SATU-LIISA PAUNIAHO

Germ Cell Tumors

Biology, Clinical Presentation and Epidemiology

ACADEMIC DISSERTATION
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To Lauri, Tuomas and Iris.

Abstract

Germ cell tumors (GCTs) are a heterogeneous group of malignant and non-malignant neoplasms putatively originating from the same precursor, the primordial germ cell. Malignant GCTs are rare, comprising only 0.7% of all cancers. However, among individuals aged less than 30 years the proportion of GCTs among all malignancies is 11%. Furthermore, malignant testicular GCTs are the most frequent malignancies in Caucasian men aged 20 to 40 years. This incidence has increased in industrialized countries during recent decades, the reason for this remaining largely unclear. However, several risk factors, including environmental, have been proposed. The molecular basis of GCTs is undefined.

The most common of all neonatal tumors, sacrococcygeal teratoma (SCT), is a typical and most often benign GCT. Sacrococcygeal teratomas can be classified by location, histology and composition of the tumor. The tumor is usually detected during antenatal ultrasound examinations, and solidity and high vasculature as well as rapid growth are regarded as predictors of a poor outcome. Surviving children who undergo prompt surgery after birth have an excellent prognosis. However, a proportion of SCTs have a tendency to recur, at least 50% of the recurrences being malignant. Thus, and in order to detect possible long-term functional problems related to the tumor and the surgery, these children are followed up for several years after the initial surgical treatment.

This thesis comprises four publications. Study I was based on a prospective scheme of serial serum tumor marker evaluations. All children with SCT diagnosed and treated at Helsinki University Hospital between 1985 and 2006 (n=33) were included in the study, and made regular follow-up visits. The focus of attention was the possible relationship between abnormal sample values and cases with recurrences. This study showed that the role of multiple markers in the follow-up of SCT is limited. In addition to the viability of alpha-fetoprotein (AFP) as a marker in detecting malignant recurrences, we found that elevated serum CA 125 may indicate non-malignant recurrences, and thus recommend monitoring of these two tumor markers at follow-up visits. The second study (II) was based on the national Finnish Cancer Registry data,

and assessed the incidence, histological distribution and locations of malignant GCTs in both sexes. The study included essentially all malignant GCTs encountered in Finland in 1969-2008 (over 3000 cases). The main findings in study II were that there are significant differences in both the GCT incidences and distribution of morphologies and locations between men and women. The incidence of gonadal GCTs in Finland is increasing in men between 15-44 years of age whereas no such changes are seen in figures for women. The risk factors for GCTs are thus likely to differ between the two sexes. Study III was again register-based, and evaluated the prevalence of SCT in Finland, along with the effects of SCT on pregnancy outcome. All SCT cases, including live births, stillbirths and terminations of pregnancy on fetal indications were identified in the Finnish Register of Congenital Malformations, along with data on associated abnormalities. The Medical Birth Register and the Finnish Cancer Registry were used as additional data sources. This study revealed the birth prevalence of SCT in Finland to lie at 1:15 000, markedly higher than previously reported in other countries. Associated abnormalities were found in a third of cases, and 28% (excluding terminations) were stillborn or succumbed perinatally. Finally, the fourth study (IV) comprised an epidemiological analysis of GCTs in the pediatric and adolescent population (0-19 years of age) in Finland in 1969-2008. Data on 334 malignant GCTs obtained from the Finnish Cancer Registry were analyzed, focusing on histology, location and stage of the tumor at diagnosis. Additionally, the 5-year survival rates were calculated for the two consecutive study periods. The study revealed the proportion of malignant GCTs of all malignancies among children and adolescents to be increasing, mainly due to the increase in testicular GCTs in adolescents. However, the limited number of cases in children, especially girls, made analysis of incidence trends difficult.

In conclusion, this study comprises a comprehensive analysis of pediatric and adult germ cell tumors. Epidemiological register studies are only feasible in countries with reliable national registering, and our data thus add to the limited population-based literature on these tumors. As these GCTs in children are very rare, extension of the study population to e.g. the Nordic scale would enhance detection of even minute incidence trends and insights to biological background of these tumors.

Tiivistelmä

Itusolukasvaimet ovat harvinainen ja monimuotoinen ryhmä hyvän- ja pahanlaatuisia kasvaimia, joiden katsotaan saavan alkunsa ns. alkuitusolusta. Vaikka koko väestössä pahanlaatuiset itusolukasvaimet ovat harvinaisia (vain n. 0.7 % kaikista syövistä), alle 30-vuotiaiden syövistä jo 11 % on itusolusyöpiä. Lisäksi pahanlaatuiset kiveksen itusolukasvaimet ovat 20–40-vuotiaden, etnisesti kaukasialaisten miesten syövistä yleisimpiä. Niiden ilmaantuvuus teollisuusmaissa on kasvanut, ja syy ilmaantuvuuden kasvuun on suurelta osin epäselvä. Useita, mm. ympäristöön liittyviä riskitekijöitä on kuitenkin esitetty yleistymisen syyksi. Itusolukasvainten molekulaarinen perusta on avoin.

Vastasyntyneiden tavallisin kasvain, ns. sakrokokkygeaalinen teratooma (sacrococcygeal teratoma, SCT), on tyypillinen ja useimmiten hyvänlaatuinen itusolukasvain. SCT voidaan jaotella kasvaimen sijainnin, histologian ja koostumuksen mukaan. Kasvain todetaan nykyisin yleensä jo raskaudenaikaisissa ultraäänitutkimuksissa. Raskauden ja sikiön kannalta huonoja ennustetekijöitä ovat mm. kasvainkudoksen kiinteys ja runsas verisuonitus sekä kasvaimen nopea kasvu. Elävänä syntyneillä lapsilla, jotka leikataan pian syntymän jälkeen, on erinomainen ennuste. Osalla kasvaimista on kuitenkin taipumus uusiutua, ja vähintään 50 % uusiutumisista on pahanlaatuisia. Tästä syystä sekä mahdollisten tuumoriin ja leikkaukseen liittyvien toiminnallisten pitkäaikaisongelmien löytämiseksi potilaita seurataan kliinisesti useiden vuosien ajan.

Väitöskirjatyö koostui neljästä itsenäisestä osasta. Ensimmäinen osatyö (I) perustui prospektiiviseen tuumorimarkkeri-seurantatutkimukseen. Kaikki Helsingin Lasten ja Nuorten Sairaalassa vuosina 1986–2008 todetut ja hoidetut SCT-potilaat (n=33) otettiin mukaan tutkimukseen, ja he kävivät säännöllisesti seurannassa Lastenklinikalla. Keskityimme erityisesti poikkeavien verikoearvojen ja kasvaimen uusiutumisen mahdolliseen yhteyteen. Alfa-fetoproteiinin (AFP) on jo aiemmin todettu ennustavan pahanlaatuisia uusiutumisia. Ensimmäisen osatyön tulokset osoittivat lisäksi, että koholla oleva seerumin CA 125 saattaa ennustaa hyvänlaatuisia uusiutumisia. Näin ollen suosittelemme näiden kahden tuumorimarkkereiden käyttöä seurannassa.

Toinen osatyö (II) perustui Suomen Syöpärekisterin tietoihin, ja siinä määritettiin pahanlaatuisten itusolukasvainten ilmaantuvuus (insidenssi), histologinen jakautuminen ja sijainnit miehillä ja naisilla. Tutkimukseen otettiin mukaan kaikki Suomessa vuosina 1969–2008 todetut itusolusyövät (yli 3000 tapausta). Tämän osatyön tärkeimmät löydökset olivat, että sekä itusolukasvainten ilmaantuvuudessa että histologisessa ja sijainnin jakautumisessa on eroja miesten ja naisten välillä. Kiveksissä ja munasarjoissa esiintyvien itusolukasvainten ilmaantuvuus 15–44-vuotiailla miehillä on nousussa, kun taas naisilla vastaavaa nousua ei todettu. Näin ollen itusolukasvainten riskitekijät ovat todennäköisesti erilaisia miehillä ja naisilla. Osatyö III oli jälleen rekistereihin perustuva, ja siinä selvitettiin SCT:n vallitsevuus (prevalenssi) Suomessa, ja lisäksi SCT:n vaikutukset raskauden kulkuun. Tutkimus sisälsi kaikki SCT-tapaukset, mukaan lukien elävänä ja kuolleena syntyneet sekä sikiöindikaatiolla tehdyt raskauden keskeytykset. Tapaukset haettiin THL:n Epämuodostumarekisteristä, josta saatiin myös tietoa tapausten muista anomalioista. Lisätietoja haettiin myös THL:n Syntymärekisteristä sekä Suomen Syöpärekisteristä. Tämä osatyö osoitti, että SCT:n syntymähetken vallitsevuus (birth prevalence) Suomessa on n. 1:15 000, mikä on huomattavasti enemmän kuin aiemmin on raportoitu muista maista. Liitännäispoikkeavuuksia todettiin kolmasosalla tapauksista, ja 28 % tapauksista (pois lukien keskeytykset) joko syntyi kuolleena tai menehtyi vastasyntyneisyyskaudella. Neljäs osatyö (IV) oli epidemiologinen analyysi itusolukasvaimista lapsilla ja nuorilla (0-19-vuotiaat) Suomessa vuosina 1969–2008. Analysoimme yhteensä 334 pahanlaatuisen itusolukasvaimen Syöpärekisteritiedot, ja keskityimme tuumorin histologiaan, sijaintiin ja levinneisyysasteeseen diagnoosihetkellä. Laskimme lisäksi eloonjäämisluvut kahdelle peräkkäiselle ajanjaksolle. Tämä osatyö osoitti, että itusolukasvainten osuus kaikista lasten ja nuorten pahanlaatuisista kasvaimista on noussut, pääasiassa teini-ikäisten kiveskasvainten osalta. Ilmaantuvuuden muutosten analysointi oli kuitenkin haasteellista, sillä lapsilla ja erityisesti tytöillä näitä kasvaimia esiintyy hyvin vähän.

