medication, nutrient and hormone deficiencies and decreased physical activity may contribute to poor bone health (Sochett & Mäkitie 2005).

Based on self-reported late effects in adult survivors, the CCSS has published data on an increased risk of osteoporosis in childhood BT survivors (Gurney *et al.* 2003a). Reduced BMD, osteopenia and osteoporosis have been reported in young childhood BT survivors (Barr *et al.* 1998, Krishnamoorthy *et al.* 2004, Odame *et al.* 2006, Petraroli *et al.* 2007, Kang *et al.* 2011). Misinterpretation of DXA may lead to overdiagnosis in osteoporosis in children (Gafni & Baron 2004), and the diagnosis of osteoporosis is challenging (Rauch *et al.* 2008, Valta & Mäkitie 2011); published results on the proportions of osteopenic or osteoporotic children and adolescents must thus be assessed with caution.

Reduced BMD in long-term survivors of childhood ALL has been found to be associated with cranial irradiation (Arikoski *et al.* 1998). This association has also been found in childhood BT survivors (Odame *et al.* 2006). Cranial irradiation, apparently by reducing GH secretion and by causing hypogonadotropic hypogonadism, interferes with normal bone turnover (Sala & Barr 2007).

Completion of normal skeletal growth and development and bone mineral accrual require adequate interaction of several hormones (GH, insulin-like growth factors, sex steroids and thyroid hormone) (Mora & Gilsanz 2003). GHD in children, as well as in adults, is associated with decreased BMD (Degerblad *et al.* 1992, Boot *et al.* 1997). Much of the GH action on bone is mediated through IGF-1, which functions as a bone trophic hormone positively affecting osteoblasts and stimulates collagen synthesis (Hock *et al.* 1988). Secretion of sex steroids during puberty increases BMD and PBM (NIH consensus statement 2000). Gonadal steroids influence skeletal health in both men and women all through life (NIH consensus statement 2000, Sinnesael *et al.* 2011). Reduction in estrogen production at menopause is the major cause of BMD loss during later life (NIH consensus statement 2000). Estrogens have also been related to the growth and maturation of the male skeleton (NIH consensus statement 2000, Mora & Gilsanz 2003, Sinnesael *et al.* 2011). Adult patients with hypogonadotropic hypogonadism commonly have low BMD values resulting from inadequate bone mineral accrual during puberty (Finkelstein *et al.* 1987). Amenorrhea or oligomenorrhea in adolescence has been found to be associated with reduced BMD in adulthood (Wiksten-Almstromer *et al.* 2009). Idiopathic delayed puberty has been implicated as a cause of reduced PBM (Finkelstein *et al.* 1996). Hypothyroidism in children results in growth arrest and delayed bone maturation. Juvenile thyrotoxicosis accelerates growth and advances bone age, but

results in short stature due to premature fusion of the growth plate (Waung *et al.* 2011). Excessive production of thyroid hormone impairs bone mineralization during growth and therefore does not allow normal bone mineral accrual. A study of hyperthyroid girls has demonstrated significantly reduced whole body and lumbar spine bone density at diagnosis compared with healthy girls matched for age and body size (Mora *et al.* 1999). Hypothyroidism in adults results in reduced bone turnover (Waung *et al.* 2011). Large population-based studies have identified an increased risk of fracture in individuals with hypothyroidism. Adult thyrotoxicosis is an established cause of high-bone-turnover osteoporosis, which results from a net increase in bone resorption (Waung *et al.* 2011). Thus, hyperthyroidism is associated with reduced BMD and an increased susceptibility to fragility fracture also in adults. Hyperprolactinemia is associated with reduced BMD (Shibli-Rahhal & Schlechte 2009). Low calcium intake may account for an elevation in PTH levels, which is harmful to bone metabolism (Dawson-Hughes & Bischoff-Ferrari 2007, Valta & Mäkitie 2011). BMD may be reduced in primary hyperparathyreoidism (Marcocci & Cetani 2011).

Glucocorticoids have profound effects on bone metabolism, and exposure of skeletal tissue to steroids results in osteoporosis (Sochett & Mäkitie 2005). In vivo, glucocorticoids enhance bone resorption and reduce bone formation. Both methotrexate and ifosfamide are associated with reduced BMD (van Leeuwen *et al.* 2000, Sala & Barr 2007, Kaste *et al.* 2008). Nephrotoxic cytostatic agents may cause skeletal abnormalities by demineralization of bone due to reduced kidney function (van Leeuwen *et al.* 2000). Cyclophosphamide exposure has been found to be associated with low BMD in survivors of sarcoma (Kaste *et al.* 2008). Alkylator therapy may contribute to osteopenia indirectly via the mechanism of hypogonadism (Sala & Barr 2007). Antiepileptic drugs have a negative effect on bone health through various mechanisms (Fitzpatrick 2004).

Exercise has a beneficial effect on bone mass (Heaney *et al.* 2000, Mora & Gilsanz 2003). Children with motor disability have been found to be at high risk of peripheral and vertebral fractures and low BMD (Kilpinen-Loisa *et al.* 2010).

Local skeletal irradiation, e.g. of the spine, interferes with skeletal growth and may cause direct bone loss at the site of the therapy (Neuhauser *et al.* 1952, Fletcher 1997). The spinal deformities and other skeletal changes which may result after radiation therapy are now seen less frequently by reason of lower doses and newer radiation techniques (Dickerman 2007). Among long-term childhood BT survivors osteonecrosis (avascular necrosis) is rare but documented in other childhood cancer survivors at higher rates (Kadan-Lottick *et al.* 2008, Niinimäki *et al.* 2008).

2.5.3.7 Metabolic syndrome

The metabolic syndrome consists of factors of metabolic origin such as central obesity, insulin resistance, hyperglycemia, hypertension, high plasma triglyceride levels and low plasma high-density lipoprotein cholesterol (HDL-C) levels, which tend to occur together (de Haas *et al.* 2010, Jung *et al.* 2012). It is associated with an increased risk of type-2 diabetes mellitus and atherosclerotic disease. Long-term survivors of childhood cancer forms other than BTs have an increased risk of metabolic syndrome (Talvensaari *et al.* 1996). Decreased GH secretion accounts for the metabolic abnormalities involved. Impaired glucose tolerance, dyslipidemia and signs of metabolic syndrome occur after bone marrow transplantation in childhood (Taskinen *et al.* 2000). A higher risk of dyslipidemia, central obesity and elevated systolic BP among survivors of childhood brain cancer has been reported, particularly for those with GHD (Heikens *et al.* 2000).

2.5.4 Neurological late effects

2.5.4.1 Neurological deficits

Major differences in the incidence of neurological deficits during the follow-up of children with BTs reflect variation in tumor histology, degree of malignancy, localization, treatment modalities, type of study and scoring methods used (Sønderkaer *et al.* 2003). Focal neurological deficits or seizures may occur depending on the area of brain involved. After a median follow-up of 10.7 years, 65 patients who in childhood had received only surgery for a benign BT had a good chance of total or partial recovery of preoperative and postoperative neurological deficits, although only 31% patients had no long-term neurological deficits. Thirty-five percent of patients had moderate or severe deficits such as severe ataxia, spastic paresis, seriously reduced vision, or epilepsy with more than two seizures per year. At the time of the diagnosis, approximately 12% of children with BTs have seizures (Ibrahim & Appleton 2004). Total tumor resection and early surgery after the onset of seizures seem to be important prognostic factors for seizure-free outcome (Iannelli *et al.* 2000, Sønderkaer *et al.* 2003). Perioperative complications have been associated with poor motor function and epileptic seizures in childhood BT survivors with malignant tumors (Ilveskoski *et al.* 1996a).

Chemotherapeutic agents may cause peripheral neuropathy. All vinca alkaloids cause this condition, vincristine being the most neurotoxic, causing sensomotor neuropathy (London & Albers 2007). The mechanism of vincristine neuropathy is believed to be related to impairment of the function of microtubules involved in axonal transport. Vincristine might also cause autonomic involvements.

Cisplatin is likewise neurotoxic, causing sensory neuropathy (London & Albers 2007). The mechanism underlying this effect is unknown, but it is believed to be related to distruption of fast axonal transport and induction of apoptosis in dorsal root ganglion cells. The symptoms of peripheral neuropathy caused by these drugs may be long-lasting.

The primary ototoxicity of chemotherapy in pediatric CNS tumors manifests as a sensorineural hearing loss, a variant of peripheral neuropathy (Reddy & Witek 2003). The major part of this toxicity is secondary to platinum compounds, in particular cisplatin and to a lesser degree carboplatin. Cranial irradiation alone can cause conductive hearing loss secondary to middle and external ear alterations (Kwong *et al.* 1996). Radiation-induced sensorineural hearing loss is uncommon, but more likely to be permanent than conductive hearing loss (Kwong *et al.* 1996). A synergistic effect between cranial radiation and cisplatin treatment on hearing loss has been documented (Reddy & Witek 2003).

In a study involving 31 malignant childhood BT survivors after a mean follow-up of 5.3 years, 29% had normal motor function, 45% clumsiness or hemisyndrome, 19% hemiplegia, and 7% severe hemi- or tetraplegia, being unable to walk and eat without help (Ilveskoski *et al.* 1996a). Nineteen percent developed strabismus, while other cranial nerve dysfunctions were rare. Treatment resulted in severe hearing loss in 16%. Thirteen percent suffered from intractable epileptic seizures. In a study of late sequelae in 56 childhood BT survivors with a wide range of tumors, craniopharyngiomas and pituitary tumors excluded, 25% had significant motor, and 20% visual dysfunctions (Lannering *et al.* 1990). In adult survivors of childhood BTs coordination problems were reported in 49% and motor control problems in 26% (Packer *et al.* 2003).

2.5.4.2 Intellectual and cognitive function

The tumor location, tumor type, surgery, radiation, chemotherapy, hydrocephalus, age and gender have been shown to have effects on neurocognitive functioning. Most research examining neuropsychological outcomes of childhood BTs has focused on survivors of medulloblastoma.

Hemispheric tumor location has been associated with lower cognitive functions (Kun *et al.* 1983, Ellenberg *et al.* 1987, Reimers *et al.* 2003), and hypothalamic location likewise with poor cognitive skills (Danoff *et al.* 1982, Ellenberg *et al.* 1987). Inadequate hormone levels place the child at risk of physical and cognitive disabilities (Morris *et al.* 2007). It has been noted that the cerebellum is involved in cognitive functions in addition to its involvement in motor functions (Gottwald *et al.* 2004, Cantelmi *et al.* 2008). Increasing evidence has shown that patients with damage to the cerebellum might have deficits similar

to those seen in patients with damage to the cerebral cortex. Patients with tumors of the posterior fossa can sustain damage to the cerebellum from tumor growth, during surgical resection of the tumor, due to the effects of chemotherapy and radiotherapy, or from a combination of any of these factors (Cantelmi *et al.* 2008). The posterior fossa syndrome of cerebellar mutism typically arises 1 to 2 days after posterior fossa surgery (Robertson *et al.* 2006, Gudrunardottir *et al.* 2011), but it can also occur after resection of a supratentorial tumor (Ellis *et al.* 2011). The overall incidence of postoperative cerebellar mutism is 11–29%, and patients with medulloblastomas and/or brainstem invasion are at greater risk (Gudrunardottir *et al.* 2011). The syndrome consists of mutism, emotional lability, ataxia and hypotonia. Recovery occurs in nearly all patients, but speech rarely normalizes, and cognitive deficits are usually permanent (Mulhern *et al.* 2004, Robertson *et al.* 2006, Gudrunardottir *et al.* 2011). Perioperative complications have been shown to correlate with neurocognitive deficits (Kao *et al.* 1994, Hoppe-Hirsch *et al.* 1995, Ilveskoski *et al.* 1996a).

Cranial irradiation is associated with cognitive decline (Danoff *et al.* 1982, Kun *et al.* 1983, Ellenberg *et al.* 1987, Ilveskoski *et al.* 1996a, Lannering *et al.* 1990, Reimers *et al.* 2003, Duffner 2004, Mulhern *et al.* 2004, Reimers *et al.* 2009). In addition to impairment in global cognitive abilities, adverse neurocognitive outcomes after cranial irradiation for pediatric CNS tumors include impairment in executive function, memory and attention (Reeves *et al.* 2006, Ellenberg *et al.* 2009). Animal studies of the pathophysiology of late effects of cranial radiation therapy suggest primary apoptosis of endothelial and oligodendroglial cells as well as secondary cell injury and death mediated by hypoxia/ischemia and neuro-inflammation, resulting in a cascade of events which alter the microenvironment, this leading to further endothelial dysfunction, disruption of the blood–brain barrier, inhibition of neurogenesis, demyelination and tissue necrosis (Ellenberg *et al.* 2009).

Longitudinal studies have consistently shown significant declines in intelligence quotient (IQ) over time in patients treated with craniospinal radiotherapy for medulloblastoma (Mulhern *et al.* 2004). The larger the volume of radiation, the poorer is the cognitive outcome. Patients who have received craniospinal or whole brain radiation fare worse than those with local or no radiation (Ellenberg *et al.* 1987, Hoppe-Hirsch *et al.* 1995). Higher doses of radiation to the brain are associated with more severe cognitive decline (Silber *et al.* 1992, Mulhern *et al.* 2004). High radiation dose levels (≥ 30 Gy) to temporal regions are associated with a higher risk of memory impairment compared with cases with no radiation exposure (Armstrong *et al.* 2010). No such association was seen with radiation exposure to other regions.

Cranial radiation predisposes the recipient to moyamoya syndrome, a vasculopathy where cerebral hypoperfusion due to progressive occlusion of the

internal carotid arteries results in abnormal collateral formation in the area of the Circle of Willis (Ullrich *et al.* 2007, Morris *et al.* 2009). A study of 345 children irradiated for primary BTs revealed that 3.5% developed evidence of moyamoya (Ullrich *et al.* 2007). Risk factors for moyamoya include suprasellar and/or chiasmatic tumor location, young age at the start of radiation therapy, intense radiotherapy near the Circle of Willis, and a diagnosis of neurofibromatosis 1 (NF1) (Ullrich *et al.* 2007, Morris *et al.* 2009).

Methotrexate and cranial radiation, either separately or together, have been associated with clinical or neuroradiological evidence of leukoencephalopathy in survivors of childhood BTs (Duffner 2004, Kellie *et al.* 2005). Reduced normal-appearing white matter volumes among children surviving treatment for BTs have been associated with decreased attentional abilities, and decline in IQ and academic achievement (Duffner 2004, Mulhern *et al.* 2004, Kellie *et al.* 2005, Ellenberg *et al.* 2009).

There is evidence of subtle long-term neurocognitive deficits in survivors of childhood ALL after treatment with chemotherapy only, involving mainly processes of attention and of executive functioning (Anderson & Kunin-Batson 2009, Buizer *et al.* 2009).

The role of hydrocephalus in the development of cognitive difficulties in children treated for BTs is unclear. There have been reports of an absence of association between hydrocephalus and cognitive function (Danoff *et al.* 1982, Kun *et al.* 1983). Hydrocephalus has on the other hand been found to be a significant risk factor for impaired intellectual outcome in children treated for BTs (Reimers *et al.* 2003). In a study of children with infratentorial ependymomas, treatment of hydrocephalus with shunt improved cognition (Merchant *et al.* 2004).

Young age at the time of radiation and/or chemotherapy has in earlier studies consistently proved a major risk factor for cognitive decline in children treated for BTs (Danoff *et al.* 1982, Packer *et al.* 1989, Mulhern *et al.* 2004). Young children with BTs might also have cognitive deficits prior to receiving either radiation or chemotherapy (Duffner *et al.* 1993). Young age at diagnosis has as such been a significant predictor of lower cognitive function (Reimers *et al.* 2003). Contrary to previous findings, younger age at diagnosis was not correlated with greater reported neurocognitive dysfunction in a large sample of adult survivors of childhood CNS malignancy in the CCSS (Ellenberg *et al.* 2009). The rate of IQ decline is also associated with female sex (Mulhern *et al.* 2004).

In a study of 31 malignant childhood BT survivors, the mean full-scale IQ was 85 (45–138) in 25 patients tested on the average 3.1 years (range 0.7–6.2) after irradiation (Ilveskoski *et al.* 1996a). Six (24%) had full-scale IQ below 70, and nine (36%) over 90. Specific, selective deficits in attention and motor-sensory and visuospatial functions were noted. In a study of late sequelae in

56 childhood BT survivors with a wide range of tumors, 38% had intellectual dysfunctions (full-scale IQ < 90) (Lannering *et al.* 1990). Memory dysfunction was found in 22% of patients with normal intelligence. In a Finnish study of scholastic achievements of children with BTs upon completion of comprehensive education, patients fared worse than controls in each subject, and the difference was most pronounced among girls (Lähteenmäki *et al.* 2007). Grades in foreign languages (representing verbal performance) were most affected.

2.5.4.3 Psychosocial problems

Childhood BT survivors are at increased risk of various adverse psychosocial outcomes compared to other childhood cancer survivors (Ellenberg *et al.* 2009, Gurney *et al.* 2009, Zeltzer *et al.* 2009, Armstrong *et al.* 2010, Kunin-Batson *et al.* 2011). Neurological and neurocognitive deficits may diminish physical, cognitive and social functioning and quality of life (Lannering *et al.* 1990, Mulhern *et al.* 2004, Ellenberg *et al.* 2009, Gurney *et al.* 2009, Reimers *et al.* 2009, Zeltzer *et al.* 2009). Childhood cancer survivors with medical morbidities and poor overall health have been identified in several CCSS studies as having an increased risk of poor psychosocial adaptation; particularly vulnerable are former BT survivors (Zeltzer *et al.* 2009). Physical ability influences the ability to perform daily tasks and to participate fully in life roles. Limitations to physical performance among childhood cancer survivors can have a negative impact on their participation in expected adult social roles (Gurney *et al.* 2009). The CCSS study found the survivors of childhood CNS malignancy to be at significant risk of neurocognitive impairment, which continues into adulthood and is correlated with lower socioeconomic achievement (Ellenberg *et al.* 2009).

Childhood BT survivors carry an increased risk of educational problems, unemployment, having no close friends and a lower likelihood of marriage when compared with other childhood cancer survivors or healthy subjects/siblings (Lannering *et al.* 1990, Ellenberg *et al.* 2009, Gurney *et al.* 2009). An elevated risk of psychosocial problems is associated with cranial irradiation (Lannering *et al.* 1990, Ilveskoski *et al.* 1996a, Ellenberg *et al.* 2009, Gurney *et al.* 2009, Harila *et al.* 2009, Reimers *et al.* 2009, Zeltzer *et al.* 2009). Radiotherapy has been found to be an important predictor of health-related quality of life primarily due to its effect on general intelligence, which suggests that IQ is a strong determinant of health-related quality of life (Reimers *et al.* 2009). A report from the CCSS showed that survivors of childhood CNS malignancies with a history of radiation exposure of temporal brain regions are at an increased risk of impairment to memory and social functioning, whereas exposure of frontal regions is associated with general health problems and physical performance limitations (Armstrong *et*

al. 2010). Another CCSS study found in a comparison of healthy survivors who did not receive CNS treatment and the siblings of survivors, that those survivors who received high-dose cranial radiation to the frontal areas of the brain (i.e. ≥ 35 Gy) reported significantly more problems with attention and processing speed, memory and emotional regulation (Zeltzer *et al.* 2009). Young age at diagnosis (Ilveskoski *et al.* 1996a, Lannering *et al.* 1990, Gurney *et al.* 2009, Reimers *et al.* 2009) and treatment-induced hearing loss (Ellenberg *et al.* 2009, Gurney *et al.* 2009) have emerged as risk factors for neurocognitive impairment and educational problems.

Thirty percent of Finnish malignant childhood BT survivors have been found to need special educational services (Ilveskoski *et al.* 1996a). Major disabilities were found in almost half; one half of the survivors were able to lead an active life and had only mild neurologic disabilities. Among Swedish childhood BT survivors moderate or severe disability was found in 34% (Lannering *et al.* 1990). Sixty-six percent had no or mild disability compatible with active life and employment, but were less often married or had fewer children compared with a control group of healthy subjects. The self-reported quality of life was not related to degree of disability. Patients with psychological-emotional sequelae self-evaluated their quality of life as lower than did patients with other types of long-term sequelae.

3. Aims of the study

The purpose of the present study was to evaluate the late effects of childhood primary BTs and their treatment.

The specific aims were as follows:

1. to evaluate the renal consequences of treatment with cytostatics (Study I).
2. to evaluate the possible risk of hypertension and to identify factors associated with it (Studies I and III).
3. to determine the prevalence of low BMD and to identify factors associated with it (Study II).
4. to estimate the prevalence of obesity, abnormalities in lipid and glucose metabolism, and metabolic syndrome and identify factors associated with these problems (Study III).
5. to analyze neurological and neurocognitive sequelae, social competence and quality of life (Study IV).

4. Patients and methods

4.1 Study design

This project was a population-based cross-sectional study undertaken in the Tampere region with a population of ~1 million. Tampere University Hospital is a regional centre. All the children in the district with a suspicion or diagnosis of a BT are remitted to the hospital. A total of 104 primary BT patients diagnosed below 17 years of age between 1983–1997 were treated in Tampere University Hospital. When the study began in summer 1998, 24 of them had died. Of the 80 survivors 75 were invited to attend for examinations which took place between September 1998 and January 2000 in Tampere University Hospital, the UKK Institute and the University of Tampere. Five patients were excluded as the study protocol was considered too demanding for them.

4.2 Patients

Fifty-two out of 75 potentially eligible patients (69%) participated in the study at a mean age of 14.2 years (range 3.8–28.7 years), after a mean follow-up of 7.5 (range 1.5–15.1) years (Table 1). Distance between hospital and home was the main reason for declining in nine cases. Three patients declined to participate because they were doing well and did not wish to make further visits to the hospital. The remaining non-participants (n=11) gave no specific reason. Forty-six patients were able to attend for bone densitometry (Study II). Reasons why all 52 study patients did not undergo bone densitometry pertained to co-operation, schedule or technical problems.

4.3 Treatment of the tumor

Tumor localization is presented in Table 1.

4.3.1 Surgery

All 52 participants had undergone one or more surgical procedures (Table 1). Twenty-nine (56%) were treated by surgery only.

TABLE 1. Clinical data on the 52 brain tumor patients diagnosed below 17 years of age.

Median age at diagnosis, years	6.0 (0.1–15.5)
< 7 years	30 (58)
< 1 years	4 (8)
< 3 years	14 (27)
7–12 years	14 (27)
≥ 13 years	8 (15)
Mean follow-up time, years	7.5 (1.5–15.1)
Mean time after treatment, years	6.2 (1.2–14.8)
Mean age at evaluation, years	14.2 (3.8–28.7)
< 7 years	8 (15)
7–12 years	13 (25)
13–17 years	15 (29)
≥ 18 years	16 (31)
Sex, male/female	27/25
Neurofibromatosis	3 (6)
Site of the tumor	
Infratentorial	25 (48)
Brain stem	5 (10)
Supratentorial	27 (52)
Cerebral hemisphere	13 (25)
Pituitary	1 (2)
Hypothalamus	5 (10)
Resection/biopsy	51/1 (98/2)
Grossly total	30 (58)
Partial	21 (40)
Reoperation/biopsy	17/1 (33/2)
One	11/1 (21/2)
Two	6 (12)
Severe perioperative complications[a]	15 (29)
Chemotherapy	17 (33)
Radiotherapy	20 (38)
Median age at start of radiotherapy, years	7.2 (0.2–20.9)
Cranial	12 (23)
local	9 (17)
cranial only	3 (6)
including hypothalamo-pituitary axis	11 (21)
Craniospinal	8 (15)
including hypothalamo-pituitary axis	8 (15)
Median tumor dose, Gy	50.5 (16.0–60.0)
Both chemotherapy and radiotherapy	14 (27)
Residive or residual tumor at evaluation	13 (25)
Hydrocephalus	30 (58)
Shunted hydrocephalus	29 (56)
Shunt revisions	17 (33)
One	7 (14)
Two	6 (12)
Three	2 (4)
More than five	2 (4)
Some kind of shunt at evaluation	27 (52)

Categoric data shown as number of patients (%) and continuous data as mean or median (range).
[a]Need of multiple operations, shunt revisions, meningitis, ventriculitis with ventriculostomy, expanding intracranial effusions or cysts, prolonged impaired consciousness, intractable seizures and neurological deficits.

4.3.2 Radiotherapy

Twenty (38%) patients were treated with radiotherapy (Table 1). Grade III–IV tumors, five grade II tumors (ependymoma, mixed glioma, astrocytomas), grade I–II mixed pilocytic astrocytoma, grade I pilocytic astrocytoma, and pituitary adenoma were treated with radiotherapy. Tumor location in the supratentorial midline areas, subtotal tumor resection or tumor residive were reasons for radiotherapy in some benign tumors. Six (12%) patients had received radiotherapy without chemotherapy, and nineteen irradiation to the HPA.

4.3.3 Chemotherapy

Seventeen (33%) patients had received chemotherapy, three (6%) without radiation. Of the 17 children who received chemotherapy 10 were on an ”eight drugs in one day” protocol, and eight received chemotherapy according to other protocols. One of these eight patients also received ”8 in 1” chemotherapy, and one chemotherapy according to two other different protocols. In the “8 in 1” protocol seven cytostatic drugs (CCNU, vincristine, hydroxyurea, procarbazine, cisplatin, cytarabine (ARA-C), and either dacarbazine or cyclophospamide) and methylprednisolone were administered (Ilveskoski *et al.* 1996b, Zeltzer *et al.* 1999). Other combinations were bleomycin and CCNU (one patient), vincristine and CCNU plus prednisolone or dexametasone (two patients), bleomycin and VP-16 plus cisplatin (one patient), bleomycin, vinblastine and VM-26 plus cisplatin (one patient), vincristine, VP-16 and cyclophosphamide plus cisplatin (two patients) followed by maintenance with vincristine, VP-16 and carboplatin (and cyclophosphamide). In progressive disease two patients received oral VP-16 treatment (Needle *et al.* 1997).

Altogether 14 patients received cisplatin treatment. The maximal cisplatin doses varied from 60 to 90 mg/m^2 in six- or eight-hour intravenous infusions. Two courses in the “8 in 1” chemotherapy were administered postoperatively with a two-week interval and eight courses after radiotherapy at six-week intervals. Nine patients received from 8 to 10 “8 in 1” courses; one patient only two. In the other protocols, two patients received cisplatin at three-week, and one at longer intervals five times. In seven cases cisplatin doses had to be reduced owing to nephrotoxicity. One patient received cisplatin 20 mg/m^2 in one-hour infusions for five days at three-week intervals, five courses. Cisplatin was always given with forced diuresis (fluids and mannitol).

4.3.4 Glucocorticoids

Glucocorticoids in variable doses and courses were included in the treatment of all patients. Dexamethasone was given for 5 to 8 days in conjunction with the tumor operation. Most patients received dexamethasone 2–4 mg/m^2/day during irradiation in courses of 4–12 weeks. In the "8 in 1" protocol methylprednisolone 300 mg/m^2 three times per course was administered (Ilveskoski *et al.* 1996b, Zeltzer *et al.* 1999). In the other combinations of chemotherapy, including steroids, one patient received prednisolone 40 mg/m^2 for 14 days per course and the other (who had also received "8 in 1" chemotherapy) dexametasone 2 mg/m^2 for 3 days per course. Additionally some occasionally received glucocorticoids during cytostatics. Some patients received dexamethasone for the treatment of nausea. Hydrocortisone substitution was given after these treatments if needed.

4.4 Hydrocephalus

Thirty (58%) subjects had had hydrocephalus; all except one had been shunted (Table 1). Shunt dysfunction was the primary reason for revision; only three patients experienced shunt infections. The longest time a patient had symptoms of fluctuating intracranial pressure before shunt revision was about one year.

4.5 Methods

4.5.1 Medical records and interview

Patients' medical records were checked for clinical history, and if necessary, their medical records were completed from other hospitals. A structured interview was used at evaluation, this being completed by a questionnaire filled by the patient and/or parent. Assessment of the activities of daily living included basic tasks of everyday life as adjusted for age; eating, dressing, bathing, toileting, transferring, and taking care of medication. Daily calcium intake was estimated to be normal or decreased according to Nordic recommendations, 1996 (Nordic nutrition recommendations 1996). Physical activity was estimated in hours per week. Intensity of exercise was not evaluated. The reasons for impaired mobility were assessed (e.g. hemiparesis). Anamnestic information on hearing difficulties was supplemented from medical records. Audiograms were used when available.

Hearing loss greater than 40 dB in the speech range or in the high frequency range was considered abnormal.

4.5.2 Physical examination

A structured form was used in physical examination. This included estimation of the visual impression of the patients' appearance classified into five categories: thin, slim, normal, overweight and obese. Height was measured with a Harpenden stadiometer (Holtain, Crymych, Dyfed, UK) and weight on electronic scales. Height SDS and relative weight (expressed as % of median weight for height) were assessed from Finnish growth charts (Sorva *et al.* 1984). A relative weight more than 120% was considered overweight (Talvensaari *et al.* 1996, Hakanen *et al.* 2006), and a relative weight 140% or more obesity (Hakanen *et al.* 2006). BMI was calculated according to the formula: weight (kg)/height^2 (m^2). Waist circumference was measured midway between the lowest rib and the iliac crest to the nearest millimeter with a metallic tape measure. All anthropometric measurements were taken three times and the mean value was used. Pubertal development was assessed according to Tanner and Whitehouse (Tanner & Whitehouse 1976).

BP was measured by an oscillometric method (DINAMAP Adult/Pediatric and Neonatal Vital Signs Monitor Model 1846 SX, Criticon, Inc., USA) preferentially on the right arm first in sitting position, and thereafter lying with the cuff covering at least two thirds of the upper arm. BP measured in sitting position was used in the analysis. In Study I patients 18 years or older were classified in an elevated BP category if systolic BP was 140 mmHg or greater, or if diastolic BP was 90 mmHg or greater (Joint National Committee 1997, Guidelines Subcommittee 1999) and in Study III if systolic BP was 130 mmHg or greater, or if diastolic BP was 85 mmHg or greater (Alberti *et al.* 2005). In Studies I and III for patients younger than 18 years BP at the 95th percentile or greater by height, sex and age according to Rosner and associates was considered elevated (Rosner *et al.* 1993, Joint National Committee 1997).

The neurological examination included estimation of the need for help (co-operation/following instructions/undressing and dressing), walking, speech, using hands, writing, reading and recognizing the clock/time, Romberg's test, straight line walking, jumping squats, side straddle hops and alternate leg hopping, standing and hopping on one foot, strength examinations, coordination tests including diadochokinesia, finger to finger test and point-to-point movement evaluation (finger to nose and heel to knee or doctor's hand), cranial nerves II–VIII, X and XII, reflexes and vibration sense. The E chart was used for visual acuity

testing. The chart was placed at a distance of five meters. One eye was covered at a time and the vision of each eye was recorded separately, as well as both eyes together. Simultaneous vision of both eyes < 0.5 was defined as impaired vision. Hearing was tested by whispering at a distance of five meters.

4.5.3 Tumor classification

The tumors were classified according to the current WHO classification (Table 2) (Louis *et al.* 2007a). All available histological samples were reanalyzed by Docent Hannu Haapasalo, MD. In reanalysis the diagnoses of astrocytic tumors were specified in six cases to pilocytic astrocytomas and grading changed from grade I–II to grade I in four cases. In addition, the diagnosis of one grade II cerebellar astrocytoma changed to grade I–II mixed pilocytic astrocytoma, one grade III anaplastic astrocytoma to grade II diffuse astrocytoma, one grade II malignant glioma to grade II pleomorphic xanthoastrocytoma and one grade II diffuse astrocytoma to grade II oligoastrocytoma.

4.5.4 Laboratory analyses (Studies I–III)

Blood and urine samples were taken in the morning after overnight fasting. The laboratory samples were analyzed using standard methods in Tampere University Hospital Laboratory, which also provided appropriate reference values for interpreting the results.

4.5.4.1 Renal function (Study I), glucose and uric acid (Studies I and III)

Tests for renal glomerular function included plasma creatinine, serum cystatin C and GFR. Glomerular proteinuria, measured as urine protein, may be reflected in serum albumin levels, which were measured. For tubular function blood glucose, plasma uric acid (I, III), sodium, potassium, acid-base balance from the capillary blood, and urine alpha-1-microglobulin, glucose and osmolality were measured. Plasma creatinine measurements were made enzymatically using a Vitros analyzer (Johnson & Johnson Clinical Diagnostic, Rochester, NY, USA) (Harmoinen 1996). Serum cystatin C concentrations were determined by a particle-enhanced turbidimetric immunoassay (Dako, Glostrup, Denmark) using a Hitachi 704 analyzer (Ylinen *et al.* 1999). GFR was measured during the study in patients who had received cisplatin treatment if the former value was abnormal or measured over two years earlier. GFR was determined by plasma clearance of 51Cr-EDTA

TABLE 2. WHO classification of the 52 childhood brain tumors.

	Grade	n (%)	n (%)
Astrocytic tumors		25 (48)	
Pilocytic astrocytoma	I		20 (38)
Mixed pilocytic astrocytoma	I–II		2 (4)
Diffuse astrocytoma	II		2 (4)
Pleomorphic xanthoastrocytoma	II		1 (2)
Oligodendroglial tumors		1 (2)	
Oligodendroglioma	II		1 (2)
Mixed gliomas		4 (8)	
Oligoastrocytoma	II		2 (4)
Other mixed glioma	II		1 (2)
Anaplastic mixed glioma	III		1 (2)
Ependymal tumors		5 (10)	
Ependymoma	II		2 (4)
Ependymoma	II–III		1 (2)
Anaplastic ependymoma	III		2 (4)
Choroid plexus tumors		2 (4)	
Choroid plexus papilloma	I		1 (2)
Choroid plexus carcinoma	III		1 (2)
Neuronal and mixed neuronal-glial tumors		2 (4)	
Desmoplastic infantile ganglioglioma	I		1 (2)
Ganglioglioma	II		1 (2)
Embryonal tumors		4 (8)	
Medulloblastoma	IV		2 (4)
PNET[a]	IV		2 (4)
Germ cell tumors[b]		4 (8)	
Germinoma			3 (6)
Mixed germ cell tumor (teratogerminoma)			1 (2)
Meningeal tumors		1 (2)	
Meningioma	I		1 (2)
Tumors of the sellar region		3 (6)	
Craniopharyngioma	I		2 (4)
Pituitary adenoma[c]			1 (2)
Tumor-like lesion (hamartoma)		1 (2)	

[a]Supratentorial primitive neuroectodermal tumor.

[b]Grading is not presented in the current WHO classification.
In statistical analysis corresponding to grade IV tumor.

[c]Grading is not presented in the current WHO classification.
In statistical analysis corresponding to grade I tumor.

assessed by the single injection method (Garnett *et al.* 1967). Values below 87 ml/min/1.73 m^2 were considered abnormal (Barrat 1974). Urinary alpha-1-microglobulin was measured nephelometrically (Behring BN II Nephelometer, Dade Behring, Marburg, Germany) with a sensitivity of about 5 mg/l. In the case of proteinuria (value over 0.1 g/l), 24-hour urine specimens were collected in order to analyze protein, phosphate, magnesium, calcium and creatinine excretion and creatinine clearance. If there was continuous glucosuria (value over 0.05 g/l in two samples) without proteinuria, an oral glucose tolerance test was applied.

4.5.4.2 Calcium metabolism (Studies I and II)

The tests for calcium metabolism included plasma calcium, serum ionized calcium, plasma alkaline phosphatase, phosphate, magnesium, intact PTH, serum $1,25(OH)_2D$ and 25-hydroxyvitamin D (25(OH)D).

4.5.4.3 Hormonal tests (Studies II and III)

Hormonal tests included serum estradiol in female and testosterone in male patients, for both sexes serum follicle-stimulating hormone (FSH), luteinizing hormone (LH), prolactin, IGF-1, insulin, free thyroxine (T4) and TSH.

4.5.4.4 Lipids (Study III)

Tests included plasma triglycerides, total cholesterol (TC), serum HDL-C and low-density lipoprotein cholesterol (LDL-C). TC was considered elevated if it was ≥ 5.0 and LDL-C if it was ≥ 3.0 mmol/l (De Backer *et al.* 2003).

4.5.5 Bone mineral density and body composition measurements (Studies II and III)

Total body bone mineral density (TBBMD), lean body mass (LBM), fat mass (FM) and body fat percentage were determined by DXA (Norland XR-26, software 2.5.2., Norland Corp. Fort Atkinson, WI, USA), as previously described (Fogelholm *et al.* 1996). The precision for these measurements was approximately 1 %. As most of the patients were under 18 years Z-scores were used for the assessment of skeletal status. Low BMD was defined as a TBBMD Z-score < -2.0. The Z-score for TBBMD was calculated as follows: Z-score = (patient´s TBBMD – mean TBBMD in the reference data)/ standard deviation in the reference data. For the reference data, age- and gender-specific TBBMD data measured with an

identical DXA device were used (Zanchetta *et al.* 1995). For patients over 20 years of age the reference values for 18–20-year-olds were used. DXA-measured fat percentage ≥ 33% was regarded as obesity in all male patients and prepubertal girls, while for pubertal girls and women limits ranging from approximately 35 to 50% depending on age were taken from appropriate reference data (Higgins *et al.* 2001, van der Sluis *et al.* 2002).

4.5.6 Definition of metabolic syndrome (Study III)

The definition issued by the International Diabetes Federation (IDF) was used to determine metabolic syndrome. The basic criterion for this disorder was central obesity: waist circumference 94 cm or more in men, and 80 cm or more in women (Alberti *et al.* 2005). For patients younger than 18 years, waist-height ratio ≥ 0.50 was considered to indicate central obesity (McCarthy & Ashwell 2006). In addition to central obesity at least two of following findings were required for diagnosis: triglycerides > 1.7 mmol/l; HDL-C < 1.03 mmol/l in men, and < 1.29 mmol/l in women; systolic BP ≥ 130 mmHg, or diastolic BP ≥ 85 mmHg; and fasting plasma glucose ≥ 5.6 mmol/l (Alberti *et al.* 2005). For patients younger than 18 years BP at the 95th percentile or greater by height, sex and age according to Rosner and associates was considered elevated (Rosner *et al.* 1993, Joint National Committee 1997). In 2007 IDF presented a definition for children and adolescents aged 10–15 years (Zimmet *et al.* 2007). In this study, the IDF criterion for adults as mentioned above was used for every patient, as only a part of the study patients belonged to that age-group and the two definitions are fairly similar.

4.5.7 Cognitive function tests (Study IV)

Cognitive abilities were tested using a Finnish version of the Wechsler Scale for Children – Revised, WISC-R (Wechsler 1984). Tests were made by MA Riitta Alalantela on patients aged from 6 to 16 years.

4.5.8 Estimation of motor disability (Study IV)

Motor disability was divided into four categories: 1. normal motor function, 2. clumsiness/mild asymmetry (including difficulties in balance, running, jumping, diadochokinesia or in coordination tests), 3. hemiparesis, 4. severe hemi- or tetraparesis (inability to walk or eat without help).

4.5.9 Estimation of quality of life (Study IV)

Quality of life was assessed using four categories based on Bloom's scale I–IV (Bloom *et al.* 1969, Ilveskoski *et al.* 1996a): group I: active life, no disability; group II: active life, mild disability (including learning disabilities involving schooling with special services within the normal school system, clumsiness, mild asymmetry, mild hemiparesis); group III: partial disability, capable of self-care if old enough (including clear evidence of intellectual impairment, severe learning disabilities necessitating schooling for the mentally subnormal, hemiparesis, seriously reduced vision < 0.5); group IV: severe disability, incapable of self-care (including mental retardation necessitating schooling for the mentally retarded, intractable epilepsy, severe hemi- or tetraparesis). The information from the structured interview was used to support this classification as part of the information required in the International Classification of Functioning, Disability and Health (ICF) (World Health Organization 2001).

4.5.10 Statistical analyses

Statistical analyses were carried out using the SPSS for Windows versions 10.0, 16.0, 17.0 and 18.0.

In Study I continuous data were analyzed using Mann-Whitney U or Kruskall-Wallis test. One-way and two-way analysis of variance (ANOVA) were also used in analyzing data with normal distribution. Categorized data were analyzed using Fisher´s exact test. The Spearman correlation coefficient was used for correlation estimates and Wilcoxon's signed ranks test to estimate the association between values at completion of treatment and the latest values.

In Study II differences between the different subgroups in continuous variables were analyzed by analysis of covariance (ANCOVA), using LBM and height SDS as covariates. ANOVA was applied only when testing height SDS between different subgroups. In analysis of ordinal data such as Tanner stage 1–5 and number of shunt revisions, Mann-Whitney U test was used. Pearson's correlation coefficient was used to evaluate associations between two continuous variables. Finally, a multiple regression analysis was made to identify factors significantly associated with TBBMD Z-score. Variables were first divided into blocks, each block consisting of three to four variables. Blocks were formed so that each consisted of variables descriptive of patient characteristics, treatment, medication, hormonal abnormalities and calcium metabolism, and included LBM and height SDS. Multiple regression analyses using TBBMD Z-score as dependent variable were made separately for each block and thereafter, a final model consisting of all

significant variables from the primary blocks was formed and tested. A variable was included in the final model if its significance was < 0.05.

In Study III continuous data were analyzed using independent sample t-test or ANOVA in the case of normal distribution, and Mann-Whitney U test or Kruskal-Wallis test in the case of skewed distribution or ordinal variables. Categorized data were analyzed using Fisher's exact test, χ^2 test or exact χ^2 test as appropriate.

In Study IV associations between selected explanatory variables (gender, diagnosis below the age of three years, tumor type (pilocytic astrocytoma vs. ependymal or embryonal tumor vs. other tumors), tumor grade (grade I–II vs. higher degree of malignancy), tumor location, severe perioperative complications, treatment comprising only operation compared to more demanding treatment including operation and radiotherapy and/or chemotherapy, occurrence of residive or residual tumor upon evaluation, tumor reoperations, cranial irradiation, chemotherapy, hydrocephalus and shunt revisions) and outcome variables (motor function, full-scale IQ, verbal IQ, performance IQ, school achievement, activities of daily living and quality of life) were evaluated. Mann-Whitney U test or Kruskal-Wallis test was used for continuous data with skewed distributions or ordinal variables. Categorized data were analyzed using Fisher's exact test, χ^2 test or exact χ^2 test as appropriate.

4.6 Ethics

The study was approved by the Ethical Committee of Tampere University Hospital and was carried out with signed parental and/or patients' consent.

5. Results

5.1 Renal function (Study I)

Clinical characteristics of the patients who received and of those who did not receive cisplatin treatment are presented in Table 3.

TABLE 3. Characteristics of the cisplatin and no-cisplatin groups.

	No cisplatin treatment	Cisplatin treatment	p value
Number of patients	38	14	
Male gender	16 (42.1)	11 (78.6)	0.029
Age at evaluation (years)	13.9 (4.9–28.7)	15.5 (3.8–22.5)	0.710
Age at diagnosis (years)	6.0 (0.6–15.5)	4.3 (0.1–15.1)	0.421
Age treatment ended (years)	6.2 (0.6–21.0)	7.7 (1.3–15.6)	0.901
Follow-up time (years)	6.1 (1.5–15.1)	8.9 (2.2–13.1)	0.343
Time after treatment (years)	5.2 (1.2–14.8)	7.2 (1.5–11.9)	0.710
Radiotherapy	9 (23.7)	11 (78.6)	0.001
Craniospinal radiation reaching renal level	4 (10.5)	3 (21.4)	1.000
Cumulative dose of cisplatin (mg/m^2)	0	528 (181–882)	
Number of patients with CCNU treatment	2	10	<0.001
Number of patients with carboplatin treatment	0	2	0.069
Number of patients with cyclophosphamide treatment	0	5	0.001
Weight (% of median weight for height)	107 (74–155)	111 (81–176)	0.297
Body mass index (kg/m^2)	19.5 (13.0–28.0)	20.7 (13.6–34)	0.415
Systolic blood pressure (mmHg)	114 (92–164)	128 (90–155)	0.312
Diastolic blood pressure (mmHg)	65 (50–100)	70 (50–105)	0.352

Categoric data shown as number of patients (%) and continuous data as median (range).

5.1.1 Glomerular function

Five patients in the cisplatin group (36%) had abnormal GFR immediately after treatment. Their cumulative doses of cisplatin ranged from 490 mg/m^2 to 880 mg/m^2. During the study only one patient showed recovery from previous renal

glomerular dysfunction: thus altogether four patients in the cisplatin group (29%) had abnormal GFR (Table 4). In two of these the levels of plasma creatinine and serum cystatin C were elevated. The latest GFR values showed a weak negative correlation with the creatinine (r=-0.547) but not with the cystatin C values (r=-0.401). All patients had normal serum albumin levels.

TABLE 4. Results of renal glomerular function tests in the cisplatin and no-cisplatin groups.

	No cisplatin treatment (n=38)	Cisplatin treatment (n=14)	p value
GFR (ml/min/1.73 m^2)		106 (69–149)	
GFR <87 ml/min/1.73 m^2	0	4 (28.6)	0.004
Plasma creatinine (µmol/l)	61 (34–94)	70 (23–153)	0.283
Serum cystatin C (mg/l)	1.06 (0.78–1.45)	1.04 (0.65–1.70)	0.765
Serum albumin (g/l)	42 (38–49)	44 (39–48)	0.137
Proteinuria (dU-protein > 100 mg/l)	2 (5.3)	1 (7.1)	1.000

Categoric data shown as number of patients (%) and continuous data as median (range).

In Figure 1 the GFR values are presented at the end of treatment and after follow-up. There was no statistically significant difference between the latest GFR values and values at close of treatment (p=0.594), but some patients showed improvement and some deterioration in GFR.

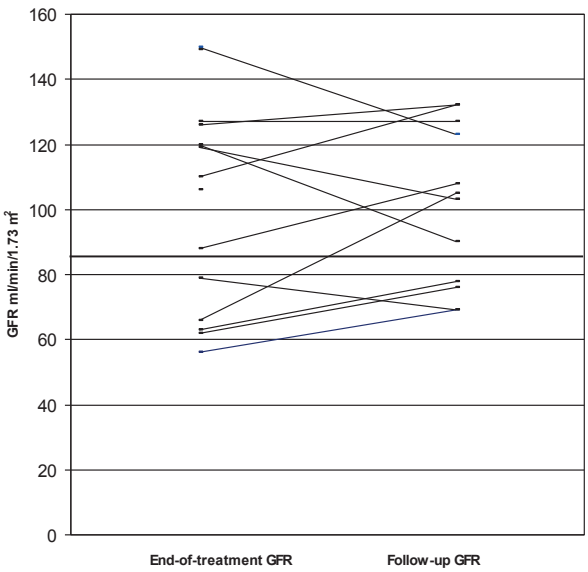

FIGURE 1. Glomerular filtration rate (GFR) measured by plasma clearance of 51Cr-EDTA in 14 brain tumor patients diagnosed in childhood and treated with cisplatin. The median follow-up time was 6.0 years (range 1.2-14.8). Abnormal values < 87 ml/min/1.73 m^2.

Patients with renal glomerular dysfunction had received higher cumulative doses of cisplatin (mg/m^2) when compared with those without renal glomerular dysfunction (p=0.039 at the end of the treatment, p=0.016 during the study) and the cumulative dose of cisplatin (mg/m^2) showed a moderate negative correlation with the GFR values measured at the end of treatment (r=-0.710). The two patients in the cisplatin group who had received carboplatin treatment showed no renal glomerular dysfunction, but one of them had tubular proteinuria. All four patients with abnormal GFR had also received CCNU treatment, and none of them had received cyclophosphamide. The two patients in the no-cisplatin group who had received CCNU treatment showed no signs of renal impairment. Spinal radiation did not increase the risk of abnormal renal function.

5.1.2 Tubular function

There were several signs of disturbed tubular function in the cisplatin group (Tables 5 and 6). The commonest manifestation of tubular toxicity was hypomagnesemia. Low plasma phosphate and potassium levels, tubular proteinuria, metabolic alkalosis and hyperuricemia were also more common in patients on cisplatin treatment. All patients with renal glomerular dysfunction also yielded several laboratory findings indicating tubular dysfunction.

TABLE 5. Results of renal tubular function tests in the cisplatin and no-cisplatin groups.

	No cisplatin treatment (n=38)	Cisplatin treatment (n=14)	p value
Fasting blood glucose (mmol/l)	4.4 (3.6–5.3)	4.5 (4.0–5.3)	0.346
Plasma uric acid (mmol/l)	0.23 (0.10–0.46)	0.30 (0.11–0.65)	0.112
Hyperuricemia[a]	2 (5.3)	3 (21.4)	0.114
Plasma sodium (mmol/l)	142 (137–147)	142 (140–148)	0.721
Plasma potassium (mmol/l)	3.8 (3.3–4.5)	3.7 (3.2–4.4)	0.026
Hypokalemia (P-potassium < 3.3 mmol/l)	0	1	0.269
Metabolic acidosis (BE < -3.0)	1 (2.7) (n=37)	0	1.000
Metabolic alkalosis (BE > 3.0)	0 (n=37)	2 (14.3)	0.071
Tubular proteinuria (U-alfa-1-microglobulin ≥8 mg/l)	1 (2.6)	3 (21.4)	0.055
Urine osmolality (mosm/kg H_2O)	759 (288–1204) (n=37)	810 (348–1203)	0.429
Low urine osmolality (U-osmolality < 600 mosm/kg H_2O)	12 (32.4) (n=37)	4 (28.6)	1.000
Continuous glucosuria (U-glucose > 0.05 g/l)	4 (10.8) (n=37)	2 (14.3)	1.000

Categoric data shown as number of patients (%) and continuous data as median (range).

[a]Hyperuricemia: P-uric acid > 0.34 mmol/l in children, > 0.32 mmol/l in women and > 0.45 mmol/l in men.

5.1.3. Calcium metabolism (Studies I and II)

At close of treatment, 9/14 patients in the cisplatin group were hypomagnesemic. Thereafter the magnesium level further declined in 10/14 cases (p=0.006). In the cisplatin group, the patient with the lowest magnesium level (0.34 mmol/l) had muscular weakness. The cumulative dose of cisplatin showed a weak negative correlation with magnesium values (r=-0.676). In spite of magnesium supplementation, three out of seven patients had low magnesium levels.

TABLE 6. Results of calcium metabolism tests in the cisplatin and no-cisplatin groups.

	No cisplatin treatment (n=38)	Cisplatin treatment (n=14)	p value
Plasma magnesium (mmol/l)	0.85 (0.69–0.96)	0.64 (0.34–0.93)	<0.001
Hypomagnesemia (P-magnesium < 0.75 mmol/l)	4 (10.5)	10 (71.4)	<0.001
Plasma calcium (mmol/l)	2.37 (2.18–2.58)	2.38 (2.24–2.62)	0.358
Serum ionized calcium (mmol/l)	1.30 (1.23–1.39)	1.28 (1.20–1.43)	0.419
Plasma alkaline phosphatase (U/l)	350 (77–727)	272 (75–706)	0.829
Plasma phosphate (mmol/l)	1.32 (0.96–1.71)	1.09 (0.77–1.58)	0.013
Hypophosphatemia[a]	0	3 (21.4)	0.016
Plasma intact parathyroid hormone (pmol/l)	3.2 (0.8–10.6)	2.7 (1.1–7.1)	0.926
Serum 1,25-dihydroxyvitamin D (pmol/l)	76 (50–121) (n=37)	77 (50–116)	0.751

Categoric data shown as number of patients (%) and continuous data as median (range).
[a]Normal limits for 2–12-year-old children 1.20–1.80 and 13–16-year-old children 1.10–1.80 and for adults 0.80–1.40 mmol/l.