Loppupäätelmänä voidaan todeta, että tämä tutkimus muodostaa kattavan analyysin lasten ja aikuisten itusolukasvaimista. Epidemiologisia rekisteritutkimuksia on mahdollista toteuttaa vain sellaisissa maissa, joissa on luotettava kansallinen rekisterijärjestelmä. Tästä syystä tutkimuksemme on merkittävä lisä aiempiin itusolukasvaimia käsitteleviä väestöpohjaisiin tutkimuksiin. Koska itusolukasvaimet ovat hyvin harvinaisia lapsilla, tutkimuksen laajentaminen esim. yhteispohjoismaiseksi voisi helpottaa jopa pienten ilmaantuvuuden muutoksien toteamista ja näiden tuumoreiden biologisen taustan ymmärtämistä.

Contents

List of original communications

The present thesis is based on the following original publications, referred to in the text by the Roman numerals I-IV:

I. Pauniaho SL, Tatti O, Lahdenne P, Lindahl H, Pakarinen M, Rintala R, Heikinheimo M: Tumor markers AFP, CA 125, and CA 19-9 in the long-term follow-up of sacrococcygeal teratomas in infancy and childhood. Tumour Biol. 2010 Aug; 31(4):261-265.

II. Pauniaho S-L, Salonen J, Helminen M, Vettenranta K, Heikinheimo M and Heikinheimo O: The incidence of malignant germ cell tumours is different in men and women – a population-based study covering over 40 years in Finland. Cancer Causes Control. 2012 Dec; 23(12):1921-1927

III. Pauniaho S-L, Heikinheimo O, Vettenranta K, Stefanovic V, Ritvanen A, Rintala R, Heikinheimo M: Sacrococcygeal teratoma in Finland: High prevalence and hidden mortality- A nationwide population-based study. Acta Paediatr. 2013 Jun; 102(6):251-256

IV. Pauniaho S-L, Salonen J, Helminen M, Heikinheimo O, Vettenranta K, Heikinheimo M: Germ cell tumors in children and adolescents in Finland – trends over 1969-2008. Submitted.

Abbreviations

AFP	alpha-fetoprotein
CA 125	carbohydrate antigen 125
CA 19-9	carbohydrate antigen 19-9
CEA	carcinoembryonic antigen
CI	confidence interval
CIS	carcinoma in situ
CNS	central nervous system
CS	Currarino syndrome
DIC	disseminated intravascular coagulopathy
EG	extragonadal
FRCM	Finnish Register of Congenital Malformations
GCT	germ cell tumor
hCG	human chorionic gonadotropin
HE4	human epididymis protein 4
ICD	international classification of diseases
ICD-O-3	international classification of diseases for oncology, 3rd edition
IT	immature teratoma
LB	live birth
LD	lactate dehydrogenase
MoM	multiple of median
MRI	magnetic resonance imaging
MT	mature teratoma
OEIS	Omphalocele, cloacal Extrophy, Imperforate anus, Spinal defects
PGC	primordial germ cell
PSA	prostate-specific antigen
SCT	Sacrococcygeal teratoma
TDS	testicular dysgenesis syndrome
TFR	tumor volume to fetal weight ratio

TGCT	testicular germ cell tumor
TOP	termination of pregnancy
US	ultrasound
WHO	World Health Organization
YST	yolk sac tumor

Introduction

Germ cell tumors (GCTs) constitute a diverse group of both malignant and non-malignant neoplasms, putatively sharing a common origin, the primordial germ cell (PGC) (Bussey et al. 2001, Schneider et al. 2001). GCTs can be benign or malignant, and they occur in both gonadal (testis and ovary) and extragonadal locations. Over 90% of all malignant GCTs occur in industrialized countries in the testis (Arora et al. 2012). The incidence of malignant testicular GCTs (TGCTs) has increased during the last few decades, the reason for this remaining unclear (Huyghe et al. 2003, McGlynn et al. 2003, Schmiedel et al. 2010).

GCTs are the most common neoplastic tumor type in the newborn period (Frazier et al. 2012). Most of these tumors are sacrococcygeal teratomas (SCTs), and only 5% of these contain malignant components (Frazier et al. 2012). The reported incidence of SCT is 1: 35,000 – 1: 40,000 (Pantoja, Lopez 1978). Histologically SCTs can be mature, immature or malignant. As a proportion (5-10%) of SCTs have a tendency to recur (De Corti et al. 2012), children are followed up after initial surgery carried out in most cases in the first days of life. Up to 50% of recurrences are malignant (De Corti et al. 2012).

This study focused firstly on the epidemiology and incidence of malignant GCTs in general and secondly, on the characterization of the biology, clinical features, epidemiology and associated anomalies in SCTs.

Review of the literature

1 Origin and classification of germ cell tumors

Germ cells are cells which are destined to become gametes, the spermatozoon (the sperm cell) or the ovum (the egg cell). The gametes derive from primordial germ cells (PGCs), which are "the stem cells of species". This means that they are the only cells in the body possessing the ability to form and generate an entire new organism (Wylie 1999). This property is called pluripotency or totipotency.

PGCs can be recognized in the wall of the yolk sac of the developing embryo at 5-6 weeks of human development (Wylie 1999). At 28 to 36 days, the PGCs begin to proliferate as they migrate out of the yolk sac, along the midline of the body and into to the genital ridge on the posterior abdominal wall of the embryo (McMurray 2010, Frazier et al. 2012). At this point they are referred to as gonocytes (Oosterhuis, Looijenga 2005).

Failure of proper migration of PGCs or failure of apoptosis of these ectopically located cells can result in various types of malignant and non-malignant GCTs along the migratory route of the PGCs, the midline of the body (Oosterhuis, Looijenga 2005, Oosterhuis et al. 2007). Typical extragonadal locations for GCTs are the sacrococcygeal and retroperitoneal regions; the head and neck and the pineal and hypothalamic-hypophyseal region of the brain (Oosterhuis, Looijenga 2005).

The PGCs are thought to be the precursor cells in most GCT types. A more complex differentiation pattern has also been suggested in the development of testicular GCTs (TGCTs), based on a division into seminomas and non-seminomas (Oosterhuis, Looijenga 2005). Seminomas have been found to resemble PGCs, and non-seminomas are either differentiated or undifferentiated (with a degree of embryonic (teratomas) or extraembryonic (yolk sac tumors, choriocarcinomas) origin) (Oosterhuis, Looijenga 2005).

A classification of GCTs into groups according to location, and a schematic representation of their assumed origins are shown in Figure 1. Again, the locations and cell of origin of the above-mentioned GCT types, as proposed by Oosterhuis and Looijenga (2005), are shown in Table 1. In this classification, spermatocytic seminoma (an exclusively testicular tumor found predominantly in patients older than 50 years) is referred to as a Type III GCT. Additionally, the authors classify

dermoid cysts as Type IV and mola hydatidosa as Type V GCT (Table 1), both of these having a differentiation pattern dissimilar to tumors historically regarded as GCTs.

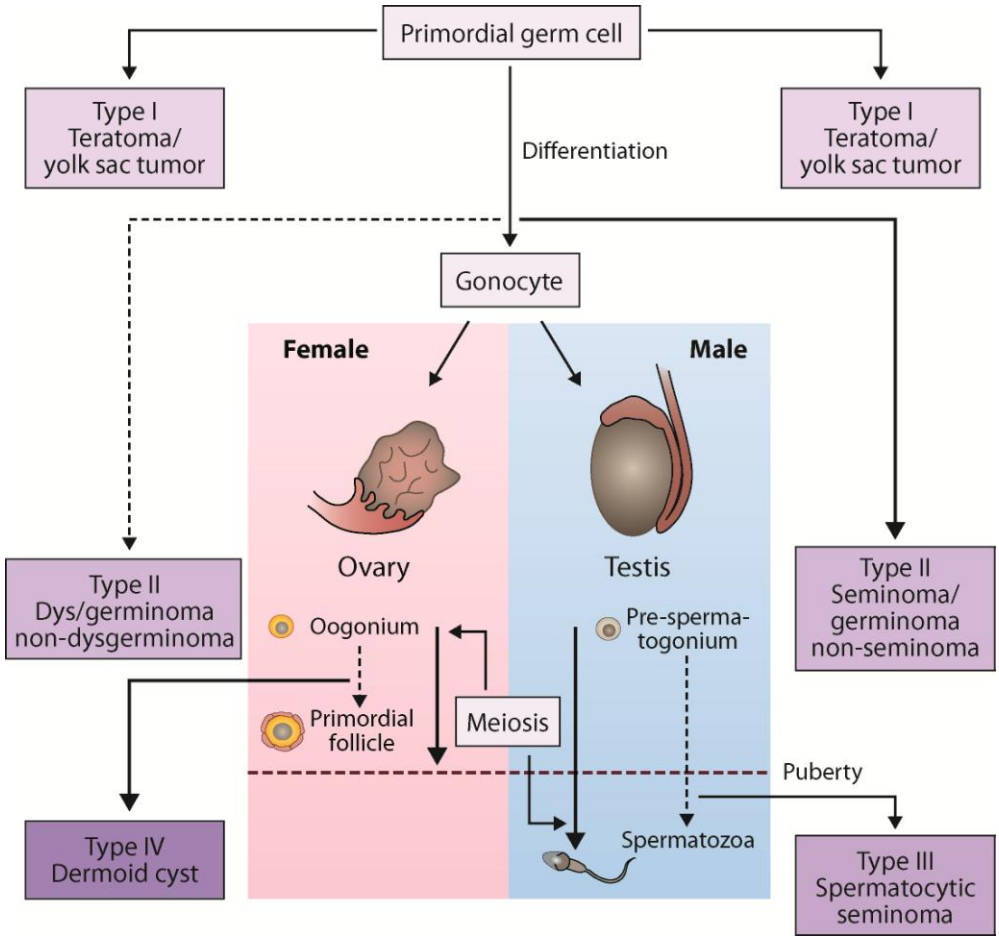

Figure 1. Schematic presentation of the assumed origin of different types of germ cell tumors. Modified from Oosterhuis and Looijenga, 2005

Table 1. Classification of the five types of Germ Cell Tumors: locations, phenotype, typical age and cell of origin. (Modified from Oosterhuis and Looijenga, 2005)

Type	Anatomical location	Phenotype	Age	Cellular origin
I	Testis/ovary/sacral region/retroperitoneum /mediastinum/neck/ midline brain/other	(immature) teratoma/ yolk sac tumor	Neonates and children	Early PGC/ gonocyte
II	Testis	Seminoma/ non-seminoma	>15 years	PGC/gonocyte
	Ovary	Dysgerminoma/ non-dysgerminoma	>4 years	PGC/gonocyte
	Dysgenetic gonad	Dysgerminoma/ non-seminoma	Congenital	PGC/gonocyte
	Anterior mediastinum (thymus)	Seminoma/ non-seminoma	Adolescents	PGC/gonocyte
	Midline brain (pineal gland/hypothalamus)	Germinoma/ non-seminoma	Children	PGC/gonocyte
III	Testis	Spermatocytic seminoma	>50 years	Spermatogonium / spermatocyte
IV	Ovary	Dermoid cyst	Children /adults	Oogonia/oocyte
V	Placenta/uterus	Hydatiform mole	Fertile period	Empty ovum/ spermatozoa

Interference with early male maturation can lead to the development of carcinoma in situ, CIS, due either to environmental factors or genetic mutation (Kristensen et al. 2008). It has been suggested that malignant TGCTs originate from these CIS lesions, with the exception of infantile TGCTs (non-seminomas) and spermatocytic seminomas (Kristensen et al. 2008, Oosterhuis, Looijenga 2005). In women, however, no comparable pre-cancerous lesion has been identified.