Secondary hyperparathyroidism had previously been diagnosed in one patient with renal dysfunction. There was one patient in both the cisplatin and no-cisplatin group with an elevated (over 6.8 pmol/l) plasma intact PTH concentration. Both had a low dietary calcium intake. All patients had normal plasma calcium, serum ionized calcium, plasma alkaline phosphatase and vitamin D levels according to laboratory reference values. The reference values used for serum 25(OH)D were lower for winter than for summer according to the standards of that time. In the whole group the median serum 25(OH)D was 39.7 nmol/l (range 18.0–81.4, n=51). In Study II the 25(OH)D level was below 38 nmol/l in 21 out of 45 patients, and seven patients had low dietary calcium intake.

5.2 Blood pressure (Studies I and III)

In Study I eight patients (15%) were hypertensive. Elevated BP was more common among those who had received cisplatin treatment (p=0.003), cranial irradiation (p=0.003), had renal glomerular dysfunction (p=0.009) or were hypomagnesemic (p=0.025). The risk of elevated BP was higher if the patients were exposed to both cisplatin and cranial irradiation (p=0.002) (Table 7). Additional spinal radiation did not seem to affect the observed elevated BP (p=1.000). Three patients needed antihypertensive medication. Two of them suffered from renal glomerular dysfunction. In Study III, where the BP limits for adult patients were lower than in study I, this due to the use of the IDF criterion for metabolic syndrome, 12 patients (23%) had raised BP associated with cranial irradiation.

TABLE 7. Elevated blood pressure among 52 childhood brain tumor survivors.

	No cisplatin treatment (n=38)	**Cisplatin treatment (n=14)**
No irradiation (n=32)	1/29 (3%)	0/3 (0%)
Cranial irradiation (n=20)	1/9 (11%)	6/11 (55%)

5.3 Bone mineral density (Study II)

5.3.1 Patients

Thirty of the 46 patients who attended for bone densitometry were younger than 18 years. Fourteen were prepubertal. Treatment of the tumor at the time of puberty had occurred in 13 cases. Puberty in 27 cases had started at normal age. One 7.8-year-old girl received therapy for sexual precocity. Four patients received replacement therapy with sex steroids; in three cases treatment was started later than normal puberty (girls at 12.9 and 15.7 years, boy at 15.9 years). Two patients received GH therapy, four replacement therapy with glucocorticoids, and six thyroxin medication at the time of the present study. Altogether eight patients received some hormone drug, five of them more than one, and five received antiepileptic medication. The distribution of height SDS of the patients was normal, ranging from -4.6 SD to +2.8 SD (mean +0.0 SD). The patients who had received cranial or craniospinal irradiation or chemotherapy, had GHD (n=9; earlier diagnosis or low IGF-1 level) or sex hormone deficiency according to laboratory findings (n=4) during this study, were shorter than others (all p values

≤ 0.001). Four had hyperprolactinemia. All patients were ambulatory, but 12 had impaired mobility. Mean physical activity was 4.5 hours/week (range 0.0–13.0) (n=40, could not be calculated for children below 7 years of age).

5.3.2 Total body bone mineral density

As judged from Z-score, TBBMD was generally low, ranging from -5.7 to +0.6 (mean -1.7) (Figure 2). Fifteen patients (33 %) had TBBMD Z-scores < -2.0.

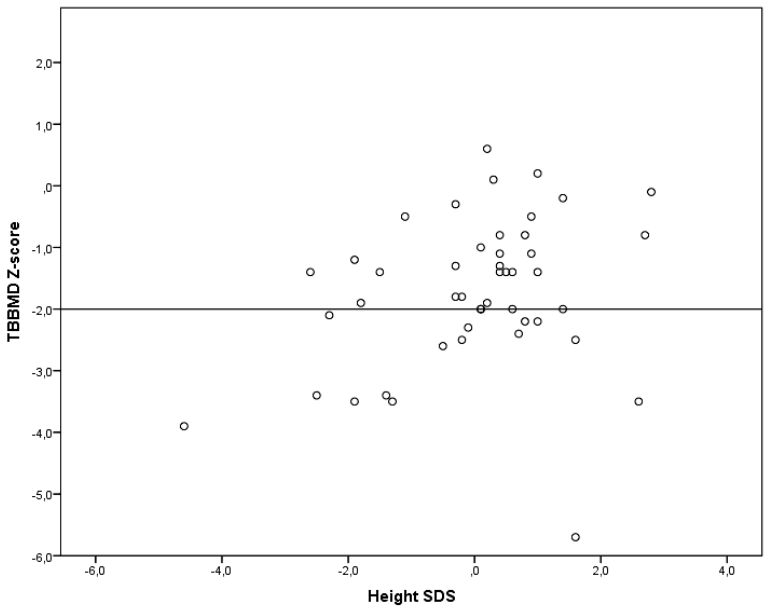

FIGURE 2. Total body bone mineral density (TBBMD) Z-score of 46 childhood brain tumor survivors as a function of height SDS. Low bone mineral density was defined as TBBMD Z-score < -2.0.

Out of a number of potential factors, only combined craniospinal irradiation was significantly associated with low Z-score (p=0.034, according to multiple regression analysis), while exclusive cranial irradiation showed a weaker association (p=0.100, according to multiple regression analysis), as did hydrocephalus (p=0.092, according to ANCOVA) and number of shunt revisions (p=0.093, according to Mann-Whitney U test). The mean Z-score for TBBMD according to radiotherapy and hydrocephalus is presented in Table 8.

TABLE 8. Mean total body bone mineral density (TBBMD) Z-score in 46 childhood brain tumor survivors according to radiotherapy and hydrocephalus.

	TBBMD Z-score (range)	p[a]
Radiotherapy		0.088
craniospinal (n=5)	-3.0 (-3.9 to -1.8)	
cranial (n=10)	-1.1 (-2.4 to +0.1)	
no (n=31)	-1.7 (-5.7 to +0.6)	
Hydrocephalus		0.092
yes (n=26)	-2.1 (-5.7 to -0.1)	
no (n=20)	-1.3 (-3.4 to +0.6)	

[a]ANCOVA

5.4 Obesity (Study III)

Ten (19%) patients were overweight and four (8%) obese. According to DXA, obesity was found in 16/46 (35%) patients. Central obesity was found in 11 (21%) patients and 10 of them had a relative weight more than 120%. According to visual impression, two patients were estimated to be thin (4%), 11 slim (21%), 27 normal (52%), 11 overweight (21%) and one obese (2%). Twelve (86%) patients with a relative weight more than 120% and all with central obesity looked on visual appraisal overweight or obese.

Altogether 13 patients were receiving thyroxine (n=10), glucorticoid (n=4), GH (n=4) and/or sex hormone (n=6) therapy at the time of the present study (Table 9). All had hypothalamic/hypophyseal damage (surgery or radiation in this area). One patient with thyroxine substitution had slightly elevated free T4, which was normal at check-up.

Cranial irradiation, hypothalamic/hypophyseal damage, GHD and impaired mobility were associated with overweight/obesity and central obesity (Table 9). Among GHD patients the tendency to general and central obesity was more marked without supplementation. Cranial irradiation alone was not as harmful as the hormonal problems caused by irradiation or the tumor itself and its surgery.

5.5 Metabolic changes (Study III)

Characteristics of the patients who had received and of those who had not received radiotherapy are presented in Table 10.

TABLE 9. Overweight/obesity and central obesity among 52 childhood brain tumor survivors with cranial irradiation, hormone therapy, growth hormone (GH) deficiency and impaired mobility.

	Relative weight (%)[a]		Body fat (%)[b]		Waist-height ratio		Relative weight > 120 %		Obesity according to DXA[b]		Central obesity[c]	
	mean (range)	p	mean (range)	p	mean (range)	p	n (%)	p	n (%)	p	n (%)	p
Cranial irradiation												
yes (n=20)	117 (89-176)	0.058	36.2 (22.3–49.6) (n=15)	0.324	0.48 (0.38–0.58)	0.014	9 (45)	0.028	6 (40) (n=15)	0.744	6 (30)	0.299
no (n=32)	106 (74–155)		33.0 (8.3–53.7) (n=31)		0.44 (0.36–0.57)		5 (16)		10 (32) (n=31)		5 (16)	
Hormone therapy[d]												
yes (n=13)	125 (94–155)	0.002	42.1 (27.8–53.7) (n=9)	0.007	0.50 (0.42–0.56)	<0.001	8 (62)	0.003	6 (67) (n=9)	0.047	8 (62)	<0.001
no (n=39)	106 (74–176)		32.1 (8.3–47.8) (n=37)		0.44 (0.36–0.58)		6 (15)		10 (27) (n=37)		3 (8)	
GH deficiency												
yes (n=12)	132 (94–176)	<0.001	41.8 (27.8–53.7) (n=9)	0.009	0.52 (0.43–0.58)	<0.001	8 (67)	0.001	6 (67) (n=9)	0.047	7 (58)	0.001
no (n=40)	104 (74–135)		32.2 (8.3–47.8) (n=37)		0.44 (0.36–0.57)		6 (15)		10 (27) (n=37)		4 (10)	
GH therapy												
yes now (n=4)	115 (94–155)	<0.001	40.8 (27.8–53.7) (n=2)	0.068	0.48 (0.43–0.56)	<0.001	1 (25)	<0.001	1 (50) (n=2)	0.088	1 (25)	0.001
yes previously (n=5)	137 (106–176)		40.7 (29.9–49.6) (n=5)		0.54 (0.45–0.58)		4 (80)		3 (60) (n=5)		3 (60)	
no never (n=3)	144 (139–147)		45.7 (38.3–53.1) (n=2)		0.55 (0.53–0.55)		3 (100)		2 (100) (n=2)		3 (100)	
no deficiency (n=40)	104 (74–135)		32.2 (8.3–47.8) (n=37)		0.44 (0.36–0.57)		6 (15)		10 (27) (n=37)		4 (10)	
Impaired mobility												
yes (n=15)	123 (74–176)	0.004	40.0 (25.4–53.7) (n=12)	0.016	0.49 (0.37–0.58)	0.003	8 (53)	0.013	6 (50) (n=12)	0.292	8 (53)	0.001
no (n=37)	105 (81–138)		32.0 (8.3–49.6) (n=34)		0.44 (0.36–0.57)		6 (16)		10 (29) (n=34)		3 (8)	

[a]Expressed as % of median weight for height; [b]percentage body fat determined by dual-energy X-ray absorptiometry (DXA) ≥ 33% was regarded as obesity in all male patients and prepubertal girls, the limits for pubertal girls and women were taken from reference data by van der Sluis et al; [c]waist ≥ 80 cm in women, ≥ 94 cm in men, waist-height ratio ≥ 0.50 in patients younger than 18 years; [d]thyroxine, glucocorticoid, GH and/or sex hormone therapy at the time of the study.

TABLE 10. Characteristics, lipid and glucose metabolism and plasma uric acid values in the 52 childhood brain tumor survivors according to cranial irradiation.

	Cranial irradiation (n=20)	No cranial irradiation (n=32)	p value
Age at study (years)	16.8 (4.9–28.7)	12.9 (3.8–24.8)	0.023
Median age at diagnosis (years)	7.1 (0.1–15.5)	5.9 (0.6–15.5)	0.486
Male gender	12 (60)	15 (47)	0.404
Median Tanner stage (breasts/genitals)	5 (1–5)	2 (1–5)	0.022
Median plasma triglycerides (mmol/l)	0.87 (0.43–2.54)	0.78 (0.32–1.74)	0.132
Serum high-density lipoprotein cholesterol (mmol/l)	1.44 (0.78–2.37)	1.52 (0.93–2.21)	0.510
Plasma cholesterol (mmol/l)	4.7 (3.0–6.9)	4.1 (2.9–5.9)	0.017
Serum low-density lipoprotein cholesterol (mmol/l)	2.8 (1.5–4.7)	2.2 (1.3–3.3)	0.012
Fasting blood glucose (mmol/l)	4.4 (3.6–5.3)	4.5 (3.9–5.3)	0.758
Hyperglycemia (blood glucose ≥ 5.6 mmol/l)	0 (0)	0 (0)	
Median serum insulin (mU/l)	9 (4–48) (n=19)	7 (4–23)	0.438
Hyperinsulinemia (serum insulin > 20 mU/l)	1 (5) (n=19)	1 (3)	1.000
Plasma uric acid (mmol/l)	0.33 (0.17–0.65)	0.24 (0.10–0.45)	0.005

Continuous data are shown as mean (range), if not otherwise stated, and categoric data as number of patients (%).

5.5.1 Lipids

Nineteen (37%) patients had at least one abnormal lipid value. Nine of these patients were neither overweight nor obese. Altogether 13 (25%) patients had hypercholesterolemia, 14 (27%) had raised LDL-C, nine (17%) had reduced HDL-C and five (10%) raised triglycerides. Cranial irradiation, hypothalamic/hypophyseal damage manifested as hormonal problems, GHD and impaired mobility were risk factors for dyslipidemia (Tables 10 and 11). Among GHD patients, GH supplementation seemed to affect the lipid values beneficially (Table 11).

5.5.2 Glucose metabolism

There were no hyperglycemic patients, and only two (4%) had fasting hyperinsulinemia (Table 10). Mean fasting blood glucose was lower among patients with hormone therapy than without [4.2 (range 3.6–5.0) vs. 4.5 (3.9–5.3) mU/l, p=0.047]. Median serum insulin was higher among patients with GHD than without [13 (range 5–48) (n=11) vs. 7 (4–23) mU/l, p=0.023]. Mean fasting blood glucose was lower among patients who had impaired mobility compared to those who did not [4.2 (range 3.6–4.8) vs. 4.5 (3.7–5.3) mmol/l, p=0.006].

TABLE 11. Dyslipidemia, metabolic syndrome, raised blood pressure (BP) and hyperuricemia among childhood brain tumor survivors with cranial irradiation, hormone therapy, growth hormone (GH) deficiency and impaired mobility.

	Triglycerides ↑[a]		HDL-C ↓[b]		Cholesterol ↑[c]		LDL-C ↑[d]		Metabolic syndrome[e]		Raised BP[f]		Hyperuricemia[g]	
	n (%)	p	n (%)	p	n (%)	p	n (%)	p	n (%)	p	n (%)	p	n (%)	p
Cranial irradiation														
yes (n=20)	4 (20)	0.066	5 (25)	0.280	9 (45)	0.019	9 (45)	0.028	4 (20)	0.018	8 (40)	0.040	4 (20)	0.066
no (n=32)	1 (3)		4 (13)		4 (13)		5 (16)		0 (0)		4 (13)		1 (3)	
Hormone therapy[h]														
yes (n=13)	3 (23)	0.093	7 (54)	<0.001	6 (46)	0.064	6 (46)	0.086	4 (31)	0.003	3 (23)	1.000	4 (31)	0.011
no (n=39)	2 (5)		2 (5)		7 (18)		8 (21)		0 (0)		9 (23)		1 (3)	
GH deficiency														
yes (n=12)	4 (33)	0.008	5 (42)	0.022	6 (50)	0.051	6 (50)	0.063	3 (25)	0.034	4 (33)	0.437	4 (33)	0.008
no (n=40)	1 (3)		4 (10)		7 (18)		8 (20)		1 (3)		8 (20)		1 (3)	
GH therapy														
yes now (n=4)	0 (0)	0.004	1 (25)	0.035	1 (25)	0.034	1 (25)	0.044	0 (0)	0.028	1 (25)	0.838	1 (25)	0.037
yes previously (n=5)	3 (60)		2 (40)		4 (80)		4 (80)		2 (40)		2 (40)		2 (40)	
no never (n=3)	1 (33)		2 (67)		1 (33)		1 (33)		1 (33)		1 (33)		1 (33)	
no deficiency (n=40)	1 (3)		4 (10)		7 (18)		8 (20)		1 (3)		8 (20)		1 (3)	
Impaired mobility														
yes (n=15)	1 (7)	1.000	4 (27)	0.419	7 (47)	0.034	7 (47)	0.081	2 (13)	0.569	4 (27)	0.726	3 (20)	0.137
no (n=37)	4 (11)		5 (14)		6 (16)		7 (19)		2 (5)		8 (22)		2 (5)	

[a]Raised triglycerides: plasma triglycerides > 1.7 mmol/l; [b]reduced high-density lipoprotein cholesterol: serum HDL-C < 1.03 mmol/l in male, and < 1.29 mmol/l in female patients; [c]hypercholesterolemia: plasma total cholesterol ≥ 5.0 mmol/l; [d]elevated low-density lipoprotein cholesterol: serum LDL-C ≥ 3.0 mmol/l; [e]metabolic syndrome was defined on International Diabetes Federation (IDF) criteria; [f]for patients 18 years or older systolic BP ≥ 130 or diastolic BP ≥ 85 mmHg were classified as raised, and for patients younger than 18 years BP values at the 95th percentile or geater by height, sex and age according to Rosner et al. were classified as raised; [g]plasma uric acid > 0.34 mmol/l in children, > 0.32 mmol/l women and > 0.45 mmol/lin men; [h]thyroxine, glucocorticoid, GH and/or sex hormone therapy at the time of the study.

5.5.3 Metabolic syndrome

Four (8%) patients had metabolic syndrome. Cranial irradiation, hypothalamic/hypophyseal damage and GHD were risk factors. The tendency to metabolic syndrome was stronger among GHD patients without GH supplementation (Table 11).

Five (10%) patients had hyperuricemia (Tables 10 and 11). Two of these had metabolic syndrome [2/47 (4%) vs. 2/5 (40%), p=0.042]. Hypothalamic/hypophyseal damage and GHD were statistically significantly associated with hyperuricemia (Table 11).

5.6 Neurological outcome (Study IV)

5.6.1 Patients diagnosed at under one year of age

Four of the participants (ages during the study 6.6–13.1) were younger than one year at diagnosis (Table 1). Three of them showed abnormal neurological status at evaluation, two clumsiness, three speech/language difficulties. All had some focal problems such as visuospatial difficulties in psychological tests. Regarding quality of life, one was classified in group I, two in group II, and one in group IV.

5.6.2 Neurological findings

All participants were ambulatory at evaluation, but only 50% showed normal motor function (Table 12). Of the selected explanatory variables shunt revisions were statistically significantly associated with motor disability (Table 13). Neurological status was abnormal in 36 (69%) cases. Cranial nerve dysfunctions were fairly common (Table 12). Visual field defects were assessed on clinical examination, but ophthalmologist's evaluation was also used. Medical records were used when deciding if there was hearing loss or not. The speech of seven was dysarthric.

TABLE 12. Neurological and neurocognitive outcome of the 52 brain tumor survivors diagnosed below 17 years of age.

Motor function	
Normal	26 (50)
Clumsiness/mild asymmetry	15 (29)
Hemiparesis[a]	11 (21)
Severe hemi- or tetraparesis	0 (0)
Changed handedness	7 (13)
Facial paresis	6 (12)
Impaired vision <0.5	9 (17)
Visual field defect (n=51)[b]	
Yes	7 (14)
Uncertain or cannot be evaluated	4 (8)
Strabismus (n=51)[b]	13 (25)
Hearing loss	9 (17)
Hearing aid	2 (4)
Speech/language difficulties	10 (19)
Cognitive function in 6–16 years old participants (n=21)	
Median full-scale IQ	85 (39–110)
IQ below 70	6 (29)
IQ 70–85	5 (24)
IQ over 85	10 (48)
Median verbal IQ	86 (41–112)
Median performance IQ	87 (54–118)
Antiepileptic medication	7 (13)
Monthly epileptic seizures	4 (8)
Intractable epileptic seizures	1 (2)
School achievement (n=44)	
School with normal syllabus	30 (68)
School with special services	14 (32)
within the normal school system	7 (16)
in a special school system	7 (16)
for mentally subnormal	5 (11)
for mentally retarded	2 (5)
Activities of daily living	
Normal	45 (87)
Need for supervision	1 (2)
Need help	6 (12)
Quality of life[c]	
Group I	20 (38)
Group II	17 (33)
Group III	11 (21)
Group IV	4 (8)

Categoric data shown as number of patients (%) and continuous data as mean or median (range).
[a]In one case hemiparesis had developed after multiple sclerosis.
[b]One participant was blind.
[c]Quality of life was evaluated using four categories: group I: no disability, active life; group II: mild disability, active life; group III: partial disability, capable of self-care; group IV: severe disability, incapable of self-care.

TABLE 13. Motor function, school achievement, activities of daily living and quality of life of the 52 childhood brain tumor survivors. Only statistically significant[a] or borderline significant[b] explanatory variables are reported.

Explanatory variable	Outcome variable				
	Motor function (%)				
Shunt revisions	Normal	Clumsiness	Hemiparesis	p value	
Yes	35	53	12	0.032	
No	57	17	26		
Tumor reoperations					
Yes	39	22	39	0.075	
No	56	32	12		
	School achievement[c] (%)				
Shunt revisions	Normal	Special1	Special2	Special3	p value
Yes	42	25	33	0	0.013
No	78	13	3	6	
Chemotherapy					
Yes	50	14	21	14	0.063
No	77	17	7	0	
	Activities of daily living (%)				
Tumor reoperations	Normal	Supervision	Help	p value	
Yes	72	6	22	0.099	
No	94	0	6		
	Quality of life[d] (%)				
Tumor reoperations	Group I	Group II	Group III	Group IV	p value
Yes	17	44	17	22	0.004
No	50	27	24	0	
Shunt revisions					
Yes	12	59	24	6	0.016
No	51	20	20	9	
Tumor location					
Supratentorial	33	22	33	11	0.070
Infratentorial	44	44	8	4	
Precise tumor location					
Hemispheric	39	23	15	23	0.018
Other supratentorial	29	21	50	0	
Brain stem	20	80	0	0	
Other infratentorial	50	35	10	5	

[a] $p < 0.05$

[b] $0.05 \leq p \leq 0.1$

[c] School achievement: normal (normal syllabus), special1 (special services within the normal school system), special2 (special services in a special school system for mentally subnormal), special3 (special services in a special school system for mentally retarded).

[d] Group 1: active life, no disability; group II: active life, mild disability; group III: partial disability, capable of self-care if old enough; group IV: severe disability, incapable of self-care.

5.6.3 Psychological tests

Twenty-one (70%) of the 30 participants between 6–16 years of age were willing to participate in psychological tests (WISC-R), where median full-scale IQ was 85 (39–110); in 29% cases IQ was <70 (Table 12). Tumor reoperations were statistically significantly associated with lower full-scale IQ, verbal IQ, and performance IQ, and chemotherapy with lower performance IQ (Table 14).

TABLE 14. Psychological test results (WISC-R) of the 21 6 to 16 years old childhood brain tumor survivors. Only statistically significant[a] or borderline significant[b] explanatory variables are reported.

Explanatory variable	Outcome variable	
	median (min-max)	p value
Tumor reoperations	Full scale IQ	
Yes	69 (39–96)	0.012
No	94 (68–110)	
Tumor reoperations	Verbal IQ	
Yes	71 (41–101)	0.041
No	86 (72–112)	
Tumor reoperations	Performance IQ	
Yes	71 (54–100)	0.014
No	98 (68–118)	
Chemotherapy	Performance IQ	
Yes	68 (54–92)	0.020
No	93 (57–118)	
Tumor location	Performance IQ	
Hemispheric	57 (54–115)	0.082
Other locations	90 (56–118)	

[a] $p < 0.05$
[b] $0.05 \leq p \leq 0.1$

5.6.4 Rehabilitation services

Overall, 63% had needed some sort of therapy such as physiotherapy, speech, occupational, hippotherapy, music, art, psychotherapy or neuropsychologic rehabilitation. At the time of the study, 21% were receiving some therapy, physiotherapy and occupational therapies being the most common.

5.6.5 School achievement

Thirty of the 44 school-aged subjects attended the normal school system with normal syllabus while 32% needed special educational services (Table 12). In six cases the beginning of school was delayed. Shunt revisions were statistically significantly associated with poorer school achievement, while chemotherapy showed a weaker association (Table 13).

Participants who needed special educational services had lower full-scale, verbal and performance IQ. Median full-scale IQ for participants who attended schools with a normal syllabus (n=11) was 94 (range 75–110). The IQ for participants who needed special services within the normal school system (n=4) was 84 (68–92), for those in a special school system for the mentally subnormal (n=3) it was 50 (47–62) and for those in a special school system for the mentally retarded (n=2) it was 42 (39–44), p=0.003. There was also a statistically significant difference between these four groups in verbal and performance IQ (verbal IQ: 94 (72–112) vs 85 (72–88) vs 52 (49–69) vs 43 (41–45), p=0.007; performance IQ: 98 (77–118) vs 86 (68–100) vs 57 (54–60) vs 55 (54–56), p=0.007).

Nineteen participants had gone through basic schooling. Thirteen of them had studied in vocational school, but two of these had dropped out. Six had attended upper secondary school. At the time of the study three of these had graduated: one had studied in vocational school and one in open university, and one had graduated from university. Six of the 16 patients over 18 years of age were working. Five had an occupation. One was working without vocational education.

5.6.6 Activities of daily living and quality of life

According to structured interview 45 (87%) coped normally in daily living (Table 12). Full-scale IQ, verbal IQ and performance IQ were statistically significantly lower among participants who needed supervision or support (n=5) compared to those who coped normally (n=16) (full scale IQ: median 47 (range 39–85) vs 93 (62–110), p=0.004; verbal IQ: median 49 (41–86) vs 87 (69–112), p=0.006; performance IQ: median 56 (54–87) vs 92 (60–118), p=0.005). Six had a personal assistant. Two of the 16 patients over 18 years of age lived alone, four with a partner, and one had a child. Thirty-one of the total 52 pursued regular recreational activities outside home.

In respect of quality of life, 38% of the participants were in group I, 33% in group II, 21% in group III, and 8% in group IV (Table 12); 71% lived an active life and had only minor disabilities, while 29% suffered major neurological,

cognitive and social disabilities. Tumor reoperations, shunt revisions and tumor location were statistically significantly associated with lower quality of life (Table 13). Patients with a hemispheric or other supratentorial tumor had poorer outcome (Table 13).

6. Discussion

6.1 Renal consequences (Study I)

About 30 % of the patients treated with cisplatin had renal glomerular dysfunction at close of treatment. Cisplatin-induced renal glomerular dysfunction seems in most cases to persist, but did not apparently progress during the follow-up, which ranged from 1.2 to 14.8 years. These findings are in line with recently reported observations (Skinner *et al.* 2009). Renal glomerular dysfunction found in this study was mild; no patient had GFR below 60 ml/min/1.73m^2. The condition was not present without tubular dysfunction.

There were several signs of tubular dysfunction in the cisplatin group, observed most clearly in the amount and severity of hypomagnesemia. Almost three out of four of the patients in the cisplatin group were hypomagnesemic during the study. This is slightly more than in previous studies, with reported proportions of patients remaining hypomagnesemic ranging between approximately one third or two thirds (Brock *et al.* 1991, Ariceta *et al.* 1997). It was found in this study that after treatment hypomagnesemia tended to progress. While there are no prior reports of cisplatin-induced potentially progressive renal disease, there are however such reports concerning ifosfamide (Rossi *et al.* 1999b, Oberlin *et al.* 2009). Hypomagnesemia may be symptomatic (Schilsky & Anderson 1979, Pratt *et al.* 1981, Gomez Campdera *et al.* 1986, Bellin & Selim 1988, Skinner *et al.* 2009). One of the study patients had severe symptomatic hypomagnesemia, and in spite of magnesium supplementation, three out of seven patients had low magnesium levels. It is not clear whether routine long-term magnesium supplementation is necessary; detailed studies of the long-term clinical consequences of chronic cisplatin-induced hypomagnesemia in children are lacking (Skinner 2004). In the present study, low plasma phosphate and potassium, hyperuricemia, metabolic alkalosis and tubular proteinuria were more common in patients who had received cisplatin, and mild hypophosphatemia was found in about 20% of patients in the cisplatin group. Ifosfamide-induced proximal tubular dysfunction may lead to hypophosphatemia (Burk *et al.* 1990, Skinner *et al.* 1990, Jones & Chesney 1995, Skinner 2004, Jones *et al.* 2008), but hypophosphatemia has not previously been associated with cisplatin treatment (Skinner 2004).

Both cisplatin dose rate and cumulative dose have been associated with nephrotoxicity in children (Knijnenburg *et al.* 2011). In this study the cumulative dose of cisplatin as a risk factor was more obvious than the dose rate. Many patients also received potentially nephrotoxic agents other than cisplatin. These may have caused further deterioration in renal function. The patients who had renal glomerular dysfunction had also received CCNU treatment, and one patient in the cisplatin group with tubular proteinuria had also received small amounts of carboplatin. Abdominal and total body irradiation may cause radiation nephropathy, characterized by hypertension, decline in glomerular filtration rate and proteinuria (Breitz 2004). Spinal radiation in this study was not associated with abnormal renal function results.

The plasma creatinine concentration is not a reliable indicator of renal glomerular function (Skinner *et al.* 1991). In this study plasma creatinine had a weak negative correlation with GFR level and would thus seem to be a better parameter to follow renal function in this patient group than cystatin C, but it does not replace the measurement of GFR or tests of tubular function. The possibility of central diabetes insipidus in BT survivors might complicate the estimation of distal tubular damage by urine osmolality results.

6.2 Hypertension (Studies I and III)

Elevated BP was a common finding, implicating approximately every fifth patient. Cisplatin treatment, cranial irradiation, renal glomerular dysfunction and hypomagnesemia were associated with elevated BP. In addition to some case reports of cisplatin-associated transient hypertension (Kletzel & Jaffe 1981, Harrell *et al.* 1982, Brock *et al.* 1991), a few papers have been published reporting hypertension as a long-term side-effect after treatment including cisplatin. In these studies the proportion of hypertensive patients after follow-up from 3.5 to 10 years has ranged from four percent to 15 percent (Hansen 1992, Skinner *et al.* 2009). Chemotherapy-associated hypertension is not necessarily related to renal impairment (Hansen 1992). In this study most of the patients with cisplatin-associated elevated BP had renal impairment, either tubular dysfunction manifested as hypomagnesemia or both tubular and glomerular dysfunction. Magnesium has an important role in the etiology of cardiovascular pathology and hypomagnesemia has been linked to cardiovascular problems and hypertension (Chakraborti *et al.* 2002).

Cranial irradiation was associated with elevated BP. Previously an association between cranial irradiation and elevated systolic BP has been reported (Heikens *et al.* 2000). In the present study cisplatin treatment and cranial irradiation were

significant risk factors individually, but the risk of elevated BP was higher if the patients had been exposed to both therapies. The CCSS reported that childhood BT survivors are at a significantly increased risk of cardiovascular late effects, particularly if treated with radiation and chemotherapy (Gurney *et al.* 2003a). Findings in this study showed a similar trend to a potential additive influence of these treatments. Hypertension may be encountered in cancer survivors as a sequela of renal irradiation (Breitz 2004, Jones *et al.* 2008). In the present study no association was found between spinal radiation and elevated BP.

In previous studies, elevated BP has been associated with early signs of atherosclerosis also in children and young adults (Tracy *et al.* 1995), and prehypertension during young adulthood with coronary atherosclerosis 20 years later (Pletcher *et al.* 2008). High BP is a strong predictor of stroke (Asplund *et al.* 2009). An increased risk of stroke among childhood BT survivors has been noted (Bowers *et al.* 2006).

In this present series, the division of patients into subgroups of raised BP and normal BP was based on a single measurement during the visit to the hospital. Hence the proportion of patients with raised BP here is probably higher than in longer follow-ups. On the other hand, a single BP measurement is an indicator of the way the patient reacts and should not be ignored (Gustavsen *et al.* 2003). BP rises with growing and aging (Uhari *et al.* 1991, Rosner *et al.* 1993, National High Blood Pressure Education Program Working Group 1996). Since many children may have growth problems after cancer therapy, the reference BP tables used should include height percentiles, age and gender.

6.3 Low bone mineral density (Study II)

The CCSS has reported an increased risk of osteoporosis in childhood BT survivors (Gurney *et al.* 2003a). One third (15/46) of the patients in this study had low TBBMD (Z-score < -2.0). The prevalence of low BMD in childhood BT survivors in previous studies has been greater (Barr *et al.* 1998, Odame *et al.* 2006). Patient cohorts in those studies were much smaller than here and as the diagnostic criterion for impaired bone health in them has varied, the prevalence of reduced BMD among childhood BT survivors is difficult to estimate.

Reduced BMD has been found to be associated with cranial irradiation (Arikoski *et al.* 1998, Odame *et al.* 2006). In the present study, a deleterious effect of craniospinal irradiation was observed. Cranial irradiation alone showed a weaker association with low Z-score. Hormonal abnormalities, GH or sex hormone deficiencies or hyperprolactinemia, as single factors, were not associated

with low TBBMD, which suggests a multifactorial role for the risk factors, but the small size of these subgroups may also have contributed to this finding. As part of the treatment all patients had received periodic, even massive glucocorticoid doses. The substitution dose of hydrocortisone used at the time of the present study was so low that it did not affect the BMD, but previous higher doses of glucocorticoids, especially during radiotherapy, might have predisposed to low TBBMD.

Hypomagnesemia has a deleterious effect on bone metabolism. It causes a decrease in bone formation, thins the growth plate, osteoblasts and osteoclasts are less active and osteopenia occurs (van Leeuwen *et al.* 2000). Hypomagnesemic patients in the present study did not have lower TBBMD Z-scores than those with normal magnesium levels. In view of the young age of the study patients this issue needs to be followed up.

Fifteen percent of the patients who attended for bone densitometry had low calcium intake and almost half had serum 25(OH)D less than 38 nmol/l. In the whole group the median serum 25(OH)D was 39.7 nmol/l. According to laboratory reference values 25(OH)D levels were within normal limits, but by current recommendations, where serum 25(OH)D less than 37.5 nmol/l is considered deficient and values between 25 and 50 nmol/l insufficient, and values greater than 50 nmol/l sufficient (Misra *et al.* 2008), they were low. Vitamin D deficiency and hypophosphatemia are associated with impaired skeletal mineralization and may cause rickets and osteomalacia (Misra *et al.* 2008, Bhan *et al.* 2010). Ifosfamide-induced proximal tubular toxicity may lead to hypophosphatemic rickets in children (Burk *et al.* 1990, Skinner *et al.* 1990, Jones & Chesney 1995). The hypophosphatemia found in the present study was mild, and none of the patients had clinical hypophosphatemic rickets. The risk of this disorder might be smaller in survivors treated with cisplatin than with ifosfamide. The two hypophosphatemic patients who attended for bone densitometry had TBBMD Z-scores within normal limits. Calcium deficiency rarely causes rickets (Heaney *et al.* 2000, Misra *et al.* 2008, Bhan *et al.* 2010), but low calcium intake during skeletal formation is associated with decreased PBM and increased fracture risk (Heaney *et al.* 2000, Kalkwarf *et al.* 2003). Calcium supplementation alone without vitamin D seems to have no effect on bone density in children (Winzenberg *et al.* 2006). Low dietary calcium intake, plasma intact PTH concentration or low serum 25(OH)D (< 38 nmol/l) were not associated with TBBMD Z-score in the present study.

Low bone mass is associated with motor disability in children (Kilpinen-Loisa *et al.* 2010). Impaired mobility was not associated with TBBMD Z-score in the present study, but there were no patients with severe motor disability as all patients were ambulatory.

There is accumulating clinical evidence of manifest osteoporosis in chronically ill children. Many risk factors compromising bone health concern childhood BT survivors. This study confirmed that reduced BMD is a common finding among BT patients treated in childhood. The reasons for this condition are apparently multifactorial, and include craniospinal irradiation.

6.4 Obesity (Study III)

Various reports on survivors of ALL suggest an obesity prevalence of approximately 10–50% (Didi *et al.* 1995, Lustig *et al.* 2003, Kourti *et al.* 2005, Diller *et al.* 2009). After a mean follow-up of 13 years, obesity defined as a relative weight more than 120% was found in 32% long-term survivors of childhood cancers other than BTs (Talvensaari *et al.* 1996). In survivors of childhood low-grade glioma, the 5-, 10- and 15-year cumulative incidence of obesity/overweight has been 18%, 35%, and 53%, respectively (Armstrong *et al.* 2011). In this study 27–35% were found to be overweight or obese after a mean follow-up of 7.5 years. This is in accord with the previously mentioned observations, and is more than the average 15% prevalence of overweight and 3% prevalence of obesity recorded among present-day Finnish children and adolescents (Kautiainen *et al.* 2002, Hakanen *et al.* 2006). In a study with adult survivors of childhood brain cancer, BMI did not differ in survivors when compared to healthy controls, but waist/hip ratio was elevated among the survivors (Heikens *et al.* 2000). In the present series central obesity was found in 21%. There are reports of greater proportions of abdominal obesity in childhood cancer survivors, up to almost 50% (Taskinen *et al.* 2007).

To define general obesity, BMI was not used in view of its limitations in the pediatric population (Daniels *et al.* 1997, Reilly *et al.* 2000). To arrive at an appropriate definition of central obesity for children and adolescents is challenging. Waist circumference cut-offs by age do not consider the patient's height and pubertal development and might thus be misleading if the patient grows and develops otherwise than average. This problem may be avoided by using waist-height ratio, which offers a useful surrogate for central obesity (McCarthy & Ashwell 2006).

Hypothalamic damage accounts for the development of obesity in children surviving BT (Lustig *et al.* 2003, Müller *et al.* 2004). This was also seen in the present cohort. Overweight/obesity and central obesity were strongly associated with hypothalamic/hypophyseal damage caused by a tumor and its surgery or irradiation and manifested as hormonal problems, but less with cranial irradiation

alone, and no association with chemotherapy was found. GHD is associated with obesity and abdominal obesity (Roemmich *et al.* 2001, Mukherjee *et al.* 2004, Bechtold *et al.* 2011). The association was also seen here, and among GHD patients, GH supplementation diminished the tendency to general and central obesity.

Children and adolescents with physical and cognitive disabilities have been reported to have a higher prevalence of overweight or obesity compared to their non-disabled peers (Rimmer *et al.* 2007, Rimmer *et al.* 2011). In this study impaired mobility was strongly associated with overweight/obesity and central obesity.

A relatively large and fairly consistent body of evidence demonstrates that overweight and obesity in childhood and adolescence have adverse consequences for premature mortality and physical morbidity in adulthood. Child/adolescent overweight and obesity are associated with a significantly increased risk of diabetes, stroke, coronary heart disease and hypertension in adult life (Reilly & Kelly 2011).

6.5 Metabolic abnormalities (Study III)

Dyslipidemia, usually reported as hypertriglyceridemia or low HDL-C has been found in approximately 20–60% of childhood cancer survivors (Taskinen *et al.* 2000, Gurney *et al.* 2006, Trimis *et al.* 2007, Hoffman *et al.* 2008). In this study 37% of patients had at least one abnormal lipid value, and about a half of them were not obese or overweight, emphasizing the need for laboratory evaluation. Cranial irradiation, hypothalamic/hypophyseal damage and GHD were risk factors for dyslipidemia. GH supplementation at the time of the study seemed to protect from dyslipidemia. It was found that impaired mobility was associated with hypercholesterolemia.

There were no hyperglycemic patients in this study. The median serum insulin was higher among patients with GHD than in those without, but hyperinsulinemia (4%) was not as common as in earlier studies involving mostly patients with leukemia, prevalences ranging from eight to 58% (Taskinen *et al.* 2007, Trimis *et al.* 2007). Differences in treatment regimens might explain the divergences.

The prevalence of metabolic syndrome according to the IDF definition in about 19-year-old healthy Finnish males entering military service in 2005 has been 6.8% (Mikkola *et al.* 2007) and in healthy 24-year-old Finnish adults 7.5% in 2001 (Mattsson *et al.* 2007). Most of the patients in this study were younger, but the prevalence of metabolic syndrome was somewhat higher (8%).

In previous studies, an increased risk of metabolic syndrome has been observed among different childhood cancer survivors (Talvensaari *et al.* 1996, Heikens *et al.* 2000, Taskinen *et al.* 2000). The published studies on childhood cancer survivors have used different criteria for the diagnosis of metabolic syndrome. The prevalence of metabolic syndrome in childhood cancer survivors other than BTs has varied from six percent to 39 percent (Kourti *et al.* 2005, Taskinen *et al.* 2007, Hoffman *et al.* 2008).

In this study cranial irradiation was associated with metabolic syndrome, and among radiated patients the prevalence of the disorder was 20%. An association between cranial irradiation and metabolic syndrome has been reported in childhood ALL survivors (Gurney *et al.* 2006, Trimis *et al.* 2007). Patients with decreased GH secretion are at special risk (Talvensaari *et al.* 1996, Heikens *et al.* 2000, Gurney *et al.* 2006, Taskinen *et al.* 2007). The observations in this study concur with these findings; patients with GHD and patients with any kind of hypothalamic/hypophyseal damage had a higher risk of metabolic syndrome and hyperuricemia. Increased levels of uric acid are associated with cardiovascular disease and metabolic syndrome (Yoo *et al.* 2005), and the association between hyperuricemia and metabolic syndrome was also seen here. GH supplementation alleviated adverse metabolic outcomes among BT survivors with GHD. None of those who received GH supplementation at the time of the study had metabolic syndrome. Most patients with isolated GHD discontinue GH treatment when final height is attained (Boot *et al.* 2009). Benefits from GH therapy have been brought out, but relatively few survivors of childhood BTs continue GH therapy into adulthood (Bowers *et al.* 2009). Lately many studies have reported that GH therapy is not associated with tumor recurrence. The CCSS has reported that for CNS tumor survivors as a whole, as well as for medulloblastoma survivors, the risk of tumor recurrence has been found to be significantly reduced in cases treated with GH compared to survivors not so treated (Sklar *et al.* 2002, Diller *et al.* 2009). There was marginal evidence suggesting that GH-treated survivors of CNS tumors develop an increased number of tumors, mostly meningiomas. However, due to the small number of events and wide confidence intervals, the data on second neoplasms need to be interpreted with caution.

BT patients carry a special risk of obesity/overweight, dyslipidemia, raised BP, metabolic syndrome and hyperuricemia. Given the association with cardiovascular morbidity (Isomaa *et al.* 2001) and type 2 diabetes (Lorenzo *et al.* 2003), metabolic syndrome is an important health problem, and particularly so if onset has been at young age (Rönnemaa *et al.* 1991, Vanhala *et al.* 1999, Katzmarzyk *et al.* 2001, Mattsson *et al.* 2008).

6.6 Neurological outcome (Study IV)

Of the present cohort only 50% showed normal motor function, but all were able to walk. It is of note that 13% had changed handedness. In this present series associated complications such as need for shunt revisions and tumor reoperations were associated with motor disability. Among participants who had needed shunt revisions, clumsiness and mild asymmetry were emphasized, and among those who had needed tumor reoperations the proportion of hemiparesis was conspicuous. The proportion of major disabilities (29%) was slightly less than observed in a study from 1990 with a moderate or severe disability in 34% (Lannering *et al.* 1990), but significantly less than in a study with malignant childhood BT survivors with major disabilities in 47% (Ilveskoski *et al.* 1996a).

Thirty-two % of the school-aged participants here needed special educational services – about the same proportion (30%) as found in childhood malignant BT survivors (Ilveskoski *et al.* 1996a). School performance has been found to be poorer in children with BTs compared with controls, and the difference to be most pronounced among girls (Lähteenmäki *et al.* 2007). In the present study there was no difference between genders in school achievement or psychological tests. However, six out of nineteen (32%) who had completed basic schooling had studied in upper secondary school, which is fewer than usual in Finland, where more than half go on to that level. Median verbal IQ and performance IQ were at about the same level as median full-scale IQ and all were lower than the medians expected in the general population. These findings raised the question whether these children had received sufficient individual care and support.

Hemispheric tumor location has been found to be a risk factor for cognitive decline in children treated for BTs (Ellenberg *et al.* 1987, Reimers *et al.* 2003), but also hypothalamic (Danoff *et al.* 1982, Ellenberg *et al.* 1987) and cerebellar tumor sites have been associated with cognitive disabilities (Cantelmi *et al.* 2008, Gottwald *et al.* 2004). A limitation to the present study was that psychological tests were carried out on only part of the study group, and in this group, aged from 6 to 16 years, performance IQ was somewhat lower in patients who had had a hemispheric tumor, but the association was not statistically significant. Hemispheric or other supratentorial tumor location was associated with major neurological, cognitive and social disabilities in the evaluation of quality of life.

Comparing the outcome of participants who had undergone only surgery to those whose treatment included operation and radiotherapy and/or chemotherapy, the former managed no better. Participants who had needed tumor reoperations had a poorer outcome; their quality of life, full-scale IQ, verbal IQ and performance IQ were significantly lower compared to those who had not needed reoperations. The number of patients with residual or residive

tumor upon evaluation was high, 25%, but the occurrence of residive or residual tumor was not associated with poorer outcome.

Cranial irradiation is known to be harmful to cognitive functions (Danoff *et al.* 1982, Kun *et al.* 1983, Ellenberg *et al.* 1987, Lannering *et al.* 1990, Ilveskoski *et al.* 1996a, Reimers *et al.* 2003, Duffner 2004, Mulhern *et al.* 2004, Reimers *et al.* 2009), but in this study no statistically significant association between cranial irradiation and neurological, cognitive and social disabilities and quality of life was found, which suggests a multifactorial role for the risk factors.

It is challenging to estimate the influence of chemotherapy on cognition in patients with BTs, as there are many different treatment protocols. In addition to the tumor itself, tumor operation, radiotherapy and hydrocephalus render estimation even more complicated. There is evidence of subtle long-term neurocognitive deficits in survivors of childhood ALL after treatment with chemotherapy only. These involve mainly processes of attention and executive functioning (Anderson & Kunin-Batson 2009, Buizer *et al.* 2009). The results of the present study are in line with these earlier findings in ALL survivors. The participants who had received chemotherapy had lower performance IQ. Chemotherapy also increased the risk of difficulties in school achievement.

The role of hydrocephalus in the development of cognitive difficulties in children treated for BTs is unclear. There have been reports of an absence of association between hydrocephalus and cognitive function (Danoff *et al.* 1982, Kun *et al.* 1983), but hydrocephalus has also been found to be a significant risk factor for impaired intellectual outcome in children treated for BTs (Reimers *et al.* 2003). In a study of 187 intracranial tumor patients (10% children) who underwent VP shunt placement, 52 (28%) experienced one or more shunt failures requiring revision(s) after a median follow-up time of 391 days, and younger patients ran a higher risk of shunt failure (Reddy *et al.* 2011). In this present study, the incidence of shunt revision was higher. This might be due to longer follow-up and the younger age of the patients. Other studies have also reported a high rate of shunt failures in pediatric patients (Liptak & McDonald 1985, Di Rocco *et al.* 1994, Tuli *et al.* 2000). Here participants with treated hydrocephalus had no poorer outcome than those without hydrocephalus, but shunt revisions were significantly associated with outcome. Shunt dysfunctions requiring revision had a clear negative impact on motor function, school achievement and quality of life. It could be speculated that recurrent, possibly long periods of variation in intracranial pressure could worsen the outcome.

One report from the CCSS showed no correlation between younger age at diagnosis and greater reported neurocognitive dysfunction (Ellenberg *et al.* 2009), but on the whole young age at diagnosis or at the time of radiotherapy and/or chemotherapy has been associated with cognitive decline (Duffner *et al.* 1993,

Reimers *et al.* 2003, Mulhern *et al.* 2004). Here diagnosis below the age of three years showed no association with neurological, cognitive and social disabilities, which suggests that the risk components are multifactorial.

According to the present results childhood BT survivors are at risk of neurological, cognitive and social problems extending into adulthood. However, most of this cohort lived an active life with age-appropriate social activities and participation. Nevertheless, all childhood BT survivors need life-long, tailor-made multiprofessional support and follow-up, which may be challenging for medical and social services especially if the sufferer has cognitive problems. It is essential to consider the possibility of reducing late neurological and neurocognitive deficits in the development of treatment protocols.

6.7 Strengths, limitations and future aspects

The proportion of the patients who did not participate in this study was rather large, but the study cohort was adequate and consistent with those in similar studies published in the literature. On the other hand, the proportion of patients who attended for bone densitometry was considerably larger than in other published studies of BT survivors. The non-participating patients included those with most severe sequelae of the tumor, but also those rating themselves as completely healthy. On average the present study group could be considered fairly representative of childhood BT survivors with a wide range of tumors and different treatments. By reason of the heterogeneity of the study population some of the subgroups evaluated were rather small. The size of the study cohort was determined by the number of the survivors willing to participate. Sample size calculations were not used.

The treatments have developed since the 1980s and 1990s; for example, the radiation fields are better focused and irradiation of healthy tissue is reduced. The study results do not allow conclusions as to whether present practices would lead to less adverse effects. However, the treatment still includes surgery, and radiotherapy and/or chemotherapy when necessary. Even though there are new treatment strategies and new chemotherapeutic agents, the same chemotherapeutic agents are being used as in this study.

The hearing loss of the participants was not evaluated by audiometry during the study, which should be done in the future.

Our knowledge is limited as to the etiology of adverse late effects, and this series raised many questions. Further studies are needed to explore among other things the very late effects, the possible effects of an increased use of chemotherapy and the combined effects of chemotherapy and radiotherapy, and hydrocephalus.

7. Conclusions and recommendations

On the basis of the present findings, the following conclusions may be drawn:

1. The cumulative dose of cisplatin is associated with its nephrotoxicity. It is possible that other nephrotoxic agents than cisplatin had caused further deterioration in renal function in the study cohort. Cisplatin-induced renal glomerular dysfunction appears mostly to be permanent. Several signs of tubular damage were seen. The most common sign of tubular dysfunction was hypomagnesemia, which may be symptomatic. Cisplatin-induced tubular dysfunction seems to persist and even progress.

2. Childhood BT survivors are at an increased risk of hypertension especially if they have received cisplatin treatment or cranial irradiation, or have renal glomerular dysfunction or hypomagnesemia. The risk of elevated BP is higher after exposure to both cisplatin treatment and cranial irradiation.

3. Childhood BT survivors have several risk factors for impaired bone health. One third of the survivors here had low TBBMD. The reasons for reduced BMD are apparently multifactorial, including craniospinal irradiation.

4. A considerable proportion of the participants had low calcium intake and vitamin D deficiency.

5. The prevalence of overweight and obesity in childhood BT survivors exceeded that in the general child and adolescent population. Survivors who have received cranial irradiation, who have hypothalamic/hypophyseal damage, GHD and/or impaired mobility are at highest risk of overweight/obesity and central obesity. GH supplementation seems to diminish the tendency to general and central obesity among GHD patients.