Various chromosomal aberrations have been linked to GCT development. These include loss of 1p, 4 and 6q, and gain of 1q, 12(p13) and 20q (type I yolk sac tumors) and aberrations of 12p in type II GCTs (Oosterhuis, Looijenga 2005). Specific gene mutations in GCTs are less frequent than chromosomal anomalies. In TGCTs, the most frequent single genes affected are: KIT, TP53, K-RAS, N-RAS and B-RAF (Gilbert et al. 2011, Sheikine et al. 2012).

1.1 Histological classification of GCTs

In 1976, WHO created a Classification of Diseases for Oncology (ICD-O-3) which has since been updated (www.who.int/classifications). The current ICD-O-3 is from the year 2000. This system is used principally in tumor or cancer registries for coding the site (topography) and the histology (morphology) of neoplasms, usually obtained from a pathology report. The main histological types (titles) are shown in Table 2. The same table gives a classification of trophoblastic tumors. These tumors arise from trophoblastic cells, which form in large part the placenta. Due to the fetal origin and pluripotency of placental cells, choriocarcinomas can also be classified as GCTs (ref). Other trophoblastic tumors are of gestational origin (ref), and thus not discussed in this thesis.

The whole histological classification of GCTs and trophoblastic tumors (subtitles included) is shown in Appendix 1

Table 2. Histological ICD-O-3 classification of Germ Cell Tumors (9060-9090) and Trophoblastic Tumors (9100-9103). WHO, 2000

Histology/Behavior codes	Histology description
9060/3	Dysgerminoma
9061/3	"Seminoma, NOS"
9062/3	"Seminoma, anaplastic"
9063/3	Spermatocytic seminoma
9064/2	Intratubular malignant germ cells
9064/3	Germinoma
9065/3	"Germ cell tumor, nonseminomatous"
9070/3	"Embryonal carcinoma, NOS"
9071/3	Yolk sac tumor
9072/3	Polyembryoma
9073/1	Gonadoblastoma
9080/0	"Teratoma, benign"
9080/1	"Teratoma, NOS"
9080/3	"Teratoma, malignant, NOS"
9081/3	Teratocarcinoma*
9083/3	"Malignant teratoma, intermediate"
9084/0	"Dermoid cyst, NOS"
9084/3	Teratoma with malignant transformation
9085/3	Mixed germ cell tumor#
9090/0	"Struma ovarii, NOS"
9090/3	"Struma ovarii, malignant"
9091/1	Strumal carcinoid
9100/0	"Hydatidiform mole, NOS"
9100/1	Invasive hydatidiform mole
9100/3	"Choriocarcinoma, NOS"
9101/3	Choriocarcinoma combined with other germ cell elements
9102/3	"Malignant teratoma, trophoblastic"
9103/0	Partial hydatidiform mole

Behavior codes 0: benign, 1: uncertain whether benign or malignant, 2:in situ, 3: malignant
*: mixed embryonal carcinoma and teratoma
#: mixed teratoma and seminoma

The major histological subtypes of GCTs are germinoma, teratoma, yolk sac tumor (YST), embryonal carcinoma and choriocarcinoma. Germinomas can be further classified into dysgerminomas (ovary), seminomas (testis) and extragonadal germinomas. Pure seminomas can also occur in the mediastinum (Takeda et al. 2003). A tumor with a combination of different histologies is usually classified as a mixed-type GCT. Again, gonadoblastoma containing both germ and stromal cells can present in a dysgenetic gonad (Frazier et al. 2012). In the literature, malignant gonadal GCTs are frequently grouped as seminomas and non-seminomas in men and dysgerminomas and as non-dysgerminomas in women.

Teratoma is the most common GCT histology in fetuses and neonates (Frazier et al. 2012, Frazier et al. 2012). Teratomas can be mature (benign), immature or malignant (see 2.1.1).

Embryonal carcinomas are unusual in neonates. Seminomas and dysgerminomas are not diagnosed in children before adolescence, but in men 15-44 years of age seminoma is the most common subtype (Arora et al. 2012). A subtype of seminoma, the so-called spermatocytic seminoma, is found in the elderly and not regarded as a true GCT (Chung et al. 2004). Most ovarian GCTs in children are teratomas, followed by yolk sac tumors, embryonal carcinomas and mixed tumors (Horton et al. 2007).

2 Benign germ cell tumors

Of the benign tumors listed in Table 2 (behavior code 0), the so-called "struma ovarii" is a rare form of monodermal teratoma, containing mostly thyroid tissue (Roth, Talerman 2007) and not discussed further in this thesis. Likewise, hydatidiform moles are gestational in origin, and are thus not discussed in this thesis.

Dermoid cysts have been described as a "specialized form of mature teratoma consisting of a squamous epithelial lined cyst with skin appendages, and small areas of teratomatous elements" (Ulbright, Srigley 2001). However, in the most recent WHO classification of diseases for oncology, ICD-O-3 (2008), the benign dermoid cyst is mentioned as an entity under germ cell neoplasms (9084/0) but separate from benign teratoma (9080/0). In this classification, adult cystic teratoma is assigned to the latter. The reports on dermoid cysts are inconsistent, often using the term "dermoid cyst" as a synonym for mature cystic teratomas.

Another entity of dermoid cysts is congenital scalp dermoids. These are benign subcutaneous tumors containing mature ectodermal tissues e.g. skin, hair follicles, sweat glands (Sorenson et al. 2013). Their incidence in children is 15-22%, and the common are near cranial fontanels. Histologically dermoid cysts can be classified into three types, one of them being a teratoma-type congenital cyst (Sorenson et al. 2013).

In children, 20-40% of all GCTs have been reported to be benign (Gobel et al. 1998, Lo Curto et al. 2003). Likewise, 63-68% of all testicular tumors in children and adolescents are benign GCTs (Taskinen et al. 2008, Nerli et al. 2010).The percentage of benign tumors among all GCTs in the adult population is less well established.

Mature cystic teratomas/ dermoid cysts, are the most common benign ovarian GCTs in women of reproductive age (Templeman et al. 2000). In children, approximately a half of all ovarian masses are neoplastic, and of these mature teratomas are the most common (48%) (Taskinen et al. 2014). In post-pubertal men, benign testicular teratomas and dermoid cysts are exceptional, and only a limited number of cases have been described (Ulbright, Srigley 2001). Primary GCTs of the mediastinum represent approximately 10–15% of all mediastinal

tumors and according to a Japanese single-center study covering over 50 years, 75% are mature teratomas (Takeda et al. 2003).

As mentioned above, benign GCTs can occur in both gonads and extragonadal locations, typically in the midline. Relative incidences of GCTs in children below 15 years of age according to site of origin are sacrococcygeal region (35%), ovary (25%), testis (20%), central nervous system (CNS; 5%), mediastinum (5%), retroperitoneum (5%), head/neck (3%), and vagina (2%). In the following sections, the main focus is on teratomas and mainly those occurring in the most common location, the sacrococcygeal region.

2.1 Sacrococcygeal teratomas

2.1.1 Embryology and pathology

The word teratoma is derived from the Greek words teratos ("of the monster") and onkoma ("swelling") (Rescorla, Breitfeld 1999). The term was introduced by Virchow in 1869 to describe "sacrococcygeal growths" (Virchow 1869), and the first reported case is inscribed on a Chaldean cuneiform tablet from approximately 2000 BC (Ballantyne 1874).

SCTs account for 35% to 60% of teratomas (gonadal included) in large series (Laberge et al. 2010). Even with stillbirths included, SCTs are the most common neonatal tumors (52%) (Werb et al. 1992, Isaacs 2004). From 75% to 90% occur in female infants (Altman et al. 1974, Billmire, Grosfeld 1986). A sacrococcygeal presentation of a teratoma in adults is exceptional (Luk et al. 2011).

Teratomas are composed of multiple tissues foreign to the site from which they arise (Dehner 1986). SCTs have been described to contain tissues from all three germ layers (ectoderm, mesoderm and endoderm). The tumors can contain hair, teeth, cartilage, intestinal mucosa and other tissue types. Occasionally, SCTs can even contain more specialized tissue, such as a limb or an organ (e.g. eye or heart) (Laberge et al. 2010).

In the Gonzalez-Crussi classification, SCTs are graded histologically from 0 to 3 (Rosai et al. 2004). Grade 0 tumors contain only mature tissue. Grades 1 through 3 have immature components, 1 containing rare foci of immature tissue, 2 moderate quantities of immature tissue, and 3 large quantities of immature tissue with or without malignant yolk sac elements. The overall risk of malignancy has historically

been reported as 13% to 27%, and a strong correlation of malignancy with age at presentation has been reported (Billmire 2006).

In a nationwide study of 84 prenatally diagnosed SCT cases from Japan, 61% were histologically mature and 39% immature, the diagnosis being established through primary surgery or autopsy (Yoneda et al. 2013). None of the cases was malignant.

2.1.2 Epidemiology

Historically, the incidence of SCT has been estimated to lie at 1 per 35,000 to 40,000 live births (Skinner 1997, Isaacs 1997, Pantoja, Lopez 1978). These estimates are usually based on material from single tertiary centers. However, there are only a few population-based epidemiological studies on SCTs on a national level.