6. Metabolic changes are common in childhood BT survivors. Survivors who have received cranial irradiation, have GHD or any kind of hypothalamic/hypophyseal damage or impaired mobility run a higher risk of dyslipidemia, metabolic syndrome and hyperuricemia. GH supplementation alleviated adverse metabolic outcomes among BT survivors with GHD.

7. Childhood BT survivors are at a high risk of adverse neurological and neurocognitive late effects, which here had the most notable impact on their daily life. Most of the childhood BT survivors lived an active life with minor disabilities, but almost one third had major neurological, cognitive and social disabilities, and eight percent were incapable of self-care. Supratentorial/ hemispheric tumor location, tumor reoperations, shunt revisions and chemotherapy were associated with neurological, cognitive and social disabilities.

8. A considerable proportion of the survivors had a residual/residive tumor or shunt problems even after recovering from the tumor.

Based on the study results the following recommendations can be made:

1. All survivors need life-long, tailor-made multiprofessional support and follow-up. With follow-up and early intervention it might be possible to improve the quality of life and diminish morbidity in later life.

2. Repeated clinical and laboratory evaluations are necessary to ensure detection of late effects and need of support and/or rehabilitation.

3. Attention should be paid to adequate neurocognitive and psychosocial support and rehabilitation, and specialized educational and vocational services, and also to employment.

4. Measurement of BP should be a part of clinical evaluation in all patients.

5. BMD measurements by DXA are justified for evaluation of bone health.

6. GH supplementation is recommended for GHD patients.

7. The need for magnesium, calcium and D vitamin supplementations should be estimated.

8. Exercise should be promoted while taking into account possible impaired mobility or other factors which might limit physical ability.

9. Follow-up should be arranged preferably by someone well acquainted with late effects of cancer therapy.

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Original Publications

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Renal Impairment and Hypertension in Brain Tumor Patients Treated in Childhood Are Mainly Associated With Cisplatin Treatment

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Background. This study was designed to evaluate the renal consequences of the treatment of brain tumor patients diagnosed in childhood. ***Procedure.*** One hundred four primary brain tumor patients diagnosed before 17 years of age from 1983 to 1997 had been treated in Tampere University Hospital, Finland. Of the 80 survivors 52 (65.0%) were examined at a median age of 14.4 years (range 3.8–28.7) and median 6.0 years (range 1.2–14.8) after the last treatment. The main outcome measures were blood pressure (BP), renal function, and calcium metabolism. ***Results.*** Eight patients (15.4%) were hypertensive. Elevated BP was observed especially after exposure both to cisplatin and cranial irradiation. Spinal radiation did not increase the risk of elevated BP. Other adverse effects were observed only in patients treated with cisplatin. Five out of 14 patients treated with cisplatin evinced renal glomerular dysfunction (GFR < 87 mL/min/1.73 m^2) immediately after treatment. They had a high cumulative dose of cisplatin (490–880 mg/m^2). Recovery from renal glomerular dysfunction was observed in one patient. Nine of 14 patients were hypomagnesemic at the close of cisplatin treatment. Thereafter the magnesium level decreased in 10/14 cases ($P = 0.006$). During the study 10/14 were hypomagnesemic ($P < 0.001$); one evinced severe symptomatic hypomagnesemia. Low plasma phosphate ($P = 0.016$) and potassium levels ($P = 0.026$), tubular proteinuria ($P = 0.055$), metabolic alkalosis ($P = 0.071$), and hyperuricemia ($P = 0.114$) were also more common in patients on cisplatin treatment. ***Conclusions.*** Elevated BP is common among brain tumor patients treated in childhood. After cisplatin treatment renal glomerular dysfunction appears mostly to be permanent. Persistent and even progressive changes in renal tubular function are seen. Pediatr Blood Cancer 2005;44:363–369. © 2004 Wiley-Liss, Inc.

Key words: brain tumor; childhood; cisplatin; hypertension; renal impairment

INTRODUCTION

Brain tumors are the most common solid tumors in children [1,2]. Recent therapeutic advances coupled with refinements in neuroimaging techniques facilitating earlier diagnosis and improved treatment planning, have raised the percentage of affected children who survive to adulthood [2–4], increasing the importance of the possible late effects of the treatment.

Cisplatin (*cis*-diamminedichloroplatinum) is an important anticancer drug used in treatment protocols for childhood brain tumors [4–8]. Its most important dose-limiting side effect is nephrotoxicity [9,10]. Despite the prophylactic use of hyperhydration and forced diuresis, considerable reductions in GFR and tubular toxicity have been described in children receiving the drug [11–14]. It has been reported that there is some recovery from cisplatin glomerular toxicity, but the long-term outcome of nephrotoxicity has remained unclear [14].

The goal of this study was to evaluate the renal consequences, including possible risk of hypertension, of the treatment of brain tumor patients diagnosed in childhood, especially those treated with cisplatin. Laboratory samples were taken to evaluate renal glomerular and tubular function, and adverse late effects related to renal dysfunction in order to help assess risks when planning anticancer treatment and to find the best parameters for follow-up.

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MATERIALS AND METHODS

Patients

A total of 104 primary brain tumor patients diagnosed below 17 years of age, between the years 1983 and 1997, had been treated in Tampere University Hospital, Finland. Of the 80 survivors 52 (65.0%) took part in the study. They were examined at a median age of 14.4 years (range 3.8–28.7), a median 6.9 years (range 1.5–15.1) after diagnosis, and a median 6.0 years (range 1.2–14.8) after last treatment. A median age at diagnosis was 6.0 (range 0.1–15.5).

Treatment of the Tumor

All of the 52 children underwent surgery, except one who had a biopsy of the tumor only. Twenty-nine children (55.8%) were treated by surgery only and 17 (32.7%) with chemotherapy. Three patients (5.8%) received chemotherapy without radiation, and 14 (26.9%) also received radiotherapy. Six (11.5%) received radiotherapy without chemotherapy, making a total of 20 patients (38.5%) treated with radiotherapy. Twelve received cranial, and eight craniospinal irradiation. In seven cases craniospinal irradiation reached renal level, and among these patients the treatment was combined with chemotherapy in five cases, three of them receiving cisplatin as one of the cytostatic drugs (Table I).

Of the 17 children who received chemotherapy 10 were on ''eight drugs in one day'' chemotherapy, and eight received chemotherapy according to other protocols. One of these eight patients also received ''8 in 1'' chemotherapy, and one received chemotherapy according to two other different protocols. The ''8 in 1'' chemotherapy was used during the years 1986–1992, the other combinations of chemotherapy were used from 1984 to 1998.

In the ''8 in 1'' protocol seven cytostatic drugs (CCNU, vincristine, hydroxyurea, procarbazine, cisplatin (60 or 90 mg/m^2 per course), ARA-C, and either dacarbazine or cyclophosphamide) and methylprednisolone were administered in a scheduled sequence within 12 hr [15]. Two courses were administered postoperatively with a 2-week interval and eight courses after radiation therapy at 6-week intervals. Nine patients received from 8 to 10 ''8 in 1'' courses.

The other combinations of chemotherapy were bleomycin and CCNU (one patient), vincristine, CCNU plus prednisolone, or dexametasone (two patients) bleomycin and VP-16 plus cisplatin (one patient), bleomycin, vinblastine, and VM-26 plus cisplatin (one patient), vincristine, VP-16, and cyclophosphamide plus cisplatin (two patients) followed by maintenance with vincristine, VP-16, and karboplatin (and cyclophosphamide). In progressive disease two patients received per oral VP-16 treatment [16]. Altogether 14 patients received cisplatin treatment (Table I). The maximal cisplatin doses varied from 60 to 90 mg/m^2 in 6- or 8-hr intravenous infusions, and one received cisplatin 20 mg/m^2 in 1 hr infusions for 5 days at 3-week intervals. Cisplatin was always given with forced diuresis (fluids and mannitol).

All patients also received glucocorticosteroids in their treatment. Dexametasone (2–4 mg/m^2) was given with radiotherapy for several days and it was also given following the tumor operation. The 10 patients who received ''8 in 1'' chemotherapy containing cisplatin received methylprednisolone at a dose of 300 mg/m^2. One patient

TABLE I. The Characteristics of the Cisplatin and No-Cisplatin Groups

	No cisplatin treatment	Cisplatin treatment	*P* value
Number of patients	38	14	
Male gender	16 (42.1)	11 (78.6)	0.029
Age at evaluation (years)	13.9 (4.9–28.7)	15.5 (3.8–22.5)	0.710
Age at diagnosis (years)	6.0 (0.6–15.5)	4.3 (0.1–15.1)	0.421
Age treatment ended (years)	6.2 (0.6–21.0)	7.7 (1.3–15.6)	0.901
Follow-up time (years)	6.1 (1.5–15.1)	8.9 (2.2–13.1)	0.343
Time after treatment (years)	5.2 (1.2–14.8)	7.2 (1.5–11.9)	0.710
Radiotherapy	9 (23.7)	11 (78.6)	0.001
Craniospinal radiation reaching renal level	4 (10.5)	3 (21.4)	1.000
Cumulative dose of cisplatin (mg/m^2)	0	528 (181–882)	
Number of patients with CCNU treatment	2	10	0.000
Number of patients with carboplatin treatment	0	2	0.069
Number of patients with cyclophosphamide treatment	0	5	0.001
Renal glomerular dysfunction (GFR <87 mL/min/1.73 m^2)	0	4 (28.6)	0.004
Weight (% of median weight for height)	107 (74–155)	111 (81–176)	0.297
Body mass index (kg/m^2)	19.5 (13.0–28.0)	20.7 (13.6–34.0)	0.415
Systolic blood pressure (mmHg)	114 (92–164)	128 (90–155)	0.312
Diastolic blood pressure (mmHg)	65 (50–100)	70 (50–105)	0.352

Categoric data shown as number of patients (%) and continuous data as median (range).
P value shows the statistical significance between the patients with and without cisplatin treatment.

with other combination of chemotherapy including steroids received prednisolone 40 mg/m^2 for 14 days per sytostatic course and the other dexametasone 2 mg/m^2 for 3 days per course. He had also received "8 in 1" chemotherapy. Some patients received dexametasone for treatment of nausea.

Research Methods

The medical records of the patients were checked for clinical history. The patients were interviewed and examined by the same physician (SP). Physical examination included blood pressure (BP), measured by an oscillometric method (DINAMAP Adult/Pediatric and Neonatal Vital Signs Monitor Model 1846 SX, Criticon, Inc., Tampa, FL, USA) preferentially on the right arm in sitting position so that the cuff covered at least two-thirds of the upper arm. Patients 18 years or older were classified into an elevated BP category, if systolic BP was 140 mmHg or greater, or if diastolic BP was 90 mmHg or greater [17,18]. For patients younger than 18 years BP at the 95th centile or greater by height, sex, and age according to Rosner and associates, was considered elevated [17,19].

Glomerular filtration rate (GFR) was measured during the study in patients who had received cisplatin treatment if the former value was abnormal or measured over 2 years earlier. GFR was determined by plasma clearance of 51Cr-EDTA assessed by the single injection method [20]. Values below 87 mL/min/1.73 m^2 were considered abnormal [21].

Laboratory samples to evaluate renal glomerular and tubular function were taken in the morning after overnight fasting. Laboratory tests for glomerular function included plasma creatinine, serum cystatin C, and albumin- and urine protein. For tubular function plasma uric acid, sodium, potassium, acid-base balance from the capillary blood, blood glucose, and urine alpha-1-microglobulin, glucose, and osmolality were measured. The tests for calcium metabolism included plasma calcium, serum ionized calcium, plasma alkaline phosphatase, phosphate, intact parathyroid hormone, and serum 1,25-dihydroxycholecalciferol and plasma magnesium.

Plasma creatinine measurements were done enzymatically using a Vitros analyzer (Johnson & Johnson Clinical Diagnostic, Rochester, NY) [22]. Serum cystatin C concentrations were determined by a particle enhanced turbidimetric immunoassay (Dako, Glostrup, Denmark) using a Hitachi 704 analyzer [23]. Urinary alpha-1-microglobulin was measured nephelometrically (Behring BN II Nephelometer, Dade Behring, Marburg, Germany) with a sensitivity of about 5 mg/L.

In case of proteinuria (value over 0.1 g/L), 24-hr urine specimens were collected in order to analyze protein, phosphate, magnesium, calcium, and creatinine excretion and creatinine clearance. If there was continuous glucosuria (value over 0.05 g/L in two samples), an oral glucose tolerance test was applied. Tampere University Hospital Laboratory reference values were used when analyzing laboratory samples.

Statistical Analysis

The continuos data were analyzed using Mann–Whitney U- or Kruskall–Wallis test. One- and two-way analysis of variance were also used when analyzing data with normal distribution. Categorized data were analyzed using Fisher exact test. The Spearman correlation coefficient was used for correlation estimates and Wilcoxon signed ranks test to estimate the association between values at end of treatment and the latest values. A P-value less than 0.05 was considered significant. All statistical analyses were performed using the SPSS for Windows version 10.0 Statistical Software. The study was approved by the Ethical Committee of Tampere University Hospital and was carried out with signed parental and/or patients' consent.

RESULTS

Blood Pressure

Eight patients (15.4%) were hypertensive. Elevated BP was more common among patients who had received cisplatin treatment ($P = 0.003$), cranial irradiation ($P = 0.003$), had renal glomerular dysfunction ($P = 0.009$), or were hypomagnesemic ($P = 0.025$). The risk for elevated BP was higher if the patients were exposed both to cisplatin and cranial irradiation ($P = 0.002$) (Tables II and III). Additional spinal radiation did not seem to affect the observed elevated BP ($P = 1.000$, Fisher exact test). Three patients needed antihypertensive medication. Two of them suffered from renal glomerular dysfunction.

Renal Glomerular Function

Five patients in the cisplatin group (35.7%) had renal glomerular dysfunction (GFR below 87 mL/min/1.73 m^2) immediately after treatment. During the study only one patient evinced recovery from previous renal glomerular dysfunction: so altogether four patients in the cisplatin group (28.6%) had abnormal GFR (Table I). Patients with renal glomerular dysfunction had higher cumulative doses of cisplatin (mg/m^2) when compared with the

TABLE II. Elevated Blood Pressure among 52 Brain Tumor Patients Diagnosed in Childhood

	No cisplatin treatment (n = 38)	Cisplatin treatment (n = 14)
No irradiation (n = 32)	1/29 (3%)	0/3 (0%)
Cranial irradiation (n = 20)	1/9 (11%)	6/11 (55%)

TABLE III. The Characteristics of Eight Brain Tumor Patients with Elevated Blood Pressure Treated in Childhood

Age (years)	Sex	Systolic BP (mmHg)	Diastolic BP (mmHg)	Time after treatment (years)	Cisplatin treatment	Radiation therapy	Renal glomerular dysfunction	Hypomagnesemia	BMI (kg/m^2)
*13	Male	144 (↑)	83	10.1	Yes	***Yes	Yes	Yes	21.8
13	Male	134 (↑)	57	11.9	Yes	Yes	No	Yes	24.2
16	Male	152 (↑)	88 (↑)	10.4	Yes	Yes	Yes	Yes	34.0
**18	Male	147 (↑)	83	2.5	Yes	Yes	No	No	27.4
21	Male	155 (↑)	87	7.9	Yes	Yes	No	Yes	25.8
21	Female	164 (↑)	100 (↑)	5.9	No	No	No	No	21.4
22	Female	148 (↑)	105 (↑)	7.2	Yes	Yes	Yes	Yes	21.6
28	Female	145 (↑)	71	7.7	No	Yes	No	No	25.2

*For patients younger than 18 years blood pressure (BP) values at the 95th percentile or greater by height, sex and age by Rosner et al. were classified as elevated.
**For patients 18 years or older systolic BP 140 mmHg or greater and diastolic BP 90 mmHg or greater were classified as elevated.
***Craniospinal radiation reaching renal level.

patients without renal glomerular dysfunction ($P = 0.039$ at the end of treatment, $P = 0.016$ during the study) and the cumulative dose of cisplatin showed a moderate negative correlation with the GFR values measured at the end of treatment (−0.710, Spearman correlation coefficient). In Figure 1 the GFR values are presented at the end of treatment and after follow-up. There was no statistically significant difference between the latest GFR values and values at close of treatment ($P = 0.594$, Wilcoxon signed ranks test), but some patients showed improvement and some deterioration of GFR. In two patients with abnormal GFR, the levels of plasma creatinine and serum cystatin C were elevated (Table IV).

The two patients in the cisplatin group who had received carboplatin treatment evinced no renal glomerular dysfunction, but one of them had tubular proteinuria. All four patients with abnormal GFR had also received CCNU treatment. The two patients in the no-cisplatin group who had received CCNU treatment showed no signs of renal impairment. Spinal radiation did not increase the risk of abnormal renal function results.

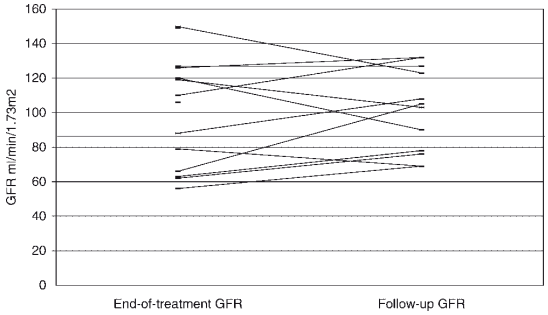

Fig. 1. Glomerular filtration rate (GFR) measured by plasma clearance of (51)Cr-EDTA in 14 brain tumor patients diagnosed in childhood and treated with cisplatin. The median follow-up time was 6.0 years (range 1.2–14.8). Abnormal values <87 mL/min/1.73 m^2.

Renal Tubular Function and Calcium Metabolism

There were several signs of disturbed tubular function in the cisplatin group, observed most clearly by the amount and severity of hypomagnesemia (Table IV). All patients with renal glomerular dysfunction also had several laboratory findings indicating tubular dysfunction. Gout had previously been diagnosed in one patient with renal dysfunction in the cisplatin group. In clinical examination no patient had specific joint symptoms indicating gout.

At the end of treatment, 9/14 patients in the cisplatin group were hypomagnesemic. After treatment, the magnesium level decreased in 10/14 cases ($P = 0.006$, Wilcoxon signed ranks test). During the study, 10/14 (71.4%) in the cisplatin group and 4/38 (10.5%) in the no-cisplatin group had decreased plasma magnesium level ($P < 0.001$). In the no-cisplatin group, the plasma magnesium level was just below the lower reference level that hardly has special significance. In the cisplatin group, the patient with the lowest magnesium level (0.34 mmol/L) had muscular weakness. The cumulative dose of cisplatin showed a weak negative correlation with magnesium values (−0.676). In spite of magnesium supplementation, three of seven patients had low magnesium levels. Hypophosphatemia was observed in 21.4% of patients treated with cisplatin ($P = 0.016$). Secondary hyperparathyroidism had previously been diagnosed in one patient with renal dysfunction. There was one patient in both groups with an elevated (over 6.8 pmol/L) plasma intact parathyroid hormone concentration. They both had a low dietary calcium intake.

DISCUSSION

Elevated BP seems to be a common finding in our material: every sixth patient had elevated BP. In this study, cisplatin treatment, cranial irradiation, renal glomerular

TABLE IV. The Results of Renal Function and Calcium Metabolism Tests in the Cisplatin and No-Cisplatin Groups

	No cisplatin treatment (n = 38)	Cisplatin treatment (n = 14)	*P* value
GFR (mL/min/1.73 m^2)		106 (69–149)	
Plasma creatinine (μmol/L)	61 (34–94)	70 (23–153)	0.283
Serum cystatin C (mg/L)	1.06 (0.78–1.45)	1.04 (0.65–1.70)	0.765
Proteinuria (dU-protein over 100 mg/L)	2 (5.3)	1 (7.1)	1.000
Plasma uric acid (mmol/L)	0.23 (0.10–0.46)	0.30 (0.11–0.65)	0.112
Hyperuricemia*	2 (5.3)	3 (21.4)	0.114
Plasma sodium (mmol/L)	142 (137–147)	142 (140–148)	0.721
Plasma potassium (mmol/L)	3.8 (3.3–4.5)	3.7 (3.2–4.4)	0.026
Hypokalemia (P-potassium below 3.3 mmol/L)	0	1	0.269
Metabolic acidosis (BE below −3.0)	1 (2.7) (n = 37)	0	1.000
Metabolic alkalosis (BE over 3.0)	0 (n = 37)	2 (14.3)	0.071
Tubular proteinuria (U-alfa-1-microglobulin 8 mg/L or more)	1 (2.6)	3 (21.4)	0.055
Urine osmolality (mosm/kg H_2O)	759 (288–1204) (n = 37)	810 (348–1203)	0.429
Low urine osmolality (U-osmolality below 600 mosm/kg H_2O)	12 (32.4) (n = 37)	4 (28.6)	1.000
Continous glucosuria (U-glucose over 0.05 g/L)	4 (10.8) (n = 37)	2 (14.3)	1.000
Plasma magnesium (mmol/L)	0.85 (0.69–0.96)	0.64 (0.34–0.93)	<0.001
Hypomagnesemia (P-magnesium below 0.75 mmol/L)	4 (10.5)	10 (71.4)	<0.001
Plasma calcium (mmol/L)	2.37 (2.18–2.58)	2.38 (2.24–2.62)	0.358
Serum ionized calcium (mmol/L)	1.30 (1.23–1.39)	1.28 (1.20–1.43)	0.419
Plasma alkaline phosphatase (U/L)	350 (77–727)	272 (75–706)	0.829
Plasma phosphate (mmol/L)	1.32 (0.96–1.71)	1.09 (0.77–1.58)	0.013
Hypophosphatemia**	0	3 (21.4)	0.016

Categoric data shown as number of patients (%) and continuous data as median (range).
*Hyperuricemia: P-uric acid over 0.34 mmol/L in children, over 0.32 mmol/L in women and over 0.45 mmol/L in men.
**Normal limits for 2–12-year-old children 1.20–1.80 and 13–16-year-old children 1.10–1.80 and for adults 0.80–1.40 mmol/L.

dysfunction, and hypomagnesemia increased the risk of elevated BP. Cisplatin treatment and cranial irradiation were significant factors individually, but the risk to elevated BP was higher if the patients were exposed to the both therapies.

In previous studies, cranial irradiation has been associated with metabolic syndrome and elevated systolic pressure in other childhood cancer forms than brain tumors [24], but also in survivors of childhood brain cancer, this association has been reported [25]. Hypertension has also been described during intra-arterial cisplatin chemotherapy [26]. In one previous study after a follow-up of 1.5–7 years only 1 of 40 children treated with cisplatin had transient hypertension concomitant with hydrocephalus and precocious puberty [11]. Also, a case report has been published on a 30-year-old man who developed renal failure and became hypertensive during vinblastine, bleomycin, and cisplatin therapy and whose hypertension accelerated 3 months after completion of therapy [27]. Magnesium has an important role in the etiology of cardiovascular pathology and hypomagnesemia is associated with cardiovascular problems and hypertension [28]. All of these studies refer to the variable and complex etiology of hypertension in children with brain tumor.

BP rises with growing and aging [19,29]. Since many children have growth problems after cancer therapy, the reference BP tables used should also include besides gender age and height percentiles. BP is associated with early signs of atherosclerosis also in children and young adults [30]; and for long term survivors of childhood brain cancer, the risk for cardiovascular disease has been reported to be strongly increased due to dyslipidemia, central obesity, and elevated systolic BP [25]. As treated brain tumor patients might harbor many risk factors for cardiovascular problems, this emphasizes the finding of elevated BP.

About 30% of the patients treated with cisplatin had renal glomerular dysfunction at the end of treatment. Cisplatin-induced renal glomerular dysfunction seems in most cases to be permanent, but did not apparently progress during the follow-up, which ranged from 1.2 to 14.8 years. Earlier studies have established that chronic renal failure may ensue in severe cases [11,13]. The present results differ from those in earlier studies, in that even though the cisplatin-induced renal glomerular toxicity was not severe, it seemed to persist, and it was combined with many signs of tubular dysfunction. Cisplatin dose rate has been found to be a risk factor for nephrotoxicity in children [14]. In this study, the cumulative dose of cisplatin as risk factor was more obvious.

Many patients also received potentially nephrotoxic agents other than cisplatin. Hypomagnesemia [31] and with high cumulative doses significant reductions in GFR are associated with carboplatin treatment [32]. This present study is not comparable here, as only two patients

in the cisplatin group had received small amounts of carboplatin. Occasionally nephrotoxicity with CCNU has been reported [33,34]. The two patients in the no-cisplatin group who had received CCNU treatment evinced no signs of renal dysfunction. All four patients with renal glomerular dysfunction had also received CCNU treatment. It is possible that this mode had caused further deterioration of renal function.

It has previously been established that cisplatin tends to cause magnesuria with resultant hypomagnesemia [35,36]. We agree with these findings when almost three of four of our patients were hypomagnesemic, and hypomagnesemia tended to progress. We did also recognize low plasma potassium level and one mild hypokalemia but not hypocalcemia. Ifosfamide-induced proximal tubular toxicity has been reported to lead to hypophosphatemic rickets in children [37]. Hypophosphatemia was quite common but mild in our study after cisplatin treatment, and none of these patients had rickets. It might be speculated that the risk of hypophosphatemic rickets is smaller in survivors treated with cisplatin than with ifosfamide. However, persistent magnesium wasting may lead to osteopenia as a long-term adverse effect [38]. Hypomagnesemia may also cause tetany, muscular weakness, and even occasional seizures [39]. In our study, one hypomagnesemic patient had muscular weakness.