A retrospective analysis of a multicenter study in the Netherlands including all children with SCT treated between 1970-2003 found the incidence for SCT to be 1:77 600 in the 1970s, 1:31 300 in the 1980s and 1 per 28,500 in the 1990s (Derikx et al. 2006). In a population-based regional database study on SCT from Northern England (1985-2006), a prevalence of 1 per 27,000 live births was detected (Swamy et al. 2008). Again, in an epidemiological study on teratomas from Hawaii (1986-2001), the SCT rate per 10,000 live births was 0.43, giving a live birth prevalence of 1 per 23 300 (Forrester, Merz 2006). As noted above, researchers have used the terms prevalence and incidence when reporting the frequency of SCT, it is thus difficult to compare true differences in SCT frequency between populations.

2.1.3 Associated abnormalities

A variety of anomalies and abnormalities have been reported in association with SCT. Some studies have noted only major anomalies, while others describe all abnormal conditions of the fetus and child, thus making comparison between studies difficult. One study on 214 cases of perinatal SCTs from the United States showed that 15% had associated significant congenital defects, such as pulmonary hypoplasia, renal dysplasia and or absence of kidneys (Isaacs 2004). In the above-mentioned study from Northern England congenital anomalies were reported in 13% (5/38) (Swamy et al. 2008), while in a small study from Australia associated anomalies were detected in 42% (n=7/17) (Ho et al. 2011).

A high incidence of urogenital abnormalities, due either to the mass effect of the tumor or to true structural anomalies, has been described in association to SCT (Gucciardo et al. 2011, Isaacs 2004). Furthermore, these abnormalities may not become apparent at the time of initial surgery. In a study from Scotland in 2011, 12% of girls with SCT were described as having a subsequent urogenital anomaly detected between 6 weeks to 13 years of age (Shalaby et al. 2012). All of these anomalies included a proximal connection of bladder and vagina along with a short, stenosed or absent distal urethra.

SCT has been found to be associated with gonadal dysfunction in men, detected after a follow-up of 20 to 32 years (Lahdenne et al. 1991a). Again, an association with orthopedic conditions such as developmental dysplasia of the hip and vertebral anomalies has been described (Lahdenne et al. 1991b). A family history of twins has also been reported in as many as 10% of patients with SCT (Laberge et al. 2010).

Currarino syndrome (Currarino triad)

The Currarino syndrome (CS), often referred to as the Currarino triad, is a rare complex of congenital caudal anomalies, commonly characterized by three clinical features: an anorectal malformation (usually rectal stenosis), a sacral bony defect and a presacral mass (Currarino et al. 1981). The latter can be a teratoma, an anterior meningocele or, less commonly, a dermoid cyst, duplication cyst or hamartoma. On the other hand, it has been postulated that the mass is not a teratoma at all but a hamartoma. A hamartoma is not classified as a true neoplastic tumor but a disorganized local tissue growth which may in some instances contain components from all three germ layers (Weinberg 2000). Unlike teratomas, hamartomas carry no risk of malignant transformation.

A majority (57%) of CS have been described as familial and have an autosomal dominant inheritance. The female: male ratio in Currarino syndrome is 1.5:1 (Laberge et al. 2010).

The underlying cause of CS has been pinned down to the HLXB9 homeobox gene, at 7q36 (Ross et al. 1998). Over 40 different types of mutations to this gene (e.g. small insertions or deletions, nonsense mutations and missense mutations) have been described, and the phenotype can vary from asymptomatic to patients presenting with the complete triad (Emans et al. 2005). The rate of mutations is likely to be higher than reported, and CS should be considered when an incomplete phenotype is detected (Cretolle et al. 2008). Again, 70% of patients with a mutation

have been described to have neural tube defects. Thus, in patients with any form of detected sacral agenesis, MRI of the terminal spinal cord and mutation analysis of the patient and relatives should be considered (Cretolle et al. 2008).

In contrast to the usual SCT, teratomas associated with CS can be detected as late as in adulthood. While a vast majority of cases have been histologically benign (mature teratomas), malignant transformation of a teratoma in CS has been described and the risk is estimated at 1% (Pendlimari et al. 2010). It can be argued that the reported cases of malignant transformation have rather been secondary carcinoma developing in a chronically inflamed hamartoma, thus supporting the hamartoma theory (Pendlimari et al. 2010).

2.1.4 Diagnosis

Presentation and classification

The most common presentation of an SCT is a tumor bulging from the sacrococcygeal area. The tumor can vary significantly in size, and in premature infants even outsize the baby itself. The American Academy of Pediatrics' surgical section has classified the types of SCT according to the extent of the tumor as follows (Altman et al. 1974) (Figure 2):

Type I - predominantly external with minimal presacral component
Type II - external but with significant intrapelvic extension
Type III - apparent externally but predominantly a pelvic mass extending into the abdomen
Type IV - presacral with no external presentation

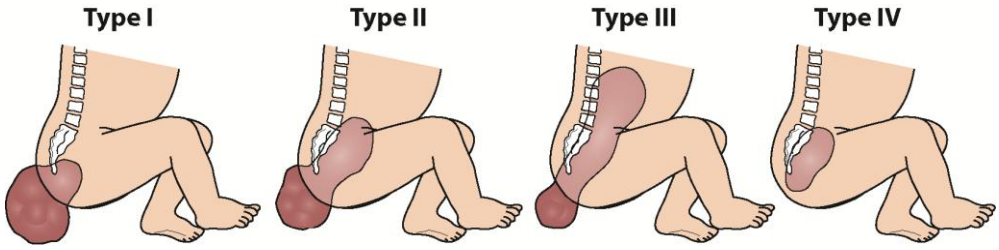

Figure 2. Classification of sacrococcygeal teratomas by Altman, 1974

The time of diagnosis of SCT depends on the size and type of the tumor. Large tumors, especially types I and II, are usually diagnosed at the antenatal ultrasound scan (US) (Flake et al. 1986). When prenatal ultrasound screening is not available or has not been performed, the diagnosis is obvious at birth, and a large tumor can in some cases cause labor dystocia. When the tumor is purely intrapelvic (type IV) the diagnosis can be delayed up to several months or even years. The symptoms and findings in these late presenting cases can include constipation, urinary retention, an abdominal mass or abdominal distention (Laberge et al. 2010). The late sequelae of SCT are discussed in greater detail in paragraph 1.1.7. Differential diagnosis of SCTs includes vascular malformations, lipomas, tail remnants and meconium pseudocysts (Laberge et al. 2010). Preoperative ultrasound and MRI are useful tools in their diagnostics, and postoperatively, the histopathology always needs to be verified.

Prenatal diagnostics

Ultrasound (US) with Doppler studies remains the key imaging method of tumor location, content and the overall hemodynamic status of the fetus (Gucciardo et al. 2011). According to their US appearance SCTs can be classified as cystic, solid or mixed (see section 2.6), the tumor composition being related to prognosis (Lakhoo 2010).

During recent decades the use of US screening programs during pregnancy has been gradually increasing. In Finland, a nationwide two-step screening program was initiated in 2011 (Decree on screening programs 339/2011; www.finlex.fi/fi). Thus, more and more SCT cases are presumably detected prenatally. Magnetic resonance imaging (MRI) can provide useful additional information as to the definition of the intrapelvic component and evaluation of the anatomy related to the tumor (Vrecenak, Flake 2013).

2.1.5 Treatment

Postnatal intervention

The goal in the treatment of SCT is complete surgical resection, usually conducted during the first days of life. The technique, usually via a posterior approach, includes en-bloc resection of the tumor and coccyx and classically, a so-called chevron-type skin closure. More recently, a variant of this closure technique has

been described (Fishman 2004). It utilizes excess skin on the tumor and enables reconstruction of the buttocks with a normal contour and hidden scars.

Even if the child has survived labor, but the tumor is large, solid and highly vascular, the intraoperative mortality has been reported to be high, from 33% (Usui et al. 2012) to 67% (Holterman et al. 1998). The mortality is mainly due to hemolysis, rupture or bleeding of the tumor. During the last few decades different techniques have been introduced to facilitate the operation and to minimize blood loss, and thus to improve the prognosis. In 1988, a simple method of controlling intraoperative bleeding using an aortic snare was described (Lindahl 1988). In 1998, the technique of laparoscopic clipping of the median sacral artery which supplies the tumor was introduced (Bax, van der Zee 1998). More recently, preoperative embolization of internal iliac arteries along with radiofrequency ablation (Cowles et al. 2006) and embolization of the median sacral artery (Lahdes-Vasama et al. 2011) have been successfully used.

Fetal intervention

Fetal surgery with clinical applications was introduced in the 1980s. Since 1995, it has been used in SCT cases in specialized centers and carefully selected cases. These have included high-risk SCTs, possibly compromising the course of pregnancy and maternal health (Vrecenak, Flake 2013). Fetal surgical centers routinely perform ultrasound and echocardiography as often as 2-3 times a week in these cases with a high risk for fetal hydrops. The only indication for fetal surgery in SCT has so far been progressive high output cardiac failure and early hydrops in fetuses of less than 30 weeks of gestation and with type I SCT (Vrecenak, Flake 2013).

The procedure, performed via hysterotomy, is called debulking. The tumor is exposed and resected using a tourniquet around the vascular pedicle, and the coccyx and deeper components are left for postnatal removal (Vrecenak, Flake 2013). The goal is to restore the physiology of the mother and the fetus, and to allow the fetus to mature and have a higher probability of survival. However, the procedure involves a high risk of preterm labor and preterm rupture of membranes, and red blood cell transfusion is often required (Vrecenak, Flake 2013).

In cases with high-risk SCT and progressive cardiac failure and fetal hydrops after 30 weeks of pregnancy, either emergency cesarean section or EXIT -Ex Utero Intrapartum Treatment- is recommended (Vrecenak, Flake 2013). In the latter, the

partially delivered fetus is maintained on placental circulation while the tumor is removed, and the fetus is then delivered by cesarean section.

Recently, minimally invasive antenatal treatment methods for SCT have been described (Mieghem et al. 2014). Of cases in question, treated with fetoscopic laser ablation, radiofrequency ablation or interstitial laser ablation, only 2/5 (40%) survived, but which long-term morbidity related to prematurity. Again, amnioreduction and cyst aspiration have been used to facilitate maternal comfort and reduce uterine irritability (Hedrick et al. 2004).

All fetal interventions involve a risk of mortality or serious morbidity, both to the fetus and mother. Thus, fetal surgery remains challenging and controversial as a method of treatment (Vrecenak, Flake 2013).

2.1.6 Prognosis

The overall prognosis of SCT among live-born infants who undergo early surgery is favorable. Mortality rates as low as 2% in predominantly cystic and, conversely, as high as 33% in predominantly solid tumors have been reported (Usui et al. 2012). As some SCTs can recur, the children are initially followed up with clinical examinations and tumor marker sampling. The use of tumor markers in SCT is addressed separately in the Discussion (4.3).

The prognosis of prenatally diagnosed SCTs is poorer. Hence, specific tools for setting the prognosis have been described. Benachi and associates described a prognostic classification for prenatally diagnosed SCTs by size, vascularity and growth (Table 3).

Table 3. Prognostic classification for prenatally diagnosed sacrococcygeal teratoma (according to Benachi et al. 2006)

	Group A	Group B	Group C
tumor size (diameter)	< 10 cm	≥10 cm	≥10 cm
vascularity of the tumor	absent or low vasculature	pronounced vascularity	absent or low vascularity, predominantly cystic tumor
tumor growth	slow	fast	slow

The authors found groups A and C to be associated with a good maternal and perinatal outcome. Group B was associated with higher perinatal mortality and morbidity, with a total loss of 52% of cases (Benachi et al. 2006).

Another proposed novel tool for early prognostic classification of SCT is tumor volume to fetal weight ratio, TFR (estimated with MRI or US). Estimated fetal weight and tumor volume are calculated based on a prenatal US scan or MRI. A TFR less than or equal to 0.12 at 24 weeks of gestation predicted a significantly better outcome than one greater than 0.12 (Rodriguez et al. 2011).

In several studies, cases diagnosed prenatally have had a poor prognosis when compared to those diagnosed postnatally. The factors related to a poor outcome among the former include fetal hydrops, placentomegaly, predominantly solid tumor and polyhydramnion (Holterman et al. 1998, Makin et al. 2006, Usui et al. 2012). The overall mortality in prenatally diagnosed cases varies from 16% to 48% (Usui et al. 2012), (Wilson et al. 2009), (Holterman et al. 1998). Fetal mortality approaches 100% once fetal hydrops and placentomegaly develop (Vrecenak, Flake 2013).

In a nationwide survey from Japan focusing on the prognostic impact of tumor histology, an immature histology was associated with significantly higher mortality (death at delivery-/-delivered alive) than a mature histology (immature 8/31, mature 2/48) (Yoneda et al. 2013). This was, however, probably due to the poorer condition of neonates with an immature teratoma, rather than solely to the histology of the tumor (Yoneda et al. 2013).

Risk factors for recurrence

The recurrence of SCT can be local or metastatic and arise from malignant foci residing within a mature or immature SCT (Weinberg 2014). These can remain undetected in the initial pathological analysis, even when multiple samples from the tumor have been evaluated. Thus, follow-up of all SCTs, regardless of the histology of the primary tumor (mature, immature or malignant) is of key importance.

Recurrences of benign neonatally resected SCTs have been described as late as 21-43 years after the initial surgery (Lahdenne et al. 1993). Failure to remove the coccyx has been reported to be associated with a high recurrence rate (Laberge et al. 2010). Thus, as described in paragraph 2.1.5, the coccyx needs to be removed along with the tumor at the initial surgery.

A large, multicenter study in the Netherlands reported a recurrence rate of 11% within 3 years of operation (Derikx et al. 2006). Several significant risk factors for recurrence were identified: i.e. pathologically proven incomplete resection during primary surgery ($p=0.001$) and immature ($p=0.011$) or malignant ($p<0.001$) histology. In another large study from Japan on 72 prenatally detected SCT cases, histology was not found to be related to the risk of recurrence, as 7.8% of mature (4/51 cases) and 6.0% of immature (2/33 cases) teratomas had a late recurrence (Yoneda et al. 2013). All recurrences in the series were detected before the age of 2 years.

2.1.7 Long-term sequelae

Long-term functional sequelae of SCT have been described in several studies, and they remain relatively common. Postulated mechanisms of injury to pelvic structures include tumor invasion and the extent of resection versus local mass effect with compression injury (Partridge et al. 2013). These injury mechanisms can possibly explain anatomical defects such as urethral or vaginal necrosis, possibly detected later in childhood (Shalaby et al. 2012). All of these anomalies have involved a proximal connection of bladder and vagina along with a short, stenosed or absent distal urethra.

In a national study from the Netherlands, nearly a half of patients reported impaired bowel function and/or urinary incontinence (Derikx et al. 2007). Similarly, in a recent study from the United States, anorectal complications such as chronic constipation and fecal incontinence were found in 29% and urologic

complications (neurogenic bladder, vesicoureteral reflux and urinary incontinence) were present in 33% (Partridge et al. 2014).

In a study on anorectal function and quality of life among adults who underwent surgery for benign SCT in infancy, only 27% had completely normal bowel habits and some soiling was present in 27%. However, 88% reported good continence (Rintala et al. 1993). In another study of 45 patients, urodynamic abnormalities were seen in 78% and 50% of patients reported urinary incontinence (Lahdenne 1992). However, only 18% reported subjective complaints.

Psychosocial aspects related to SCT have recently been studied in Scotland. Even though 9/31 (29%) of participants responding to the psychosocial questionnaire reported concern over their appearance, the ensuing stress levels were low (Shalaby et al. 2013).

3 Malignant germ cell tumors

Germ cell tumors differ significantly with regard to their biology, clinical presentation and histology at different ages and between the two sexes. Twenty percent of all GCTs are malignant, and account for 3% of all childhood malignancies (Gobel et al. 2006, Lo Curto et al. 2003). In young men, TGCTs are the most common of all solid tumors, and comprise 98% of all testicular malignancies (Jorgensen et al. 2011). In all women, it has been estimated that only 2-5 % of ovarian malignancies worldwide are GCTs.

The origin of malignant GCTs is discussed in chapter 1. A simplified histological classification of GCTs (with their typical locations, ages and possible origin) is presented in Table 4.

Table 4. Classification of malignant germ cell tumors.

Histology (typical location)	Typical age	Origin and specific features
Germinomatous tumors		
Seminoma (testis) (Spermatocytic seminoma)	Adolescents and adults (Older men)	Morphological features of undifferentiated germ epithelium
Dysgerminoma (ovary)	15-35 years	Precursor: carcinoma in situ (CIS)? (Different origin from true GCTs?)
Germinomas (brain)	In females 10-20 years In males 10-30 years	
Non-germinomas		
Teratoma (testis, SC, ovary)	All ages	Embryonal differentiation, typically all germ cell layers
Yolk sac tumor (endodermal sinus tumor)	Neonates and children	Extraembryonic differentiation pattern
Embryonal carcinoma (testis, ovary, mediastinum)	Adults	Tumors of immature totipotent cells
Choriocarcinoma	Rare in all age groups	Extraembryonic differentiation pattern
Mixed-type tumors		

SC= sacrococcygeal

Data modified from Göbel et al. Ann Oncol 2000 and Arora et al, Cancer, 2012

3.1 Locations

Proper PGC migration is critical for the survival of the germ cells and formation of the gonad. Failure of this migration can result in ectopic germ cells anywhere from the brain to the coccygeal area, usually in the midline (Frazier et al. 2012). Aberrant migration during embryogenesis is a possible mechanism for the occurrence of extragonadal GCTs (discussed above in chapter 1).

The locations of GCTs differ significantly according to age group. Among adults, the vast majority of GCTs -more than 90% in males and more than 80% in females- develop in gonads (Arora et al. 2012). Nonetheless, the locations vary significantly in different age groups. In neonates and infants under the age of 5 years the majority occur at extragonadal sites, most commonly in the sacrococcygeal region (Arora et al. 2012, Gobel et al. 1998). In contrast, tumors in the central nervous system (CNS) are most common among adolescents and young adults (Arora et al. 2012)

In a large nationwide study from England covering 25 years, 3.2% of all malignant GCTs were extragonadal, most commonly in the CNS in both sexes (61% and 74% in men and women, respectively), followed by mediastinum and thorax in men (30%) and abdomen and pelvis in women (17%) (Arora et al. 2012).

3.2 Epidemiology

There are only a few population-based studies reporting on the overall incidence of malignant GCTs. In the abovementioned study from England they comprised 0.7% of all cancers (all ages included), but 11.2% in the younger population (<30 years) (Arora et al. 2012). Again in the same study, a vast majority of all malignant GCTs were testicular (92.5%), only 4% and 3% being found in the ovary and in extragonadal locations, respectively.

There are two age peaks in the incidence of malignant GCTs in childhood. The first is seen during the first two years of life, and the second starts at the age of 7 years in girls and 10 years in boys (Schneider et al. 2004).

Malignant testicular GCTs

Testicular germ cell cancer affects mainly young men, 85% presenting between 15 and 44 years of age (Horwich et al. 2013). In the United Kingdom, the lifetime risk

for a man has been estimated to be about one in 200 (Horwich et al. 2013). The increasing incidence of male TGCTs has been well documented, and has in fact doubled over the last 40 years in industrialized countries (Huyghe et al. 2003). Both seminomas and non-seminomas have been shown to be on the increase, the increase being more modest for non-seminoma (McGlynn et al. 2003). In the United States, the incidences of TGCTs have been reported to be much higher among the white population (Stang et al. 2012).

Very high incidences of TGCTs have been shown in the Nordic countries, with significant differences between populations (e.g. high rates in Denmark, much lower in Finland). Nevertheless, these differences seem to have leveled off over the last few years (Jorgensen et al. 2011). Again, it has been postulated that testicular GCT rates are reaching a plateau in the United States and Switzerland, and possibly even declining in France and some Far-East-Asian populations (Chia et al. 2010).

Malignant ovarian and extragonadal GCTs

As extragonadal as well as ovarian GCTs are rarer than TGCTs, no potential change in their occurrence and incidence has been established. In the study by Arora and associates, the incidences of germinomas of the CNS and dysgerminomas of the ovary were shown to have increased significantly (Arora et al. 2012). A study on ovarian cancer in Japan, however, showed the GCT incidence to have remained stable between 1980 and 1999 (Ioka et al. 2003). In the United States, the GCT incidence rates in women have been reported to have declined from 1973 to 2002 (Smith et al. 2006), while those of malignant extragonadal GCTs have been reported to be similar for both males and females (range: 1.9- 3.4 per 1 000 000) (Stang et al. 2012).