CONCLUSION

Elevated BP is a common finding among brain tumor patients treated in childhood. After cisplatin treatment renal glomerular dysfunction appears in most cases to be permanent; and persistent changes in renal tubular function are seen and may even progress. This emphasizes the need for comprehensive evaluation in the long-term follow-up of these patients.

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II

Bone mineral density is reduced in brain tumour patients treated in childhood

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Abstract

Aim: To determine the prevalence of low bone mineral density among children surviving brain tumours and to identify possible factors underlying impaired bone health. *Methods:* Cross-sectional study; total body bone mineral density (TBBMD), fat mass (FM) and lean body mass (LBM) were measured by dual-energy X-ray absorptiometry (DXA) in 46 brain tumour patients aged from 3.8 to 28.7 y (mean 14.9 y) treated in childhood 1.4–14.8 y (mean 6.4 y) after end of treatment for brain tumour. Low bone mineral density was defined as TBBMD z score < -2.0. *Results:* Fifteen patients had TBBMD z scores < -2.0, indicating a 33% prevalence of low bone density. The TBBMD z score ranged from -5.7 to 0.6 (mean -1.7). Out of several potential factors, only combined craniospinal irradiation was significantly associated with low z score ($p = 0.034$, according to multiple regression analysis), while exclusive cranial irradiation showed a borderline statistical association ($p = 0.100$, according to multiple regression analysis).

Conclusion: One third of brain tumour patients treated in childhood had reduced bone mineral density. The reasons for this condition are apparently multifactorial, including craniospinal irradiation.

Key Words: *Bone mineral density, brain tumour, childhood*

Introduction

During childhood and adolescence, bone mineral mass increases substantially, reaching its peak around the age of 20 y [1]. At least 90% of peak bone mass is acquired by 18 y of age, and 25% during the 2-y period surrounding peak height velocity [2,3]. In other words, the period when the skeleton is growing rapidly can be particularly critical for normal bone development. Exposure to illness or risk factors before and during puberty may result in bone deficits [4]. Osteopenia has been found to be common in children surviving brain tumours [5,6]. The pathogenesis of osteopenia in these cases is not well established, but it is apparently multifactorial. Children with brain tumours will obviously be particularly subject to multiple risk factors for impaired bone mineral accrual, these including decreased physical activity, glucocorticoid treatment and hormonal deficiencies. The purpose of this study was to determine the prevalence of low bone mineral density and to identify factors associated with reduced bone mass in children with brain tumours.

Patients and methods

This constitutes part of a study on late sequelae of childhood brain tumours and their therapy [7]. Of the 80 childhood brain tumour survivors who had been treated at Tampere University Hospital, Finland, 75 were invited to attend for examinations from 1998 to 2000. Five patients were excluded because the study protocol was considered too demanding for them. A total of 52 out of 75 potentially eligible patients (65.0% of the survivors) participated in the basic study, and 46 of them (22 females, 24 males) aged from 3.8 to 28.7 y (mean 14.9 y) were able to attend the bone densitometry. The reason for refusal was not specifically asked. A long distance from the hospital was the main reason for refusal in nine cases. Two

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older patients said that everything was fine and they wanted to forget about their disease. One parent refused because they had had too many visits to hospital already. The remaining non-participating patients ($n=11$) said that they were not interested in the study or did not give any specific reason. The reasons why all 52 study patients did not undergo the bone densitometry pertained to cooperation, schedule, or technical problems. The bone densitometry of 46 patients was carried out on average 6.4 y (range 1.4–14.8 y) after the last treatment for the brain tumour. The tumours were classified according to the WHO classification (Table I) [8]. Twenty-six patients had hydrocephalus at the time of diagnosis, and shunt revisions were made for 11 of them. In addition to surgical treatment of 45/46 patients, radiotherapy and/or chemotherapy were given to 15 and 11 patients, respectively (Table I).

Glucocorticosteroids in variable doses and courses were included in the treatment of all patients.

Table I. Clinical data on the 46 childhood brain tumour patients.

Mean age at evaluation (range), y	14.9 (3.8–28.7)
Mean age at diagnosis (range), y	7.4 (0.5–15.5)
Sex (male/female), *n*	24/22
Histology, *n*	
Astrocytic tumour	25
Oligodendroglioma	1
Mixed glioma	3
Ependymoma	2
Choroid plexus tumour	2
Ganglioglioma	2
Embryonal tumour (medulloblastoma)	2
Germ-cell tumour	4
Meningioma	1
Craniopharyngioma	2
Pituitary adenoma	1
Tumour-like lesion (hamartoma)	1
WHO grading of tumours, *n* [a]	
grade I [b]	25
grade I–II	2
grade II	8
grade II–III	1
grade III	2
grade IV	6
Resection/biopsy, *n*	45/1
Chemotherapy, *n*	11
Radiotherapy, *n*	
Cranial	10
Craniospinal	5
Hydrocephalus, *n*	26
Mean height SDS (range)	0.0 (−4.6 to +2.8)
Mean weight (range), % of median weight for height	110 (74–176)
Mean body mass index (range), kg/m^2	20.3 (13–34)
Mean body fat (range), %	34.1 (8.3–53.7)
Mean physical activity (range), h/wk	4.5 (0.0–13.0) ($n=40$)

[a] Hamartoma was not graded.
[b] One pituitary adenoma corresponding to grade I tumour.

Dexamethasone was given for 5 to 8 d in conjunction with the tumour operation. Most patients received dexamethasone 2–4 mg/m^2/d during irradiation in courses of about 4–12 wk, and some received glucocorticosteroids occasionally during cytostatics. Nine patients received both radiotherapy and chemotherapy. Of the 11 children having undergone chemotherapy, 10 received cisplatin. In seven cases, cisplatin was given as a part of "eight drugs in one day" chemotherapy, where seven cytostatic drugs and methylprednisolone (300 mg/m^2 per course) were administered in a scheduled sequence within 12 h [9]. Six patients received from 8 to 10 "8 in 1" courses. One who received chemotherapy according to other protocols was prescribed dexamethasone during chemotherapy. Some patients received dexamethasone for the treatment of nausea. Hydrocortisone substitution was given after these treatments, if needed.

The patients were examined by the same physician (SP). Height SDS and relative weight (expressed as% of median weight for height) were assessed from Finnish growth charts [10]. Pubertal development was assessed according to Tanner and Whitehouse [11]. Thirty of the 46 patients were younger than 18 y during the study. Fourteen were prepubertal. Puberty in 27 cases had started at normal age. One 7.8-y-old girl received therapy because of sexual precocity. Four patients received replacement therapy with sex steroids; in three cases treatment was started later than normal puberty (girls at 12.9 and 15.7 y, boy at 15.9 y). Two patients received growth hormone (GH) therapy, four replacement therapy with glucocorticoids, and six thyroxin medication at the time of the present study. Altogether, eight patients received some hormone drug, five of them more than one.

One patient was suffering from rheumatic disease and received methotrexate treatment once a week at the time of the study, and five patients received antiepileptic medication (carbamazepine, carbamazepine+valproate, valproate, ox-carbazine, lamotrigine+topiramate).

The patients were interviewed for dietary habits and physical activity. Daily calcium intake was estimated to be normal or decreased according to the Nordic Nutrition Recommendations, 1996 [12]. Physical activity was estimated in hours per week. Intensity of exercise was not evaluated. The reasons for impaired mobility were assessed (e.g. hemiparesis).

Total body bone mineral density (TBBMD), lean body mass (LBM) and fat mass (FM) were determined by dual-energy X-ray absorptiometry (XR-26, software 2.5.2., Norland Corp., Fort Atkinson, WI, USA), as previously described [13]. Subject positioning and scanning proceeded according to the manufacturer's recommendations. The scanner was

calibrated daily. According to repeated measurements of 18 subjects, the *in vivo* precision for these measurements (coefficient of variation, %) was about 1%.

In this study, low bone mineral density was defined as a TBBMD z score < -2.0. The z score for TBBMD was calculated as follows: z score = (patient's TBBMD − mean TBBMD in the reference data)/standard deviation in the reference data. For the reference data, age- and gender-specific TBBMD data measured with an identical DXA device were used [14]. For the eight patients over 20 y of age, the reference values for 18–20-y-olds were used.

Blood samples were taken in the morning after overnight fasting. The tests for calcium metabolism included plasma calcium, serum ionized calcium, plasma alkaline phosphatase, phosphate, intact parathyroid hormone (PTH) and serum 25-hydroxycholecalciferol, 1,25-dihydroxycholecalciferol and plasma magnesium. Hormonal tests included follicle-stimulating hormone (FSH), luteinizing hormone (LH), prolactin and insulin-like growth factor 1 (somatomedin C) for both sexes, and estradiol in female and testosterone in male patients. The laboratory samples were analysed using standard methods at the Tampere University Hospital Laboratory, which also provided appropriate reference values for interpreting the results.

Statistical analysis

Mean or median, minimum and maximum values for continuous data and number of observations for categorical data were given as descriptive statistics. Differences between the different subgroups in continuous variables were analysed by analysis of covariance (ANCOVA), using LBM and height SDS as covariates. Analysis of variance (ANOVA) was applied only when testing height SDS between different subgroups. When analysing ordinal data such as Tanner stages 1–5 and number of shunt revisions, the Mann-Whitney U-test was used. Pearson's correlation coefficient was used to evaluate associations between two continuous variables. Finally, a multiple regression analysis was done to identify factors significantly associated with TBBMD z score. Variables were first divided into blocks, each block consisting of three to four variables. Blocks were formed so that each block consisted of variables descriptive for patient characteristics, treatment, medication, hormonal abnormalities and calcium metabolism, and included LBM and height SDS. In addition to variables listed in Tables I, II and III, age at close of treatment, Tanner stage, number of shunt revisions and number of tumour re-operations, and laboratory test results of calcium metabolism were tested. Multiple regression analyses using TBBMD z score as a dependent variable were done separately for each block and, after that, a final model consisting of all significant variables from the primary blocks was formed and tested. The variable was included in the final model if its significance was <0.05.

A p value less than 0.05 was considered statistically significant. Because of a relatively small sample size, attention was also paid to p values of 0.05–0.1, and these are reported as borderline significance. All statistical analyses were performed using SPSS for Windows, version 10.0, statistical software.

The study was approved by the Ethical Committee of Tampere University Hospital and was carried out with signed parental and/or patients' informed consent.

Results

Patients

Table I shows patient characteristics. The distribution of the height SDS was normal, ranging from −4.6 SD to +2.8 SD (mean +0.0 SD). The patients who had received cranial irradiation or chemotherapy, had GH deficiency (earlier diagnosis or low somatomedin C level) or sex hormone deficiency according to laboratory findings during this study were shorter than others (all p values ≤ 0.001). The mean height SDS in different patient subgroups is presented in Tables II and III.

In addition, patients who had received cranial irradiation were older (mean 18.5 (range 6.0–28.7) vs 13.2 (3.8–24.8) y, $p=0.005$) and more mature (median Tanner stage 5 (range 1–5) vs 2 (1–5), $p=0.008$, Mann-Whitney U-test) than the rest, but the percentage of body fat did not differ between these groups (mean 36.2 (range 22.3–49.6) vs 33.0 (8.3–53.7)%, $p=0.324$).

When comparing the nine GH-deficiency patients with the rest, they were more obese (mean body fat 41.8 (range 27.8–53.7) vs 32.2 (8.3–47.8)%, $p=0.009$; mean relative weight 136 (range 99–176) vs 104 (74–135)%, $p<0.001$; mean BMI 24.7 (range 15.6–34.0) vs 19.3 (13.0–27.6) kg/m^2, $p=0.001$), as were the four patients who received replacement therapy with glucocorticoids at the time of the present study (mean body fat 45.0 (range 34.7–53.7) vs 33.0 (8.3–49.6)%, $p=0.023$; mean relative weight 144 (range 135–155) vs 107 (74–176)%, $p<0.001$; mean BMI 25.9 (range 22.8–28.0) vs 19.8 (13.0–34.0) kg/m^2, $p=0.008$).

Total body bone mineral density

As judged from the z score, TBBMD was generally low, ranging from −5.7 to +0.6 (mean −1.7)

Table II. Mean total body BMD z score and height SDS according to childhood brain tumour patient characteristics.

	TBBMD z score (range)	p [a]	Height SDS (range)	p [b]
Patient characteristics				
Gender		0.109		0.833
male ($n=24$)	−1.9 (−5.7 to +0.6)		0.0 (−2.6 to +2.6)	
female ($n=22$)	−1.6 (−3.9 to −0.1)		−0.1 (−4.6 to +2.8)	
Tumour grade		0.406		<0.001
I–II ($n=36$)	−1.6 (−5.7 to +0.6)		+0.4 (−2.5 to +2.8)	
more malignant ($n=9$)	−2.3 (−3.9 to −0.5)		−1.7 (−4.6 to +0.4)	
Tumour site		0.221		0.864
infratentorial ($n=22$)	−2.0 (−3.9 to +0.2)		+0.1 (−4.6 to +2.8)	
supratentorial ($n=24$)	−1.5 (−5.7 to +0.6)		−0.1 (−2.6 to +1.6)	
Hydrocephalus		0.092		0.184
yes ($n=26$)	−2.1 (−5.7 to −0.1)		−0.2 (−4.6 to +2.8)	
no ($n=20$)	−1.3 (−3.4 to +0.6)		+0.2 (−2.5 to +1.6)	
Cranial irradiation		0.435		0.001
yes ($n=15$)	−1.7 (−3.9 to +0.1)		−1.0 (−4.6 to +0.9)	
no ($n=31$)	−1.7 (−5.7 to +0.6)		+0.4 (−2.5 to +2.8)	
Radiotherapy		0.088		<0.001
craniospinal ($n=5$)	−3.0 (−3.9 to −1.8)		−2.1 (−4.6 to −0.3)	
cranial ($n=10$)	−1.1 (−2.4 to +0.1)		−0.4 (−2.6 to +0.9)	
no ($n=31$)	−1.7 (−5.7 to +0.6)		+0.4 (−2.5 to +2.8)	
Chemotherapy		0.513		0.001
yes ($n=11$)	−2.2 (−3.9 to −0.3)		−1.2 (−4.6 to +0.8)	
no ($n=35$)	−1.6 (−5.7 to +0.6)		+0.4 (−2.5 to +2.8)	
Radiotherapy and chemotherapy		0.876		0.001
both ($n=9$)	−2.0 (−3.9 to −0.3)		−1.4 (−4.6 to +0.7)	
either/or ($n=8$)	−1.7 (−3.4 to +0.1)		−0.4 (−2.3 to +0.9)	
neither ($n=29$)	−1.7 (−5.7 to +0.6)		+0.6 (−2.5 to +2.8)	
Severe perioperative complications		0.787		0.889
yes ($n=12$)	−1.9 (−5.7 to −0.2)		+0.1 (−1.9 to +1.6)	
no ($n=34$)	−1.7 (−3.9 to +0.6)		−0.1 (−4.6 to +2.8)	
Treatment at the time of puberty		0.397		0.693
yes ($n=13$)	−1.4 (−5.7 to +0.6)		−0.1 (−2.6 to +1.6)	
no ($n=33$)	−1.9 (−3.9 to −0.1)		+0.1 (−4.6 to +2.8)	
Impaired mobility		0.348		0.860
yes ($n=12$)	−2.0 (−5.7 to −0.5)		−0.1 (−1.9 to +1.6)	
no ($n=34$)	−1.6 (−3.9 to +0.6)		0.0 (−4.6 to +2.8)	

[a] ANCOVA
[b] ANOVA

(Figure 1). Fifteen patients (33%) had TBBMD z scores < -2.0. The mean z score for TBBMD in different patient groups is presented in Tables II and III.

One 9-y-old boy had sustained radius fracture in a minor accident at play. Fractures in two other cases were due to high-energy trauma. In one 6-y-old boy, osteoporosis was previously suspected after radiographic examination of his hip. A gynaecologist had previously diagnosed osteoporosis in one 18-y-old girl and had started oestrogen therapy to prevent fractures. The TBBMD z score of the patient suffering radius fracture was −1.9, of the patient with suspected osteoporosis −2.6, and of the patient with diagnosed osteoporosis −3.9.

The z score for TBBMD did not correlate with age at evaluation ($r=0.14$), age at close of treatment (0.15), height SDS (0.27), Tanner stage (0.03) or percentage body fat (−0.01). When comparing height SDS in two z-score groups (z score < -2.0 and z score ≥ -2.0), there was no significant difference between the groups (mean height SDS −0.4 (range −4.6 to +2.6) vs +0.2 (−2.6 to +2.8), $p=0.151$, ANOVA). Neither was there any significant difference between these z-score groups when testing percentage body fat (mean 33.7 (13.4–53.1) vs 34.2 (8.3–53.7)%, $p=0.289$, ANCOVA).

The number of shunt revisions was higher among the 15 patients who had TBBMD z scores < -2.0 (median 0 (range 0–8) vs 0 (range 0–6), $p=0.093$, Mann-Whitney U-test). The correlation between z score for TBBMD and physical activity estimated in hours per week was 0.30 ($n=40$, could not be calculated for children <7 y of age). The reasons for impaired mobility were neurological (hemiparesis, ataxia, clumsiness, multiple sclerosis, impaired sight) or orthopaedic (scoliosis, knee problems) (Table II).

Table III. Mean total body BMD and height SDS according to different medication, and endocrine and metabolic characteristics of childhood brain tumour patients.

	TBBMD z score (range)	p [a]	Height SDS (range)	p [b]
Medication and hormonal abnormalities				
Antiepileptic medication		0.340		0.745
yes ($n=5$)	−1.2 (−2.6 to +0.6)		+0.2 (−1.1 to +1.6)	
no ($n=41$)	−1.8 (−5.7 to +0.2)		−0.1 (−4.6 to +2.8)	
Thyroxin medication		0.198		0.262
yes ($n=6$)	−2.4 (−5.7 to −0.5)		−0.6 (−4.6 to +1.6)	
no ($n=40$)	−1.6 (−3.5 to +0.6)		0.0 (−2.6 to +2.8)	
Glucocorticoid replacement		0.424		0.264
yes ($n=4$)	−1.4 (−2.3 to −0.8)		−0.8 (−1.9 to +0.4)	
no ($n=42$)	−1.8 (−5.7 to +0.6)		0.0 (−4.6 to +2.8)	
Growth hormone deficiency		0.193		<0.001
yes ($n=9$)	−1.6 (−3.9 to −0.5)		−1.5 (−4.6 to +0.9)	
no ($n=37$)	−1.8 (−5.7 to +0.6)		+0.3 (−2.5 to +2.8)	
Sex hormone deficiency		0.598		<0.001
yes ($n=4$)	−2.5 (−3.9 to −1.2)		−2.3 (−4.6 to −1.3)	
no ($n=42$)	−1.7 (−5.7 to +0.6)		+0.2 (−2.6 to +2.8)	
Hyperprolactinaemia		0.272		0.451
yes ($n=4$)	−1.1 (−1.4 to −0.8)		−0.2 (−1.9 to +1.0)	
no ($n=42$)	−1.8 (−5.7 to +0.6)		0.0 (−4.6 to +2.8)	
Calcium metabolism				
Hypomagnesaemia		0.221		0.070
yes ($n=11$)	−1.5 (−3.5 to +0.1)		−0.7 (−2.6 to +0.8)	
no ($n=35$)	−1.8 (−5.7 to +0.6)		+0.2 (−4.6 to +2.8)	
25-hydroxycholecalciferol <38 nmol/l		0.310		0.559
yes ($n=21$)	−1.5 (−3.5 to +0.6)		+0.1 (−2.6 to +2.8)	
no ($n=24$)	−2.0 (−5.7 to +0.1)		−0.2 (−4.6 to +1.6)	
Low dietary calcium intake		0.155		0.936
yes ($n=7$)	−1.2 (−2.2 to +0.1)		+0.1 (−1.9 to +1.0)	
no ($n=39$)	−1.8 (−5.7 to +0.6)		−0.1 (−4.6 to +2.8)	
Intact parathyroid hormone (PTH) concentration		0.803		0.173
≤2.8 pmol/l ($n=21$)	−1.7 (−3.5 to +0.6)		−0.3 (−2.6 to +1.4)	
2.9 pmol/l ≤PTH ≤4.9 pmol/l ($n=18$)	−1.7 (−3.5 to +0.2)		+0.5 (−1.9 to +2.8)	
≥5.0 pmol/l ($n=7$)	−2.0 (−5.7 to −0.3)		−0.7 (−4.6 to +1.6)	

[a] ANCOVA
[b] ANOVA

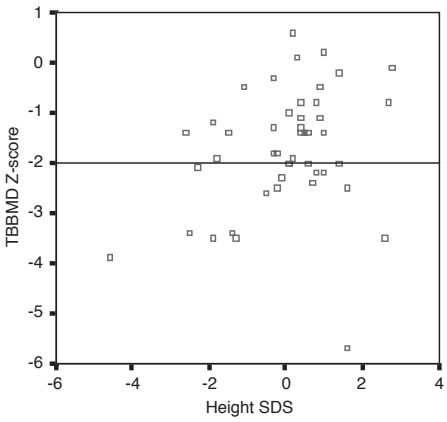

Figure 1. Z score for total body bone mineral density (TBBMD) of 46 childhood brain tumour survivors as a function of height SDS. Low bone mineral density was defined as TBBMD z score < -2.0.

Hypomagnesaemia was a common sign of tubular dysfunction in patients who had received cisplatin as one of the chemotherapeutic agents (Table III). There were two hypophosphataemic, but no hypocalcaemic patients or patients with low vitamin D levels according to the laboratory reference values. One patient who had a low dietary calcium intake had an elevated intact parathyroid hormone concentration.

Out of several potential factors, only the combined craniospinal irradiation was significantly associated with low z score ($p=0.034$, according to multiple regression analysis), while exclusive cranial irradiation showed a borderline statistical association ($p=0.100$, according to multiple regression analysis).

Discussion

Osteopenia has been found to be prevalent among children surviving brain tumours [5,6]. In line with this, one third of the patients in our study had

TBBMD z scores < -2.0. The apparent problem in bone health among these patients has not been adequately appreciated, as only one 18-y-old girl was previously diagnosed as osteoporotic. Her very low TBBMD z score of -3.9 supports this diagnosis. The TBBMD z score of the 9-y-old boy with earlier radius fracture from a minor accident was -1.9, and of the 6-y-old boy with suspected osteoporosis -2.6.

As regards the assessment of skeletal status, the T score is generally used for comparing adult patients' BMD with the reference data obtained from young healthy adults at the time of peak bone mass, but in growing children this should not be used [15,16]. As most of our patients were under 18 y, we used z scores (standard deviation scores) for the assessment of skeletal status. A z score below -2.0 is usually considered abnormal, and has been used for defining low bone mineral density [16] or severe osteopenia [6] in children. Accordingly, in our study, low bone mineral density was also defined as a TBBMD z score < -2.0. As there is no consensus on the part of the skeleton which most accurately reflects the bone health of children, we decided to use TBBMD in this study.

Reduced bone mineral density in long-term survivors of childhood acute lymphoblastic leukaemia has been found to be associated with cranial irradiation [17], and an association with radiation therapy has also been found in childhood brain tumour survivors [5,6]. In this study, we observed a deleterious effect of craniospinal irradiation, but cranial irradiation alone showed a borderline statistical association with low z score (according to multiple regression analysis) as well as hydrocephalus (according to ANCOVA) and number of shunt revisions (according to Mann-Whitney U-test). The patients who had hydrocephalus and were thus disposed to possible shunt revisions were probably more severely affected by their disease than others.

Osteopenia has also been reported in children with severe cerebral palsy suffering from gross motor function difficulties [18]. In our study, the patient with the lowest TBBMD z score (-5.7) was blind and had hemiparesis, but he could walk. In general, impaired mobility was not associated with TBBMD z score in the present study. Our material is, however, skewed in that the most severely handicapped patients were excluded from the study, which might have biased the results. On the other hand, some patients who considered themselves completely recovered from their disease were also not willing to participate in the study.

There are several studies reporting decreased bone mass among children on glucocorticoid treatment [19–21]. All brain tumour patients in our study received periodic, even massive glucocorticoid doses, given as part of the treatment. The dosage and duration of this treatment is highly variable and impossible to trace exactly. The substitution dose of hydrocortisone used at the time of the present study was so low that it did not affect the TBBMD in our patients, but previous higher doses of glucocorticoids, especially during radiotherapy, might have predisposed to osteopenia.

Hypomagnesaemic patients did not have lower z scores for TBBMD than patients with normal magnesium levels. Cisplatin treatment cannot thus be directly associated with osteopenia. However, this issue needs to be followed up, in view of the young age of these patients.

There is accumulating clinical evidence of manifest osteoporosis in chronically ill children. This study has also confirmed that reduced bone mineral density is a common finding among brain tumour patients treated in childhood. The reasons for this condition are apparently multifactorial, including craniospinal irradiation. Many risk factors compromising bone health concern this patient group. Large, well-designed studies with more specific bone measurements are needed to elucidate the factors associated with BMD impairment in these patients. More attention should be paid to this issue in long-term follow-up to identify not only cases requiring treatment but also those benefiting from preventive measures of osteoporosis.