Malignant GCTs in neonates, children and adolescents

Data on the epidemiology of malignant GCTs in children and adolescents are scant. An epidemiological analysis of over 1400 GCTs in children and adolescents from Germany (1981-2000) showed that among children <15 years of age they account for 3% of all reported malignancies (Schneider et al. 2004). The sex distribution was equal in children <5 years, while among older children a female predominance was seen. However, the sex distribution depended on tumor location: overall, non-gonadal tumors were twice as common in girls as in boys (2:1) but especially among children aged 5 years or over more common in boys. The study from England on 33 000 malignant GCTs diagnosed between 1979 and

2003 (covering all ages), reported that 42% of all GCTs in both male and female children (0-14 years) were extragonadal (Arora et al. 2012).

3.3 Associated medical conditions and male subfertility

A number of conditions in the male reproductive system have been postulated to be associated with testicular cancer, some sharing a common origin dating back to fetal life. This entity, called the testicular dysgenesis syndrome (TDS),has been described as involving impaired spermatogenesis, hypospadias, testicular cancer and cryptorchidism (undescended testis) (Skakkebaek et al. 2001, Virtanen et al. 2005).

Over the last two decades, TDS has been thoroughly investigated in a collaborative undertaking by Finnish and Danish researchers (Virtanen et al. 2005, Skakkebaek et al. 2001, Sharpe, Skakkebaek 2008, Rajpert-De Meyts et al. 2003, Olesen et al. 2007). Danish boys have been found to have higher rate of cryptorchidism and hypospadias. More recently, adverse trends have been detected in semen quality in Finnish men (Jorgensen et al. 2011). These trends have occurred simultaneously with the increase in testicular GCT incidence (see 1.6). There is, moreover, evidence that this phenomenon is time-related, as higher incidences of testicular cancer have been noted among men born more recently. Interestingly, this phenomenon seems to be more pronounced in the South-Western coastal area of Turku than in other parts of Finland (Jorgensen et al. 2011).

TGCTs have also been associated with a prior diagnosis in the contralateral testicle (Fossa et al. 2005), inguinal hernia (Coupland et al. 2004), hydrocele (Moller et al. 1996), prior testicular biopsy (Moller et al. 1998) and testicular atrophy (Moller et al. 1996).

Less is known as to associations with other GCTs. However, a strong association of Klinefelter's syndrome with mediastinal teratoma has been reported, an estimated 8% of male patients with mediastinal primary GCTs to having Klinefelter's syndrome (50 times the expected frequency) (Cohen, Weintrob 2003). Additionally, the syndrome has been reported among patients with intracranial or retroperitoneal tumors. Histiocytosis, a heterogeneous group of disease entities involving an abnormal increase in the number of histiocytes, appears to be associated with mediastinal teratoma, both with and without Klinefelter's syndrome (Laberge et al. 2010).

Moreover, the following rare associations have been reported, most often with nonsacrococcygeal teratomas: acute leukemias, Beckwith-Wiedemann syndrome, cleft lip and palate, congenital heart defects, Hodgkin's disease, Morgagni hernia (a form of diaphragmatic hernia), pterygium (benign growth of the conjunctiva), trisomy 13, trisomy 21, and rare syndromes such as Proteus and Schinzel-Giedion (Laberge et al. 2010)

Anomalies associated with SCT in particular are discussed in 2.4.

3.4 Etiologic factors

While the increasing incidence of malignant TGCTs appears well established, the potential underlying etiological factors remain less well understood. As described above in connection with TDS, cryptorchidism is a risk factor for TGCTs. According to one meta-analysis, the relative risk tof developing a tumor among men with prior undescended testis has been estimated to be 4.8 (Dieckmann, Pichlmeier 2004). Nonetheless, only 10% of all TGCTs develop in men with a history of undescended testis (McGlynn, Cook 2009). Among men with a history of unilateral testicular cancer, again, the risk of developing disease in the contralateral testis is approximately 10-25% (Batata et al. 1982).

The risk of TGCTs has also been reported to be 8- and 4-fold higher among brothers and sons of affected men, respectively, when compared to the general population (Hemminki, Chen 2006, Hemminki, Li 2004).

In addition to those detailed above, several other, including environmental, risk factors for testicular cancer have been proposed. Fetal exposure to substances possibly resulting in deficient androgen production during testicular development has been suggested (Del-Mazo et al. 2013). Historically, such substances have included both endocrine, e.g. diethylstilbestrol, as well as exogenous chemicals such as organochloride pesticides and phalates (McGlynn, Cook 2009). The association of TGCTs with chemicals in breast milk has also been suggested (Krysiak-Baltyn et al. 2012).

In a register study focusing on perinatal risk factors in Nordic countries (Sweden, Norway, Denmark and Finland), a U-shaped association between fetal growth, measured as the Ponderal Index, and childhood testicular germ-cell cancer was detected (Stephansson et al. 2011). The authors' findings suggest that an abnormally low or high fetal growth rate is a putative risk for pediatric testicular cancer.

Further, several pregnancy-related risk factors have been suggested to be associated with testicular cancer. These include preterm birth (Aschim et al. 2006), young maternal age (Depue et al. 1983) and low parity.

Even though current evidence suggests that TGCTs originate early in life, there are also possible postnatal risk factors. Again, naturally occurring or synthetic hormones in dairy food, viral infections (Epstein-Barr and cytomegalovirus) and testicular trauma have also been suggested as risk factors (McGlynn, Cook 2009).

The rapid increase in the incidence of testicular GCT would indicate toxic chemicals, e.g. pesticides and industrial chemicals (Jorgensen et al. 2011), as possibly playing a pathogenetic role. This notwithstanding, and due to the rarity of malignant ovarian as well as extragonadal GCTs in both sexes, their etiology remains difficult to study.

3.5 Current diagnostics, treatment and outcomes

The treatment of malignant GCTs is, in most cases, surgery with or without adjuvant chemotherapy and/or radiotherapy. Adjuvant therapy is chosen according to patients' age along with the location, histology and stage of the tumor. As these tumors mainly occur in gonads, most often in fertile men and women, fertility-sparing treatment is often the goal. Another objective is to reduce the risk of secondary carcinomas and other long-term health consequences. This is especially important in children in whom radiation should be avoided.

As more than 90% of all malignant GCTs occur in the testes, and on the other hand, as almost all testicular cancers are GCTs, the treatment of malignant testicular tumors will be discussed in greater detail below.

Malignant testicular GCTs

A vast majority (95%) of TGCTs present as a non-tender mass in the testis. Rarely, pain, hydrocele or symptoms of metastases can also occur. Again, tumors producing human chorionic gonadotropin can present with gynecomastia and nipple discharge (Horwich et al. 2013).

All testicular masses should be subjected to a US examination, which has a reported sensitivity of up to 100% in the diagnostics of testicular cancer in adults (Horwich et al. 2013, Oldenburg et al. 2013). In addition, serum samples for tumor marker evaluation (AFP, hCG) should be taken preoperatively, whereas a biopsy of

the testis should not be taken. In adults, orchiectomy from an inguinal approach should be performed as a standard initial measure to confirm the diagnosis. If the patient has only one testis or a bilateral tumor, partial orchiectomy can be considered (Horwich et al. 2013). As a majority testicular tumors in children are benign (Taskinen et al. 2008), frozen section and, when possible, testicle-sparing surgery is recommended.

Orchiectomy may be a sufficient treatment in localized cases (Horwich et al. 2013, Oldenburg et al. 2013) but occasionally adjuvant treatment is needed. TGCTs are sensitive to both chemotherapy and radiotherapy (Horwich et al. 2013). In stage I non-seminomas, the combination of bleomycin, cisplatin and etoposide has been reported to be effective, with a recurrence risk of 1% (Albers et al. 2008). In stage I seminomas, surveillance only or alternatively, adjuvant single-dose carboplatin (low toxicity drug) is recommended (Albers et al. 2008)

Other malignant GCTs

Malignant ovarian germ cell tumors are often large and progress rapidly, presenting most often with an abdomino-pelvic mass (Pectasides et al. 2008). They are highly chemosensitive, and fertility-sparing surgery is in most cases feasible, even in advanced cases. For dysgerminomas, unilateral salpingo-oophorectomy and close monitoring with radiological and clinical follow-up is recommended, as the majority of patients have stage 1 disease. Again, the recommended adjuvant treatment for most cases of completely removed, non-dysgerminomatous ovarian germ cell tumors is currently chemotherapy with three courses of bleomycin, etoposide and cisplatin. Cure rates approach 100% for patients with early-stage disease, and are at least 75% in more advanced-stage disease (Pectasides et al. 2008).

The optimal therapy for primary intracranial GCTs is the subject of active research. Germinomas are highly radiosensitive with 5- to 10-year survival rates of over 90% with radiotherapy alone. However, in order to reduce exposure and its endocrine, vascular and neurocognitive side-effects, current recommendations include minimizing whole-ventricle radiation and an additional boost directly into the tumor (Jackson et al. 2011). Non-germinomatous intracranial GCTs have less favorable outcomes, and a combination of surgery, radiation and chemotherapy (depending on the histology) is recommended. Mature teratomas are curable with surgery alone, but tumor expansion may require a third ventriculostomy to relieve

hydrocephalus secondary to tumor expansion. Second-look surgery after adjuvant therapy should be considered in selected cases (Jackson et al. 2011).

Malignant primary GCTs of the mediastinum are very rare and present like other mediastinal tumors (including dyspnea, chest pain and superior vena cava syndrome). Treatment consists of radical resection with or without chemotherapy, or with chemotherapy alone (Takeda et al. 2003).

4 Tumor markers

Tumor markers are substances detectable in blood, urine or tissue and used in diagnostics, staging and monitoring tumor recurrence and treatment response. They include proliferation markers, hormone receptors, oncogene products and apoptosis regulators, having shown a potential as prognostic indicators in common human cancers (Sturgeon 2002, Agnantis et al. 2003, Ricafort 2011). The differential diagnosis of conditions with elevated serum tumor markers includes neoplastic, infectious, metabolic, toxic and genetic etiologies (Barlow et al. 2010). Biochemical markers are feasible for use in relatively few tumors, GCTs among them. Below, the commonly used oncofetal antigens and other established tumor markers are discussed in greater detail.