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Obesity and Metabolic Changes Are Common in Young Childhood Brain Tumor Survivors

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Background. A population based cross-sectional study was used to examine the prevalence of metabolic syndrome and its components in childhood brain tumor survivors. ***Procedure.*** Fifty-two survivors were examined at a mean age of 14.4 years (range 3.8–28.7). Lipid and glucose metabolism, thyroid function, and plasma uric acid were evaluated. Fat mass and fat percentage were assessed by dual-energy X-ray absorptiometry (DXA). Metabolic syndrome was defined on International Diabetes Federation criteria. ***Results.*** Ten (19%) patients were overweight and four (8%) were obese. According to DXA, 16/46 (35%) patients were obese. Central obesity was found in 11 (21%) patients. Cranial irradiation, hypothalamic/hypophyseal damage, growth hormone (GH) deficiency and impaired mobility were associated with overweight/obesity and central obesity. Thirteen (25%) subjects had hypercholesterolemia, 14 (27%) had raised low-density lipoprotein cholesterol (LDL-C), 12 (23%) had raised blood pressure, four (8%) had metabolic syndrome, two (4%) had hyperinsulinemia and five (10%) had hyperuricemia. Cranial irradiation was associated with hypercholesterolemia ($P = 0.019$), raised LDL-C ($P = 0.028$), raised blood pressure ($P = 0.040$), and metabolic syndrome ($P = 0.018$). Impaired mobility was associated with hypercholesterolemia ($P = 0.034$). Hypothalamic/hypophyseal damage was associated with metabolic syndrome ($P = 0.003$) and hyperuricemia ($P = 0.011$) as was GH deficiency ($P = 0.034$ and $P = 0.008$). GH supplementation alleviated adverse metabolic outcomes among brain tumor survivors with GH deficiency. ***Conclusions.*** Obesity/overweight, dyslipidemia, hypertension, metabolic syndrome, and hyperuricemia were common in young childhood brain tumor survivors. Cranial irradiation, hypothalamic/hypophyseal damage, growth hormone deficiency, and/or impaired mobility were associated with higher risk for obesity and metabolic changes among these patients.Pediatr Blood Cancer 2009;52:853–859.

Key words: brain tumor; childhood; dyslipidemia; late effects; metabolic syndrome; obesity

INTRODUCTION

Long-term survivors of childhood cancer forms other than brain tumors (BT) have increased risk of metabolic syndrome [1]. Decreased growth hormone (GH) secretion accounts for these metabolic abnormalities [1]. Impaired glucose tolerance, dyslipidemia and signs of metabolic syndrome occur after bone marrow transplantation in childhood [2]. A higher risk of dyslipidemia, central obesity and elevated systolic blood pressure (BP) among survivors of childhood brain cancer has been reported, particularly for those with GH deficiency [3]. Also elevated BP is common among childhood BT survivors, and is associated with cisplatin therapy and cranial irradiation especially after exposure to both of these therapies [4]. The goal of this study was to evaluate the prevalence of metabolic syndrome, abnormalities in lipid and glucose metabolism, and obesity in childhood BT survivors as well as identify factors associated with these problems.

MATERIALS AND METHODS

Patients

A total of 104 primary BT patients diagnosed below 17 years of age between 1983 and 1997 were treated in Tampere University Hospital, Finland. Of the 80 survivors 75 were invited to this population based cross-sectional study in Tampere district with a population of approximately 1 million. Five patients were excluded because of too demanding study protocol. Fifty-two out of 75 potentially eligible patients (65% of the survivors) participated in the study (Table I). A long distance from the hospital was the main reason for refusal in nine cases. Two older patients said that everything was fine. One parent refused because they had had too many visits to the hospital already. The remaining non-participating patients ($n = 11$) said that they were not interested in the study or did not give any specific reason. The study was approved by the Ethical Committee of Tampere University Hospital and was carried out with signed parental and/or patients' consent.

Treatment of the Tumor

All of the 52 participants had undergone surgery (Table I). Twenty-nine (56%) children were treated by surgery only and 17 (33%) with chemotherapy. Three (6%) patients received chemotherapy without radiation, and 14 (27%) also received radiotherapy. Six (12%) received radiotherapy without chemotherapy, totaling 20 (38%) patients treated with radiotherapy. Nineteen patients had received irradiation to the hypothalamic-pituitary axis. All patients received pharmacological doses of glucocorticosteroids in the treatment connected to the tumor operation, during radiotherapy and/or as part of the chemotherapy but the exact doses could not be calculated.

Research Methods

Patients' medical records were checked for clinical history. The patients were interviewed and examined by the same physician (SP). Reasons for impaired mobility were noted (e.g., hemiparesis).

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TABLE I. Clinical Data on the 52 Brain Tumor Patients Diagnosed Below 17 Years of Age

Mean age at evaluation (range, years)	14.2 (3.8–28.7)
Mean time after diagnosis (range, years)	7.5 (1.5–15.1)
Mean time after treatment (range, years)	6.2 (1.2–14.8)
Median age at diagnosis (range, years)	6.0 (0.1–15.5)
Sex (male/female, n)	27/25
Histology (n)	
Astrocytic tumor	25
Oligodendroglioma	1
Mixed glioma	4
Ependymoma	5
Choroid plexus tumor	2
Ganglioglioma	2
Embryonal tumor (medulloblastoma, PNET)	4
Germ cell tumor	4
Meningioma	1
Craniopharyngioma	2
Pituitary adenoma	1
Tumor-like lesion (hamartoma)	1
Site of the tumor (n)	
Infratentorial	25
Supratentorial	27
Pituitary	1
Hypothalamus	5
Resection/biopsy (n)	51/1
Chemotherapy (n)	17
Radiotherapy (n)	20
Cranial (including hypothalamo-pituitary axis)	12 (11)
Craniospinal (including hypothalamo-pituitary axis)	8 (8)
Tumor dose (median, range, Gy)	50.5 (16.0–60.0)

Height and weight were measured. Height SDS and relative weight (expressed as % of median weight for height) were assessed from Finnish growth Charts [5]. Pubertal development was assessed according to Tanner and Whitehouse [6]. Waist and hip circumferences were measured to the nearest millimeter. Physical examination included BP, measured by an oscillometric method preferentially on the right arm in sitting position. Fat mass and percentage body fat were determined in 46 patients by dual-energy X-ray absorptiometry (DXA, Norland XR-26, software 2.5.2., Norland Corp. Fort Atkinson, WI), as previously described [7]. The precision of the fat assessments was approximately 1%.

Laboratory samples were taken in the morning after overnight fasting. Tests included plasma triglycerides, plasma total cholesterol (TC), serum high-density lipoprotein cholesterol (HDL-C), serum low-density lipoprotein cholesterol (LDL-C), blood glucose, serum insulin, plasma uric acid, insulin-like growth factor 1 (IGF-1), free thyroxine (free T_4), and thyroid-stimulating hormone (TSH). Samples were analyzed using standard methods in Tampere University Hospital Laboratory, which also provided appropriate reference values for interpreting results.

The definition issued by the International Diabetes Federation (IDF) was used to determine metabolic syndrome. The basic criterion for metabolic syndrome was central obesity: waist circumference 94 cm or more in men, and 80 cm or more in women [8,9]. For patients younger than 18 years, waist-height ratio $\geq$0.50 was considered to indicate central obesity [10]. In addition to central obesity at least two of following findings were needed for the diagnosis: triglycerides $>$1.7 mmol/L; HDL-C $<$1.03 mmol/L in men, and $<$1.29 mmol/L in women; systolic BP $\geq$ 130 mmHg, or diastolic BP $\geq$ 85 mmHg; and fasting plasma glucose $\geq$5.6 mmol/L [8,9]. For patients younger than 18 years BP at the 95th percentile or greater by height, sex, and age according to Rosner and associates was considered elevated [11,12]. In 2007 IDF presented a definition for children and adolescents aged 10–15 years [13]. We used the IDF criterion for adults as mentioned above for every patient, as only a part of our patients belonged to that age-group and both definitions are quite similar. TC was considered elevated if it was $\geq$5.0 and LDL-C if it was $\geq$3.0 mmol/L [14].

A relative weight more than 120% was considered overweight [1,15], and a relative weight 140% or more obesity [15]. DXA-measured fat percentage $\geq$33% was regarded as obesity in all male patients and prepubertal girls, while for pubertal girls and women limits ranging from approximately 35% to 50% depending on age were taken from appropriate reference data [16,17].

Statistical Analysis

Continuous data were analyzed using independent sample *t*-test or analysis in variance (ANOVA) in the case of normal distribution, and Mann–Whitney *U*-test or Kruskal–Wallis test in the case of skewed distribution or ordinal variables. Categorized data were analyzed using Fisher's exact test, χ^2 test or exact χ^2 test as appropriate. A *P*-value $<$0.05 was considered significant. All statistical analyses were performed using the SPSS for Windows version 10.0 and 16.0.

RESULTS

Obesity

According to relative weight (expressed as % of median weight for height), 10 (19%) were overweight and four (8%) obese. According to DXA, obesity was found in 16/46 (35%) patients. Central obesity was found in 11 (21%) patients and 10 of them had a relative weight more than 120%. Sex or age at diagnosis were not statistically significantly associated with obesity.

Altogether 13 patients received thyroxine (n = 10), glucorticoid (n = 4), GH (n = 4), and/or sex hormone (n = 6) therapy at the time of the present study (Table II). All these patients had hypothalamic/hypophyseal damage (surgery or radiation in this area). Twelve patients suffered from GH deficiency according to earlier diagnosis or low IGF-1 level during the study. Among GH deficiency patients the tendency to general and central obesity was stronger without supplementation. Cranial irradiation alone was not as harmful as hormonal problems caused by irradiation or tumor itself and its surgery. One patient with thyroxine substitution had slightly elevated free T_4, which was normal in control. Other patients had normal free T_4 levels at the time of the study.

All patients were ambulatory. Fifteen with impaired mobility (e.g., mild hemiparesis, clumsiness, ataxia, impaired vision) were more obese than the rest (Table II). Seven of these 15 patients had received radiation therapy.

Lipids

Nineteen (37%) patients had at least one abnormal lipid value, and nine of them were neither overweight nor obese and 11 had no central obesity. Altogether 13 (25%) patients had hypercholesterolemia, 14 (27%) had raised LDL-C, nine (17%) had

TABLE II. Overweight/Obesity and Central Obesity Among 52 Childhood Brain Tumor Survivors With Cranial Irradiation, Hormone Therapy, Growth Hormone (GH) Deficiency and Impaired Mobility

	Relative weight (%)[a]		Body fat (%)[b]		Waist-height ratio		Relative weight >120%		Obesity according to DXA[b]		Central obesity[c]	
	Mean (range)	*P*	Mean (range)	*P*	Mean (range)	*P*	n (%)	*P*	n (%)	*P*	n (%)	*P*
Cranial irradiation												
Yes (n = 20)	117 (89–176)	0.058	36.2 (22.3–49.6) (n = 15)	0.324	0.48 (0.38–0.58)	**0.014**	9 (45)	**0.028**	6 (40) (n = 15)	0.744	6 (30)	0.299
No (n = 32)	106 (74–155)		33.0 (8.3–53.7) (n = 31)		0.44 (0.36–0.57)		5 (16)		10 (32) (n = 31)		5 (16)	
Hormone therapy[d]												
Yes (n = 13)	125 (94–155)	**0.002**	42.1 (27.8–53.7) (n = 9)	**0.007**	0.50 (0.42–0.56)	**<0.001**	8 (62)	**0.003**	6 (67) (n = 9)	**0.047**	8 (62)	**<0.001**
No (n = 39)	106 (74–176)		32.1 (8.3–47.8) (n = 37)		0.44 (0.36–0.58)		6 (15)		10 (27) (n = 37)		3 (8)	
GH deficiency												
Yes (n = 12)	132 (94–176)	**<0.001**	41.8 (27.8–53.7) (n = 9)	**0.009**	0.52 (0.43–0.58)	**<0.001**	8 (67)	**0.001**	6 (67) (n = 9)	**0.047**	7 (58)	**0.001**
No (n = 40)	104 (74–135)		32.2 (8.3–47.8) (n = 37)		0.44 (0.36–0.57)		6 (15)		10 (27) (n = 37)		4 (10)	
GH therapy												
Yes now (n = 4)	115 (94–155)	**<0.001**	40.8 (27.8–53.7) (n = 2)	**0.068**	0.48 (0.43–0.56)	**<0.001**	1 (25)	**<0.001**	1 (50) (n = 2)	0.088	1 (25)	**0.001**
Yes previously (n = 5)	137(106–176)		40.7 (29.9–49.6) (n = 5)		0.54 (0.45–0.58)		4 (80)		3 (60) (n = 5)		3 (60)	
No never (n = 3)	144 (139–147)		45.7 (38.3–53.1) (n = 2)		0.55 (0.53–0.55)		3 (100)		2 (100) (n = 2)		3 (100)	
No deficiency (n = 40)	104 (74–135)		32.2 (8.3–47.8) (n = 37)		0.44 (0.36–0.57)		6 (15)		10 (27) (n = 37)		4 (10)	
Impaired mobility												
Yes (n = 15)	123 (74–176)	**0.004**	40.0 (25.4–53.7) (n = 12)	**0.016**	0.49 (0.37–0.58)	**0.003**	8 (53)	**0.013**	6 (50) (n = 12)	0.292	8 (53)	**0.001**
No (n = 37)	105 (81–138)		32.0 (8.3–49.6) (n = 34)		0.44 (0.36–0.57)		6 (16)		10 (29) (n = 34)		3 (8)	

[a]Expressed as % of median weight for height; [b]Percentage body fat determined by dual-energy X-ray absorptiometry (DXA) ≥33% was regarded as obesity in all male patients and prepubertal girls, the limits for pubertal girls and women were taken from reference data by van der Sluis et al.; [c]Waist ≥80 cm in women, ≥94 cm in men, waist-height ratio ≥0.50 in patients younger than 18 years; [d]Thyroxine, glucocorticoid, GH and/or sex hormone therapy at the time of the study. A *P*-value <0.05 was considered significant and is shown in bold.

reduced HDL-C, and five (10%) had raised triglycerides. Cranial irradiation, any hormonal therapy, GH deficiency and impaired mobility were risk factors for dyslipidemia (Tables III and IV). Sex or age at diagnosis were not statistically significantly associated with dyslipidemia. Among GH deficiency patients, GH supplementation seemed to affect beneficially the lipid values (Table IV).

Glucose Metabolism

There were no hyperglycemic patients, and only two (4%) had fasting hyperinsulinemia (Table III). Mean fasting blood glucose was lower among patients with hormone therapy than without [4.2 (range 3.6–5.0) vs. 4.5 (3.9–5.3) mU/L, $P = 0.047$], but median serum insulin did not differ between these groups [11 (range 5–48) (n = 12) vs. 7 (4–16) mU/L, $P = 0.165$]. Between patients with and without GH deficiency mean fasting blood glucose did not differ [4.4 (range 3.7–5.0) vs. 4.5 (3.6–5.3) mmol/L, $P = 0.500$], but median serum insulin was higher among patients with GH deficiency than without [13 (range 5–48) (n = 11) vs. 7 (4–23) mU/L, $P = 0.023$]. Mean fasting blood glucose was lower among patients who had impaired mobility [4.2 (range 3.6–4.8) vs. 4.5 (3.7–5.3) mmol/L, $P = 0.006$], while median serum insulin did not differ among patients with or without impaired mobility [10 (range 5–23) vs. 7 (4–48) mU/L, $P = 0.774$].

Hypertension, Metabolic Syndrome, and Hyperuricemia

Altogether 12 (23%) patients had raised BP compared to reference values. Their median age at diagnosis was higher than in patients without raised BP [13.2 (range 0.1–15.5) vs. 5.1 (0.5–13.2) years, $P = 0.009$]. Cranial irradiation was a risk factor for raised BP (Table IV).

Four (8%) patients had metabolic syndrome. Cranial irradiation, hypothalamic/hypophyseal damage, and GH deficiency were risk factors. The tendency to metabolic syndrome was stronger among GH deficiency patients without GH supplementation (Table IV). Sex or age at diagnosis were not statistically significantly associated with it.

Five (10%) patients had hyperuricemia (Tables III and IV) and two of them had metabolic syndrome [2/47 (4%) vs. 2/5 (40%), $P = 0.042$]. Hypothalamic/hypophyseal damage and GH deficiency were associated with hyperuricemia, but sex and age at diagnosis were not.

DISCUSSION

Obesity/overweight, dyslipidemia, raised BP, metabolic syndrome and hyperuricemia were common among young Finnish childhood BT survivors. Given the association with cardiovascular morbidity [18] and type 2 diabetes [19], metabolic syndrome is an important health problem, and particularly so, if it has started at young age [20–23].

The basic criterion for metabolic syndrome is central obesity. An appropriate definition of central obesity for children and adolescents is challenging. Waist circumference cut-offs by age do not consider patient's height and pubertal development and might thus be misleading if the patient grows and develops otherwise than average. This problem may be avoided by using waist-height ratio that offers a useful surrogate for central obesity [10]. To define general obesity, we did not use body mass index (BMI) because of its limitations in the pediatric population [24,25].

In earlier studies the prevalence of overweight among childhood cancer survivors has varied from 16% to 50% [1,3,26–28]. In our study 27–35% were overweight or obese, being in concord with earlier observations. This is more than the average 15% prevalence of overweight and 3% prevalence of obesity among present Finnish children and adolescents [15,29]. Central obesity was found in 21% of our patients, while in other studies about one third of childhood cancer survivors developed abdominal obesity [2,3].

Hypothalamic damage accounts for the development of obesity in children surviving BT [30] which was also seen in our study. In particular, children with craniopharyngiomas are at extremely high risk [31]. In our study, the overweight/obesity and central obesity were strongly associated with hypothalamic/hypophyseal damage manifested as hormonal problems, and also with impaired mobility, but less with cranial irradiation alone. Among GH deficiency patients, GH supplementation diminished the tendency to general and central obesity.

TABLE III. Characteristics, Lipid and Glucose Metabolism and Plasma Uric Acid Values in the 52 Childhood Brain Tumor Survivors According to Cranial Irradiation

	Cranial irradiation (n = 20)	No cranial irradiation (n = 32)	*P*-value
Age at study (years)	16.8 (4.9–28.7)	12.9 (3.8–24.8)	**0.023**
Median age at diagnosis (years)	7.1 (0.1–15.5)	5.9 (0.6–15.5)	0.486
Male gender	*12 (60)*	*15 (47)*	*0.404*
Median Tanner stage (breasts/genitals)	5 (1–5)	2 (1–5)	**0.022**
Median plasma triglycerides (mmol/L)	0.87 (0.43–2.54)	0.78 (0.32–1.74)	0.132
Serum high density lipoprotein cholesterol (mmol/L)	1.44 (0.78–2.37)	1.52 (0.93–2.21)	0.510
Plasma cholesterol (mmol/L)	4.7 (3.0–6.9)	4.1 (2.9–5.9)	**0.017**
Serum low density lipoprotein cholesterol (mmol/L)	2.8 (1.5–4.7)	2.2 (1.3–3.3)	**0.012**
Fasting blood glucose (mmol/L)	4.4 (3.6–5.3)	4.5 (3.9–5.3)	0.758
Hyperglycemia (blood glucose ≥5.6 mmol/L)	*0 (0)*	*0 (0)*	
Median serum insulin (mU/L)	9 (4–48) (n = 19)	7 (4–23)	0.438
Hyperinsulenemia (serum insulin >20 mU/L)	*1 (5) (n = 19)*	*1 (3)*	*1.000*
Plasma uric acid (mmol/L)	0.33 (0.17–0.65)	0.24 (0.10–0.45)	**0.005**

Continuous data is shown as mean (range), if not otherwise stated, and categoric data in italics as number of patients (%). A *P*-value <0.05 was considered significant and is shown in bold.

TABLE IV. Dyslipidemia, Metabolic Syndrome, Raised Blood Pressure (BP) and Hyperuricemia Among 52 Childhood Brain Tumor Survivors With Cranial Irradiation, Hormone Therapy, Growth Hormone (GH) Deficiency and Impaired Mobility

	Triglycerides ↑[a]		HDL-C ↓[b]		Cholesterol ↑[c]		LDL-C ↑[d]		Metabolic syndrome[e]		Raised BP[f]		Hyperuricemia[g]	
	n (%)	*P*	n (%)	*P*	n (%)	*P*	n (%)	*P*	n (%)	*P*	n (%)	*P*	n (%)	*P*
Cranial irradiation														
Yes (n = 20)	4 (20)	0.066	5 (25)	0.280	9 (45)	**0.019**	9 (45)	**0.028**	4 (20)	**0.018**	8 (40)	**0.040**	4 (20)	0.066
No (n = 32)	1 (3)		4 (13)		4 (13)		5 (16)		0 (0)		4 (13)		1 (3)	
Hormone therapy[h]														
Yes (n = 13)	3 (23)	0.093	7 (54)	**<0.001**	6 (46)	0.064	6 (46)	0.086	4 (31)	**0.003**	3 (23)	1.000	4 (31)	**0.011**
No (n = 39)	2 (5)		2 (5)		7 (18)		8 (21)		0 (0)		9 (23)		1 (3)	
GH deficiency														
Yes (n = 12)	4 (33)	**0.008**	5 (42)	**0.022**	6 (50)	0.051	6 (50)	0.063	3 (25)	**0.034**	4 (33)	0.437	4 (33)	**0.008**
No (n = 40)	1 (3)		4 (10)		7 (18)		8 (20)		1 (3)		8 (20)		1 (3)	
GH therapy														
Yes now (n = 4)	0 (0)	**0.004**	1 (25)	**0.035**	1 (25)	**0.034**	1 (25)	**0.044**	0 (0)	**0.028**	1 (25)	0.838	1 (25)	**0.037**
Yes previously (n = 5)	3 (60)		2 (40)		4 (80)		4 (80)		2 (40)		2 (40)		2 (40)	
No never (n = 3)	1 (33)		2 (67)		1 (33)		1 (33)		1 (33)		1 (33)		1 (33)	
No deficiency (n = 40)	1 (3)		4 (10)		7 (18)		8 (20)		1 (3)		8 (20)		1 (3)	
Impaired mobility														
Yes (n = 15)	1 (7)	1.000	4 (27)	0.419	7 (47)	**0.034**	7 (47)	0.081	2 (13)	0.569	4 (27)	0.726	3 (20)	0.137
No (n = 37)	4 (11)		5 (14)		6 (16)		7 (19)		2 (5)		8 (22)		2 (5)	

[a]Raised triglycerides: plasma triglycerides >1.7 mmol/L; [b]Reduced high-density lipoprotein cholesterol: serum HDL-C <1.03 mmol/L in male, and <1.29 mmol/L in female patients; [c]Hypercholesterolemia: plasma total cholesterol ≥5.0 mmol/L; [d]Elevated low-density lipoprotein cholesterol: serum LDL-C ≥3.0 mmol/L; [e]Metabolic syndrome was defined on International Diabetes Federation (IDF) criteria; [f]For patients 18 years or older systolic BP ≥130 or diastolic BP ≥85 mmHg were classified as raised, and for patients younger than 18 years BP values at the 95th percentile or greater by height, sex and age according to Rosner et al. were classified as raised; [g]Plasma uric acid >0.34 mmol/L in children, >0.32 mmol/L women and >0.45 mmol/L in men; [h]Thyroxine, glucocorticoid, GH and/or sex hormone therapy at the time of the study. A *P*-value <0.05 was considered significant and is shown in bold.

Dyslipidemia has been found in 16–39% of childhood cancer survivors [1–3,27], being in line with our finding (37%). About a half of the patients in our study with at least one abnormal lipid value were not obese or overweight emphasizing the need of laboratory evaluation. In our study cranial irradiation, hypothalamic/hypophyseal damage and GH deficiency were risk factors for dyslipidemia. GH supplementation at the time of the study seemed to protect from dyslipidemia. Notable is that also impaired mobility was associated with hypercholesterolemia.

In our study the median serum insulin was higher among patients with GH deficiency than without GH deficiency, but hyperinsulinemia (4%) was not as common as in earlier studies including mostly patients with leukemia, prevalence ranging from 16% to 52% [1,2,27,32]. The differences in the treatment regimens might explain the differences.

Cranial irradiation was associated with elevated BP. In previous studies, elevated BP is associated with early signs of atherosclerosis also in children and young adults [33], and prehypertension during young adulthood with coronary atherosclerosis 20 years later [34]. In this study, the division of patients in subgroups of raised BP and normal BP was based on single measurement during the visit in the hospital. This is why the proportion of patients with raised BP in this study is probably higher than in longer follow-ups. On the other hand, a single BP measurement is an indicator to the way the patient reacts and should not be ignored [35].

The prevalence of metabolic syndrome according to IDF criteria in healthy Finnish males entering military service and about 19 years old in 2005 has been 6.8% [36] and in healthy Finnish 24-year-old adults 7.5% in 2001 [37]. Most of our study patients were younger, but the prevalence of metabolic syndrome was somewhat higher. In previous studies, an increased risk of metabolic syndrome among different cancer patients has been observed [1–3]. Patients with decreased GH secretion are in special risk [1,3]. Our own observations agree with these findings; patients with GH deficiency and patients with any kind of hypothalamic/hypophyseal damage, most with radiation therapy, had higher risk for metabolic syndrome and hyperuricemia. Increased levels of uric acid are associated with cardiovascular disease and metabolic syndrome [38–40], and the association between hyperuricemia and metabolic syndrome was also seen in our study. GH supplementation alleviates adverse metabolic outcomes in BT survivors. None of the GH deficiency patients with GH supplementation at the time of the study had metabolic syndrome.

The proportion of patients who did not participate in our population based study was rather large. The non-participating patients included those with most severe sequelae of the tumor or those feeling themselves as completely healthy. Thus we consider the present study group quite representative of BT survivors on average. Besides relative small sample size, the heterogeneity of our study group is a limitation that made it very difficult to use multivariate methods in our analysis. It is also noted that patients are currently treated differently than the patients in the 1980s and 1990s; for example, the radiation fields are better focused and irradiation of healthy tissue is reduced. However, our results do not allow us to say whether the present practices would lead to less adverse effects on obesity, lipid values and BP.