4.1 Oncofetal antigens and other tumor markers

Oncofetal antigens are proteins or carbohydrate molecules synthesized during fetal development, either in specific fetal tissues, in the yolk sac or in the placenta (Lahdenne, Heikinheimo 2002). The two most commonly used oncofetal tumor markers are AFP and β-human chorionic gonadotropin (hCG). Other oncofetal antigens include carcinoembryonic antigen (CEA), human epididymis protein 4 (HE4) and carbohydrate antigens (CA) 125 and 19-9.

4.2 Clinical use of tumor markers

Tumor markers are widely employed in the diagnosis and follow-up of various cancers in adult patients, and there are evidence-based guidelines for their use in several types of cancer (reviewed in Sturgeon 2002). An ideal tumor marker should not be abnormally elevated in benign conditions and should be highly specific for a given type of cancer. A disseminated disease, again, should yield highest readings and these should decrease as the tumor regresses (von Eyben 2003).The most common plasma tumor markers in clinical use are PSA (prostate-specific antigen)

for prostate cancer, CA 125 in epithelial ovarian cancer and AFP for hepatoblastoma/ hepatocellular cancer (Sturgeon 2002).

4.3 Use of tumor markers in GCTs

Tumor markers have been widely used in the management of testicular and other GCTs. Among them, AFP, hCG and lactate dehydrogenase (LD) are the most widely used (Sturgeon 2002, Barlow et al. 2010). These and other known tumor markers in the context of GCTs are discussed below.

Alpha-fetoprotein

Serum AFP (S-AFP) is a glycoprotein synthesized in the yolk sac during fetal life, and later in the fetal liver and intestine. Its function is not fully understood, but it possibly serves as a binding protein for estrogen and bilirubin in the fetus, representing a fetal counterpart of albumin or functioning as an immunosuppressant (Lahdenne, Heikinheimo 2002). In fetal serum, AFP levels peak by 14 weeks of gestation, declining thereafter. The AFP level in term infants is approximately 30 000 μg/l, but adult levels of less than 10-12 μg/l are reached by one year of age (by 12 months in preterm and 9 months in term babies) (Lahdenne, Heikinheimo 2002). AFP has been used as a tumor marker for malignant GCTs, especially testicular non-seminomas (von Eyben 2003) and malignant relapses of SCT in children (Lahdenne, Heikinheimo 2002, Sturgeon 2002). Additionally, serum AFP has been found to be elevated in hepatoblastoma and less often in hepatocellular carcinoma, and non-malignant conditions such as viral hepatitis and ataxia-telangiectasia (Barlow et al. 2010). AFP is also elevated in type I hereditary tyrosinemia (Pitkänen et al. 1994).

Human chorionic gonadotropin

Serum hCG is a glycoprotein hormone containing two subunits (α- and β-) and produced by the trophoblasts of the placenta to stimulate progesterone production by the corpus luteum. GCTs containing trophoblastic elements also secrete hCG and hCG-β. hCG/ hCG-β is used in the diagnostics of choriocarcinomas, and elevated values have also been detected in seminomas and dysgerminomas (Lahdenne, Heikinheimo 2002).

Carbohydrate antigen 125

CA 125 (also known as mucin 16 or MUC16) is a high-molecular-weight membrane glycoprotein expressed in fetal tissues (Lahdenne et al. 1995) and possibly synthesized by the peritoneum (Epiney et al. 2000). It is not cancer-specific, and can be elevated in a variety of benign conditions in pre-menopausal women, including endometriosis, pregnancy and benign ovarian cysts. It has been used in the diagnosis and follow-up of ovarian cancer (Menon, Jacobs 2000), and its use in the screening of ovarian cancer is currently in progress (Menon et al. 2014). CA 125 can also be elevated in lung and breast cancer. However, its role in ovarian masses in children remains controversial (Spinelli et al. 2012). It has also been found to be a sensitive indicator in pediatric veno-occlusive disease (Petaja et al. 2000).

Carbohydrate antigen 19-9

CA 19-9 is a carbohydrate antigen expressed in fetal tissues and in certain cancers, especially those of the gastrointestinal tract (reviewed in Lahdenne, Heikinheimo 2002). It is a tumor marker commonly used in gastrointestinal and pancreatic cancer (reviewed by (Goonetilleke, Siriwardena 2007). However, elevated levels have also been found in benign conditions and various inflammatory disorders such as cholelithiasis. Again, it has been postulated that CA 19-9 as well as CA 125 could be useful in the follow-up of immature teratomas (Lahdenne, Heikinheimo 2002).

Lactate dehydrogenase

Serum lactate dehydrogenase (LD) is an enzyme found in all tissues of the body, with the highest concentrations in muscle (Barlow et al. 2010). LD has five isoenzymes, of which LD-1 is raised in seminoma more often than S-AFP and S-hCG (von Eyben 2003). LD alone lacks specificity in testicular GCT diagnostics, and should only be used together with other markers and other supporting information (Barlow et al. 2010).

International guidelines have been established for both pre- and post-treatment marker concentrations, and the International Germ Cell Cancer Collaborative Group has confirmed their prognostic value. Additionally, serum placental alkaline phosphatase is used in Europe in testicular GCT, as it is increased in up to 80% of testicular seminomas, of which only 20% produce hCG (Lamerz et al. 1999). Post-

treatment tumor marker follow-up is essential when optimal treatment is being planned, and normalization of marker values is required for optimal response (Sturgeon 2002, Salonen et al. 2008).

The use of tumor markers, mainly of AFP and hCG, in intracranial GCTs can aid in planning the required treatment. When these markers are elevated, intracranial GCTs should be treated as non-germinomatous tumors which have a poorer prognosis and require heavier treatment than IC germinomas (Sturgeon 2002).

The present study

1 Aims

The aims of the present study were to evaluate the biology, clinical features, epidemiology, associated anomalies and long-term follow-up of SCT, and secondly, to evaluate the epidemiology and incidence of other GCTs.

The specific aims were:

1. to determine the prevalence of SCT in Finland and its effects on pregnancy outcome, and additionally, to describe anomalies and conditions associated with the condition (III)
2. to establish the incidence of malignant GCTs and its change over time in Finland (II)
3. to establish the incidence, histological, age and sex distribution and survival rates in GCTs in children and adolescents (IV)
4. to evaluate the clinical significance of serial tumor marker values in the follow-up of sacrococcygeal teratomas (I)

2 Patients and methods

2.1 SCT study (III)

All cases of SCT including live births (n=89), stillbirths (n=13) and terminations of pregnancy (TOP) for fetal anomalies (n=22) were identified in the Finnish Register of Congenital Malformations (FRCM) for the period 1987-2008 inclusive. The word "teratoma" was used as the search term, and all except sacrococcygeal locations were excluded. These cases were subsequently combined with malignant SCT cases obtained from the Finnish Cancer Registry (www.cancer.fi) to ascertain inclusion cases detected outside the neonatal period, and any of which no previous notification had been made to the Register of Congenital Malformations. For cases in the Cancer Registry, histology codes shown in Table 2 and topography codes C41.4 (pelvic bones, sacrum, coccyx and associated joints), C49.5 (sacrococcygeal region) and C49.6 (buttock) were used. Data on prenatal diagnoses, pregnancy outcomes, infant deaths and associated abnormalities were collected in all cases. Data on other anomalies, obtained from the FRCM, were checked from patient records (e.g. discharge summaries and other texts sent to the FRCM by clinicians), and the anomalies of stillbirths and infant deaths as well as TOPs were verified from autopsy reports.

2.2 Register studies for malignant GCTs (II, IV)

2.2.1 Data collection and classification of tumors

The two studies in question were based on nationwide material on malignant GCTs between 1969 and 2008 in Finland. The data were obtained from the Finnish Cancer Registry. Cases were classified according to the WHO International Classification of Diseases, Oncology, 3rd edition (ICD-O-3 Behavior code 3 [malignant] tumors) (see Original publication II for histological and topography

codes). In addition to behavior code 3, benign and uncertain behavior codes (0 and 1) of tumors located in the CNS were included.

Topographical classification of the tumors used in our studies followed the WHO ICD-O-3 classification (www.who.int).The tumors were staged as follows: stage 1= local, stage 2= involvement of regional lymph nodes, stage 3= involvement of distant lymph nodes or tumor growth to adjacent tissues, stage 4= metastasized and stage 0= data not available.

All cases of extragonadal choriocarcinomas in women were excluded from this study as being potentially gestational. Additionally, spermatocytic seminomas were excluded from the analysis as they are not associated with carcinoma in situ, and their relationship with other GCTs being thus uncertain (Skakkebaek et al. 1987, Waheeb, Hofmann 2011).

2.2.2 Statistical analyses

The statistical analyses for the epidemiological studies on malignant GCTs were carried out in close collaboration with a statistician. For study II, total GCT incidences were calculated and adjusted for age against the world standard population for each 10-year time period (1969-78, 1979-88, 1989-98 and 1999-2008). Relative changes in incidence with 95% confidence intervals were calculated using Poisson distribution (Altman 2000). In addition, age-period-cohort analyses were performed to assess the birth cohort influence on male gonadal GCT incidences (study II). This was done using goodness-of-fit analysis (Clayton, Schifflers 1987a, Clayton, Schifflers 1987b).

For study IV, incidences (with 95% confidence intervals) and significances for incidence changes over time were calculated using function glm (a flexible generalization model of ordinary linear regression) in R (Software environment for statistical computing and graphics, version 2.13.0, The R Foundation for Statistical Computing), assuming Poisson distribution.

2.3 Tumor marker study (I)

All patients (n=33) who were diagnosed with SCT and underwent surgery at Helsinki University Central Hospital between 1985 and 2006 were identified from hospital records, and included in the study.

Serum samples and tumor marker measurements

We set up a follow-up scheme for SCT patients including regular clinical and ultrasound examinations as well as serial serum tumor marker evaluations in Helsinki University Hospital. The scheme is described in Appendix 2. Children detected as having SCT were divided into two subgroups by age at diagnosis. The first group consisted of neonates in whom the diagnosis of SCT was made either antenatally or at birth (n=25), the second (n=8) included children with late diagnoses, i.e. after the neonatal period. The tumors were classified according to histopathological findings as mature (MT), immature (IT) and malignant sacrococcygeal (SC) (see below).