BT patients carry a special risk of obesity/overweight, dyslipidemia, raised BP, metabolic syndrome and hyperuricemia,

particularly if they have received radiotherapy, have hypothalamic/hypophyseal damage/GH deficiency and/or impaired mobility. These changes are significant risk factors for cardiovascular diseases and type 2 diabetes in later life. GH supplementation appears to alleviate adverse metabolic outcomes among BT survivors with GH deficiency. It might be reasonable to study the role of nutritional advice during primary treatment. Exercise should also be promoted while taking into account possible impaired mobility or other factors which might limit physical ability.

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Neurological outcome of childhood brain tumor survivors

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A short title: Neurological outcome of childhood brain tumor survivors

Key Words: brain tumor, childhood, neurological outcome, quality of life

Abbreviations: brain tumor (BT), acute lymphoblastic leukemia (ALL)

Abstract

Objective: To assess neurological and neurocognitive outcome in childhood brain tumor survivors.

Methods: Altogether 75 out of 80 brain tumor survivors diagnosed below 17 years between 1983-1997 and treated in Tampere University Hospital, Finland, were invited to participate in this population-based cross-sectional study. Fifty-two (69%) participated (mean age 14.2 (3.8-28.7) years, mean follow-up 7.5 (1.5-15.1) years).

Results: Neurological status was abnormal in 69% cases. All were ambulatory, but only 50% showed normal motor function. Twenty-nine percent showed clumsiness/mild asymmetry, 21% hemiparesis. One suffered from intractable epilepsy. According to structured interview, 87% coped normally in daily living.

Median full-scale IQ was 85 (39-110) in 21 6-16-year-olds (70%); in 29% IQ was <70. Thirty of the 44 school-aged subjects attended school with normal syllabus, 32% needed special education. Six of the 16 patients over 18 years of age were working.

Regarding quality of life, 38% were active without disability, 33% active with mild disability, 21% were partially disabled, but capable of self-care, and 8% had severe disability, being incapable of self-care. Supratentorial/hemispheric tumor location, tumor reoperations, shunt revisions and chemotherapy were associated with neurological, cognitive and social disabilities.

Conclusions: Of the 52 survivors neurological status was abnormal in 69%; 71% lived an active life with minor disabilities, 29% had major neurological, cognitive and social disabilities, 8% being incapable of self-care. Predictors of these disabilities included supratentorial/hemispheric tumor location, tumor reoperations, shunt revisions and chemotherapy. Survivors need life-long, tailor-made multiprofessional support and follow-up.

Introduction

Survival rates among childhood brain tumor (BT) patients have improved over recent decades [1]. Late effects frequently observed among BT survivors include neurological and neurocognitive deficits. These may diminish physical, cognitive and social functioning and quality of life [2-5]. The aim of the present study was to analyze neurological and neurocognitive sequelae, social competence and quality of life in childhood BT survivors.

Methods

Subjects

A total of 104 primary BT patients diagnosed below 17 years of age between 1983 -1997 were treated in Tampere University Hospital, Finland. Of the 80 survivors 75 were invited to participate in this population-based cross-sectional study in the Tampere region with a population of ~1 million. Five patients were excluded in view of the demanding study protocol. Fifty-two out of 75 potentially eligible patients (69%) participated mean 6.2 (range 1.2-14.8) years after the end of the treatment (Table 1). Distance between hospital and home was the main reason for declining in nine cases. Three patients declined to participate because they were doing well and did not want to make more visits to the hospital. The remaining non-participants (n=11) gave no specific reason. The study was approved by the Ethical Committee of Tampere University Hospital and was carried out with signed parental and/or patients' consent.

Treatment of the tumor and hydrocephalus

In addition to surgical treatment, chemotherapy and/or radiotherapy were given (Table 1). Grade III-IV tumors, five grade II tumors (ependymoma, mixed glioma, astrocytomas), grade I-II mixed

pilocytic astrocytoma, grade I pilocytic astrocytoma, and pituitary adenoma were treated by radiotherapy. Twenty-nine (56%) were treated by surgery only. Fifty-eight percent had hydrocephalus; all except one had been shunted (Table 1). Shunt dysfunction was the primary reason for revision, only three patients experienced shunt infections. The longest time a patient had symptoms of fluctuating intracranial pressure before shunt revision was about one year.

Of the 17 children who received chemotherapy 10 were on an ”eight drugs in one day” protocol, and eight received chemotherapy according to other protocols. One of these eight patients also received ”8 in 1” chemotherapy, and one received chemotherapy according to two other different protocols. In the “8 in 1” protocol seven cytostatic drugs (CCNU, vincristine, hydroxyurea, procarbazine, cisplatin, ARA-C, and either dacarbazine or cyclophospamide) and methylprednisolone were administered [6]. Other combinations were bleomycin and CCNU (one patient), vincristine and CCNU plus prednisolone or dexametasone (two patients), bleomycin and VP-16 plus cisplatin (one patient), bleomycin, vinblastine and VM-26 plus cisplatin (one patient), vincristine, VP-16 and cyclophosphamide plus cisplatin (two patients) followed by maintenance with vincristine, VP-16 and karboplatin (and cyclophosphamide). In progressive disease two patients received oral VP-16 treatment [7]. All patients received pharmacological doses of glucocorticosteroids in the treatment connected to tumor surgery, during radiotherapy and/or as part of the chemotherapy.

Procedure and materials

Patients’ medical records were checked for clinical history (SP). Most of the histological samples were reanalyzed (HH), and the tumors were classified according to the current WHO classification (Table 2) [8].

The patients were interviewed and examined by the same physician (SP) using a structured interview. Estimation of the activities of daily living included basic tasks of everyday life as adjusted for age; eating, dressing, bathing, toileting, transferring, and taking care of medication. School achievement was evaluated. In Finland children usually start school at the age of seven or the year they turn seven.

Motor disability was divided into four categories: 1. normal motor function, 2. clumsiness/mild asymmetry (including difficulties in balance, running, jumping, diadochokinesia or in coordination tests), 3. hemiparesis, 4. severe hemi- or tetraparesis (inability to walk or eat without help).

Quality of life was assessed by using four categories based on *Bloom's* categories I-IV [9,10]: group I: active life, no disability; group II: active life, mild disability (including learning disabilities involving schooling with special services within the normal school system, clumsiness, mild asymmetry, mild hemiparesis,); group III: partial disability, capable of self-care if old enough (including clear evidence of intellectual impairment, severe learning disabilities necessitating schooling for the mentally subnormal, hemiparesis, seriously reduced vision < 0.5); group IV: severe disability, incapable of self-care (including mental retardation necessitating schooling for the mentally retarded, intractable epilepsy, severe hemi- or tetraparesis). The information from the structured interview (estimation of the activities of daily living, independence of the childhood family, education, working, participation in regular recreational activities) was used to support our classification as part of the information required in the International Classification of Functioning, Disability and Health (ICF) [11].

Cognitive abilities were tested using a Finnish version of the Wechsler Scale for Children - Revised, WISC-R [12]. Tests were made (by RA) on patients aged from 6 to 16 years.

Statistical analysis

Associations between selected explanatory variables (gender, diagnosis below the age of three years, tumor type (pilocytic astrocytoma vs. ependymal or embryonal tumor vs. other tumors), tumor grade (grade I-II vs. higher degree of malignancy), tumor location, severe perioperative complications, treatment comprising only operation compared to more demanding treatment including operation and radiotherapy and/or chemotherapy, occurrence of residual tumor upon evaluation, tumor reoperations, cranial irradiation, chemotherapy, hydrocephalus and shunt revisions) and outcome variables (motor function, full-scale IQ, verbal IQ, performance IQ, school achievement, activities of daily living and quality of life) were evaluated.

Mann-Whitney U-test or Kruskal-Wallis test was used for continuous data with skewed distributions or ordinal variables. Categorized data were analyzed using Fisher's exact test, χ^2 test or exact χ^2 test as appropriate. A p value less than 0.05 was considered significant, but because of the small sample size also p values between 0.05 and 0.1 are reported as being of borderline significance. All statistical analyses were performed using the SPSS for Windows version 10.0, 16.0, 17.0 and 18.0.

Results

Patients

Four of the participants (ages during the study 6.6-13.1 years) were younger than one year at diagnosis (Table 1). Three of them showed abnormal neurological status at evaluation, two clumsiness, and three speech/language difficulties. All had some focal problems such as visuospatial difficulties. Regarding quality of life, one was classified in group I, two in group II, and one in group IV.

Neurological findings

All participants were ambulatory at evaluation, but only 50% showed normal motor function (Table 3). Of the selected explanatory variables only shunt revisions were statistically significantly associated with motor disability (Table 4). The association with tumor reoperations and motor disability was of borderline significance (Table 4). Neurological status was abnormal in 36 cases (69%). Cranial nerve dysfunctions were fairly common (Table 3). The speech of seven was dysarthric.

Psychological tests

Twenty-one (70%) of the 30 participants between 6-16 years of age were willing to participate in psychological tests (WISC-R), where median full-scale IQ was 85 (39-110); in 29% IQ was <70 (Table 3).

Tumor reoperations were statistically significantly associated with lower full-scale IQ, verbal IQ, and performance IQ, and chemotherapy with lower performance IQ (Table 5). The association between hemispheric tumor location and lower performance IQ was of borderline significance (Table 5).

Rehabilitation services

Overall, 63% had needed some sort of therapy such as physio-, speech, occupational, hippo-, music, art, psychotherapy or neuropsychologic rehabilitation. At the time of the study 21% were receiving some therapy.

School achievement

Thirty of the 44 school-aged subjects attended mainstream school with normal syllabus and 32% needed special educational services (Table 3). In six cases the beginning of school was delayed.

Shunt revisions were statistically significantly associated with poorer school achievement and the association between chemotherapy and poorer school achievement was of borderline significance (Table 4).

Participants who needed special educational services had lower full-scale, verbal and performance IQ. Median full-scale IQ for participants who attended school with normal syllabus (n=11) and who needed special services within the normal school system (n=4) and in a special school system for the mentally subnormal (n=3) and mentally retarded (n=2) were 94 (range 75-110) vs 84 (68-92) vs 50 (47-62) vs 42 (39-44), p=0.003. Also in verbal and performance IQ there were statistically significant differencies between the groups (verbal IQ: 94 (72-112) vs 85 (72-88) vs 52 (49-69) vs 43 (41-45), p=0.007; performance IQ: 98 (77-118) vs 86 (68-100) vs 57 (54-60) vs 55 (54-56), p=0.007).

Nineteen participants had gone through basic schooling. Thirteen of them had studied in vocational school, but two of them had dropped out. Six had studied in upper secondary school. At the time of the study three of them had graduated: one had studied in vocational school and one in open university, and one had graduated from university. Six of the 16 patients over 18 years of age were working. Five of them had an occupation. One was working without vocational education.

Activities of daily living and quality of life

According to structured interview 45 (87%) coped normally in daily living (Table 3). Full-scale IQ, verbal IQ and performance IQ were statistically significantly lower among participants who needed

supervision or support (n=5) compared to those who coped normally (n=16) (full scale IQ: median 47 (range 39-85) vs 93 (62-110), p=0.004; verbal IQ: median 49 (41-86) vs 87 (69-112), p=0.006; performance IQ: median 56 (54-87) vs 92 (60-118), p=0.005). Six had a personal assistant. Two of the 16 patients over 18 years of age lived alone, four with a partner, and one had a child. Thirty-one of the total 52 pursued regular recreational activities outside home.

The association between tumor reoperations and the need of supervision or support in daily activities was of borderline significance (Table 4).

In respect of quality of life, 38% of the participants were in group I, 33% in group II, 21% in group III, and 8% in group IV (Table 3); 71% lived an active life and had only minor disabilities and 29% suffered major neurological, cognitive and social disabilities.

Tumor reoperations, shunt revisions and tumor location were statistically significantly associated with lower quality of life (Table 4). Patients with a hemispheric or other supratentorial tumor had poorer outcome (Table 4).

Discussion

Our assessment of the neurological findings and outcome in 52 childhood BT survivors showed that the majority (71%) lived an active life and had only minor disabilities although 50% had neurological motor disabilities, and the neurological status was abnormal in 69%. Twenty-nine percent had major neurological, cognitive and social disabilities, but only 8% were incapable of self-care. Hemispheric or other supratentorial tumor location, tumor reoperations, shunt revisions and chemotherapy were associated with these problems.

In a previous study of late sequelae in 56 childhood BT survivors with a wide range of tumors 25% had significant motor, 38% intellectual, 20% visual, 14% psycho-emotional dysfunctions, and moderate or severe disability was found in 34% [2]. In a study with 31 malignant childhood BT survivors, 26% had hemi- or tetraplegia, and major disabilities were found in 47% [10]. In a study involving adult survivors of childhood BT coordination problems were reported in 49% and motor control problems in 26% [13]. In our study only 50% showed normal motor function, but all were able to walk. Proportion of major disabilities (29%) was slightly less than in the study from 1990 [2], but significantly less than in the study with malignant childhood BT survivors [10]. In our study associated complications such as need for shunt revisions and tumor reoperations were associated with motor disability. Among participants who had needed shunt revisions, clumsiness and mild asymmetry were emphasized, and among those who had needed tumor reoperations the proportion of hemiparesis was emphasized.

Thirty-two percent of our school-aged participants needed special educational services - about the same proportion (30%) found in childhood malignant BT survivors [10]. In a study of scholastic achievements of children with BTs at the end of comprehensive education, patients fared poorer than controls in each subject, and the difference was most pronounced among girls. Grades in foreign languages (representing verbal performance) were most affected [14]. We found no difference between genders in school achievement or psychological tests. However, six out of nineteen (32%) who had completed basic schooling had studied in upper secondary school, which is less than usual in Finland, where more than half go on to upper secondary school. Median verbal IQ and performance IQ were about the same level as median full-scale IQ and all were lower than the expected medians in the general population. These findings raised the question whether these children had received sufficient individual care and support.

Young age at the time of radiation and/or chemotherapy has consistently proved a major risk factor for cognitive decline in children treated for BTs in earlier studies [15,16], but young children with BTs might also have cognitive deficits prior to receiving either radiation or chemotherapy [17], and young age at diagnosis has as such been a significant predictor of lower cognitive function [18]. In our study diagnosis below the age of three years showed no associations with neurological, cognitive and social disabilities, which suggests that the risk factors are multifactorial.

Hemispheric tumor location has been associated with lower cognitive functions [18,19]. The limitation in our study was that psychological tests were carried out on only part of the study group and in this group aged from 6 to 16 years performance IQ was somewhat lower in patients who had hemispheric tumor, but the association was of only borderline significance. Hemispheric or other supratentorial tumor location was associated with major neurological, cognitive and social disabilities in the evaluation of quality of life. Outcome was not related to a specific tumor type.

When we compared the outcome of participants who had undergone only surgery, to those whose treatment included operation and radiotherapy and/or chemotherapy, the former managed no better. The participants who had needed tumor reoperations had poorer outcome; their quality of life, full-scale IQ, verbal IQ and performance IQ were significantly lower compared to those who had not needed tumor reoperations. The number of patients with residual tumor upon evaluation was high, 25%, but the occurrence of residual tumor was not associated with poorer outcome.

The role of hydrocephalus in the development of cognitive difficulties in children treated for BTs is unclear. There have been reports of absence of association between hydrocephalus and cognitive function [16,20], but it has also been found to be a significant risk factor for impaired intellectual outcome in children treated for BTs [18]. In a study of children with infratentorial ependymomas,

treatment of hydrocephalus with shunt improved cognition [21]. In a study of 187 intracranial tumor patients (10% children) who underwent ventriculoperitoneal shunt placement, 52 (28%) experienced one or more shunt failures requiring shunt revision(s) after the median follow-up time of 391 days, and younger patients had a higher risk for shunt failure [22]. In our study of the 29 participants with shunted hydrocephalus, 17 (59%) required one or more shunt revisions: 34% had multiple shunt revisions. The incidence of shunt revision was high. This might be due to longer follow-up time and younger age of our patients. Other studies have also reported a high rate of shunt failures in pediatric patients [23-25]. In our study participants with treated hydrocephalus did not have worse outcome than participants without hydrocephalus, but shunt revisions were significantly associated with outcome. Shunt dysfunctions which needed shunt revision had a clear negative impact on motor function, school achievement and quality of life. It could be speculated that recurrent, possibly long periods of variation in intracranial pressure could worsen the outcome.

Cranial irradiation is known to be harmful to cognitive functions [2-5, 9,10,13-20], but we found no statistically significant association between cranial irradiation and neurological, cognitive and social disabilities and quality of life, which suggests the multifactorial role of the risk factors.

It is challenging to estimate the influence of chemotherapy on cognition in patients with BTs as there are many different treatment protocols. In addition to the tumor itself, tumor operation, radiotherapy and hydrocephalus render estimation even more complicated. There is evidence of subtle long-term neurocognitive deficits in survivors of childhood acute lymphoblastic leukemia (ALL) after treatment with chemotherapy only. These involve mainly processes of attention and of executive functioning [26,27]. Our results are in line with these earlier findings in ALL survivors. In our study performance IQ was lower in participants who had received chemotherapy. Chemotherapy also increased the risk of difficulties in school achievement.

Childhood BT survivors are at risk of neurological, cognitive and social problems extending into adulthood. However, most here lived an active life with age appropriate social activities and participation. All childhood BT survivors need life-long, tailor-made multiprofessional support and follow-up, which may be challenging for medical and social services especially if the sufferer has cognitive problems. The possibility to reduce late neurological and neurocognitive deficits is essential to consider in the development of treatment protocols.

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Table 1. Clinical data on the 52 brain tumor patients diagnosed below 17 years of age.

Median age at diagnosis, years	6.0 (0.1-15.5)
< 7 years	30 (58)
< 1 years	4 (8)
< 3 years	14 (27)
7-12 years	14 (27)
≥ 13 years	8 (15)
Mean follow-up time, years	7.5 (1.5-15.1)
Mean time after treatment, years	6.2 (1.2-14.8)
Mean age at evaluation, years	14.2 (3.8-28.7)
< 7 years	8 (15)
7-12 years	13 (25)
13-17 years	15 (29)
≥ 18 years	16 (31)
Sex, male/female	27/25
Neurofibromatosis	3 (6)
Site of the tumor	
Infratentorial	25 (48)
Brain stem	5 (10)
Supratentorial	27 (52)
Cerebral hemisphere	13 (25)
Resection/biopsy	51/1 (98/2)
Grossly total	30 (58)
Partial	21 (40)
Reoperation/biopsy	17/1 (33/2)
One	11/1 (21/2)
Two	6 (12)
Severe perioperative complications[a]	15 (29)
Chemotherapy	17 (33)
Radiotherapy	20 (38)
Median age at a start of radiotherapy, years	7.2 (0.2-20.9)
Cranial	12 (23)
local	9 (17)
cranial only	3 (6)
Craniospinal	8 (15)
Median tumor dose, Gy	50.5 (16.0-60.0)
Both chemotherapy and radiotherapy	14 (27)
Residive or residual tumor at evaluation	13 (25)
Hydrocephalus	30 (58)
Shunted hydrocephalus	29 (56)
Shunt revisions	17 (33)
One	7 (14)
Two	6 (12)
Three	2 (4)
More than five	2 (4)
Some kind of shunt at evaluation	27 (52)

Categoric data shown as number of patients (%) and continuous data as mean or median (range).
[a]Need of multiple operations, shunt revisions, meningitis, ventriculitis with ventriculostomy, expanding intracranial effusions or cysts, prolonged impaired consciousness, intractable seizures and neurological deficits.

Table 2. WHO classification of the 52 childhood brain tumors.

	Grade	n (%)
Astrocytic tumors		25 (48)
Pilocytic astrocytoma	I	20 (38)
Mixed pilocytic astrocytoma	I-II	2 (4)
Diffuse astrocytoma	II	2 (4)
Pleomorphic xanthoastrocytoma	II	1 (2)
Oligodendroglial tumors		1 (2)
Oligodendroglioma	II	1 (2)
Mixed gliomas		4 (8)
Oligoastrocytoma	II	2 (4)
Other mixed glioma	II	1 (2)
Anaplastic mixed glioma	III	1 (2)
Ependymal tumors		5 (10)
Ependymoma	II	2 (4)
Ependymoma	II-III	1 (2)
Anaplastic ependymoma	III	2 (4)
Choroid plexus tumors		2 (4)
Choroid plexus papilloma	I	1 (2)
Choroid plexus carcinoma	III	1 (2)
Neuronal and mixed neuronal-glial tumors		2 (4)
Desmoplastic infantile ganglioglioma	I	1 (2)
Ganglioglioma	II	1 (2)
Embryonal tumors		4 (8)
Medulloblastoma	IV	2 (4)
PNET[a]	IV	2 (4)
Germ cell tumors[b]		4 (8)
Germinoma		3 (6)
Mixed germ cell tumor (teratogerminoma)		1 (2)
Meningeal tumors		1 (2)
Meningioma	I	1 (2)
Tumors of the sellar region		3 (6)
Craniopharyngioma	I	2 (4)
Pituitary adenoma[c]		1 (2)
Tumor-like lesion (hamartoma)		1 (2)

[a]Supratentorial primitive neuroectodermal tumor.

[b]Grading is not presented in the current WHO classification. In statistical analysis corresponding to grade IV tumor.

[c]Grading is not presented in the current WHO classification. In statistical analysis corresponding to grade I tumor.

Table 3. Neurological and neurocognitive outcome of the 52 brain tumor patients diagnosed below 17 years of age.

Motor function	
Normal	26 (50)
Clumsiness/mild asymmetry	15 (29)
Hemiparesis[a]	11 (21)
Severe hemi- or tetraparesis	0 (0)
Changed handedness	7 (13)
Facial paresis	6 (12)
Impaired vision <0.5	9 (17)
Visual field defect (n=51)[b]	
Yes	7 (14)
Uncertain or cannot be evaluated	4 (8)
Strabismus (n=51)[b]	13 (25)
Hearing loss	9 (17)
Hearing aid	2 (4)
Speech/language difficulties	10 (19)
Cognitive function in 6-16 years old participants (n=21)	
Median full-scale IQ	85 (39-110)
IQ below 70	6 (29)
IQ 70-85	5 (24)
IQ over 85	10 (48)
Median verbal IQ	86 (41-112)
Median performance IQ	87 (54-118)
Antiepileptic medication	7 (13)
Monthly epileptic seizures	4 (8)
Intractable epileptic seizures	1 (2)
School achievement (n=44)	
School with normal syllabus	30 (68)
School with special services	14 (32)
within the normal school system	7 (16)
in a special school system	7 (16)
for mentally subnormal	5 (11)
for mentally retarded	2 (5)
Activities of daily living	
Normal	45 (87)
Need of supervision	1 (2)
Need help	6 (12)
Quality of life[c]	
Group I	20 (38)
Group II	17 (33)
Group III	11 (21)
Group IV	4 (8)

Categoric data shown as number of patients (%) and continuous data as mean or median (range).

[a]In one case hemiparesis had developed after multiple sclerosis.

[b]One participant was blind.

[c]Quality of life was evaluated using four categories: group I: no disability; active life, group II: mild disability, active life; group III: partial disability, capable of self-care if old enough; group IV: severe disability, incapable of self-care.

Table 4. Motor function, school achievement, activities of daily living and quality of life of the 52 childhood brain tumor survivors. Only statistically significant[a] or borderline significant[b] explanatory variables are reported.

Explanatory variable	Outcome variable				
	Motor function (%)				
Shunt revisions	Normal	Clumsiness	Hemiparesis	p	
Yes	35	53	12	**0.032**	
No	57	17	26		
Tumor reoperations					
Yes	39	22	39	**0.075**	
No	56	32	12		
	School achievement[c] (%)				
Shunt revisions	Normal	Special1	Special2	Special3	p
Yes	42	25	33	0	**0.013**
No	78	13	3	6	
Chemotherapy					
Yes	50	14	21	14	**0.063**
No	77	17	7	0	
	Activities of daily living (%)				
Tumor reoperations	Normal	Supervision	Help	p	
Yes	72	6	22	**0.099**	
No	94	0	6		
	Quality of life[d] (%)				
Tumor reoperations	Group I	Group II	Group III	Group IV	p
Yes	17	44	17	22	**0.004**
No	50	27	24	0	
Shunt revisions					
Yes	12	59	24	6	**0.016**
No	51	20	20	9	
Tumor location					
Supratentorial	33	22	33	11	**0.070**
Infratentorial	44	44	8	4	
Precise tumor location					
Hemispheric	39	23	15	23	**0.018**
Other supratentorial	29	21	50	0	
Brain stem	20	80	0	0	
Other infratentorial	50	35	10	5	

[a] $p < 0.05$

[b] $0.05 \leq p \leq 0.1$

[c] School achievement: normal (normal syllabus), special1 (special services within the normal school system), special2 (special services in a special school system for mentally subnormal), special3 (special services in a special school system for mentally retarded).

[d] Group I: active life, no disability; group II: active life, mild disability; group III: partial disability, capable of self-care if old enough; group IV: severe disability, incapable of self-care.

Table 5. Psychological test results (WISC-R) of the 21 6-16-year-old childhood brain tumor survivors. Only statistically significant[a] or borderline significant[b] explanatory variables are reported.

Explanatory variable	Outcome variable	
	median (min-max)	p
Tumor reoperations	Full scale IQ	
Yes	69 (39-96)	**0.012**
No	94 (68-110)	
Tumor reoperations	Verbal IQ	
Yes	71 (41-101)	**0.041**
No	86 (72-112)	
Tumor reoperations	Performance IQ	
Yes	71 (54-100)	**0.014**
No	98 (68-118)	
Chemotherapy	Performance IQ	
Yes	68 (54-92)	**0.020**
No	93 (57-118)	
Tumor location	Performance IQ	
Hemispheric	57 (54-115)	**0.082**
Other locations	90 (56-118)	

[a] $p < 0.05$

[b] $0.05 \leq p \leq 0.1$