Neonates

Histologically, 72% of cases (n=18) were MTs and 24% (n=6) ITs. One child had a cystic tumor with foci of specialized tissues (e.g. pancreas, intestine, brain and kidney). The kidney tissue had malignant cells typical for nephroblastoma, and the tumor was thus classified as a malignant teratoma.

During the follow-up, six children (five of them girls) developed a total of eight recurrences, three mature, three immature and two malignant. The length of follow-up ranged from 1 to 15 years (mean 7 years).

Late diagnoses

We found 8 cases (24% of all SCTs) diagnosed after the neonatal period (between 4 months and 14 years of age). Seven of these late occurrences were MTs and one IT. Currarino syndrome was found in four out of the eight. Only one of these children with a late diagnosis developed a mature recurrence. The mean length of follow-up in this group was 8 years (range, 3–14 years).

Serum tumor marker measurements

In our study material, serum AFP, CA 125, and CA 19-9 were measured in an average of 81%, 64%, and 65% of patients at each visit during the first 5 years of follow-up. An average of 16 samples for AFP and 10 samples for both CA125 and CA 19-9 were obtained from each child. Initially, hCG sampling was included in

the tumor marker follow-up scheme, but unfortunately, only a minor fraction of the samples were taken. Hence, all hCG values were excluded from the final analyses.

AFP was analyzed with immunofluorometry throughout the period. For CA 125 and CA 19-9, the evaluation methods changed twice during the study period, first from immunoradiometric assay (before 1995) to Immuno-1 assay (1995–2005) and then to immunoluminometry (2006 onwards). Thus, for comparison between the methods, values were transformed according to our laboratory's instructions. Reference values for children had been previously determined in the same laboratory (Lahdenne et al. 1991c, Lahdenne et al. 1995).

Values higher than the normal 90% (AFP) and 95% (CA 125 and CA 19-9) confidence intervals (CI) were found in 25%, 15%, and 10% of the values, respectively. Thus, for AFP, a cut-off value of 2.5 multiples of the median (MoM) was chosen. MoM for a specific patient is calculated by dividing his/her sample value by the median value in that patient population. Given that median values were not available for CA 125 and CA 19-9, and that values only slightly above the upper limit of 95% CI could not be considered truly pathological, we analyzed these values with the aid of multiples of the upper limits of 95% CI. Values higher than 1.5 times 95% CI were regarded as elevated.

3 Results

3.1 Sacrococcygeal teratoma in Finland (III)

3.1.1 Epidemiology

In our study of all cases with SCT diagnosed in Finland over a 22-year period, we found a total of 124 cases, with a female: male ratio of 4: 1. The pregnancy outcome of the subjects in question is shown in Figure 3 and Table 5. Again, one child died due to massive intraoperative bleeding and disseminated intravascular coagulopathy (DIC). When TOPs, stillbirths and infant deaths were included, the total loss of fetuses and children with SCT was 42% (52/124), and when TOPs were excluded, the total loss was 29% (30/102).

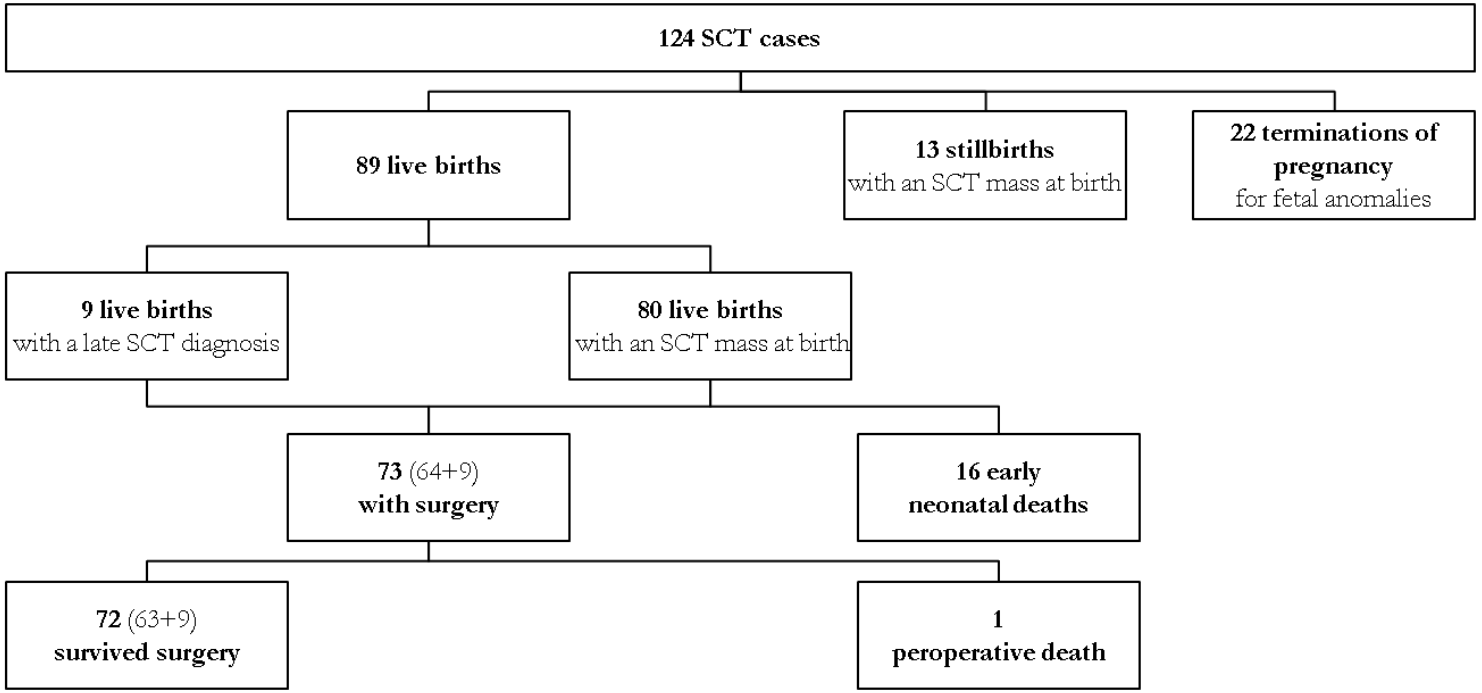

Figure 3. Outcome of SCT in Finland 1986–2008. Reprinted from a publication in Acta Paediatrica (2013), Pauniaho et al, with permission from Wiley (III).

Table 5. Pregnancy outcome of SCT cases (n=124), numbers of cases and their distribution, and gestational age at birth or at termination. Finland 1987-2006.

Outcome	Number of cases (% of females)	%	Mean gestational age; weeks + days
Live births	89 (70)	72	36+6 (range 28+2 to 41+2)
Survivors	73 (56)	(82)	38+0 (range 31+1 to 43+0)
Late diagnoses	9 (7)	(7)	*(diagnosed at 5 mo to 14 yrs of age)*
Perinatal deaths	16 (14)	(13)	31+3(range 28+2 to 35 + 6)
Stillbirths	13 (11)	10	27+2 (range 22+0 to 40+6)
TOPs	22 (20)	18	19+2 (range 13+2 to 23+3)

The total prevalence of SCT (including TOPs and stillbirths) during the study period was 1: 10 700. The birth prevalence was 1: 13 000 and the live birth prevalence 1: 14 900. The prevalence remained stable during the study period. The exclusion of potentially hereditary Currarino cases (n=4) and those diagnosed outside the neonatal period had an effect on prevalence (Table 6).

Table 6. Prevalence values for SCT in Finland, 1987-2008.

	Prevalence
Total (all births and terminations)	1: 10 700
Total, potentially hereditary cases excluded	1: 11 300
All births	1: 13 000
Live births (LB)	1: 14 900
LB, potentially hereditary cases excluded	1: 15 600
LB, late cases excluded	1: 16 600

3.1.2 Associated abnormalities

Associated abnormalities were reported to the FRCM in 38 cases (30%). The most common (16% of all SCT cases) were those related to the urinary tract, for example dilatation (hydronephrosis, hydroureter) or a double renal system. Associated anomalies and conditions are shown in Table 1 in original publication III.

Nine children had either anomaly complexes or syndromes. One child was suspected of having Sotos syndrome, an autosomal dominant disorder with characteristic facial appearance, learning disabilities and childhood overgrowth (Cole, Hughes 1994). Again, three cases with trisomies were detected (18, 13 and 21; one each). Additionally, we found two cases classifiable as OEIS complex (Omphalocele, cloacal Extrophy, Imperforate anus, Spinal defects), a rare anomaly with a prevalence of 1: 250 000 live births (Carey et al. 1978, Keppler-Noreuil et al. 2007). Further there were 4 Currarino cases (see 1.1.3), all detected after the neonatal period. Five children had hypoplastic lungs, with all succumbing during the first day of life.

3.1.3 Antenatal diagnostics and pregnancy outcome

According to the data derived from the FRCM, during the study period of 22 years SCT was diagnosed in an antenatal US scan in 68 cases (55% of all). The rate of prenatal diagnosis improved with time, being 50% in 1987-1994 and 72% in 2001-2008.

During the whole study period, one third of the antenatally diagnosed cases were terminated, on fetal indications (either for SCT or other prenatally detected or suspected anomaly or complex). Of the TOPs, SCT was the only prenatally diagnosed anomaly in 15 (68% of terminations). The rest of the cases terminated included trisomies (n=3) and the two with suspected OEIS.

Of the TOPs with SCT as the only true anomaly in the US scan, 5/15 were reported to be "large" in size, 2/15 to develop polyhydramnion and one fetal hydrops. Five cases carried a description of the echogenity of the tumor, one described as "solid" and four as "cystic".

Fetal hydrops and polyhydramnion were predictors of poor outcome. Of the 10 cases with hydrops, only one fetus (presenting with hydrops at 36 weeks), survived and was born at 38+6. Only one third (5/15) of the SCT cases diagnosed with polyhydramnion survived.

3.2 Malignant GCTs (II)

Between 1969 and 2008, a total of 3015 malignant GCTs were diagnosed in Finland, 2714 in men and 301 in women. When compared to all malignancies diagnosed in Finland, GCTs accounted for 0.7% of all cases in men and 0.08% in women. A male predominance was seen in all age groups (0-14, 15-44 and 45 or older). Extragonadal tumors were rare in both men and women (Figure 4). The main findings in males and females (including children), and children and adolescents separately are discussed below.

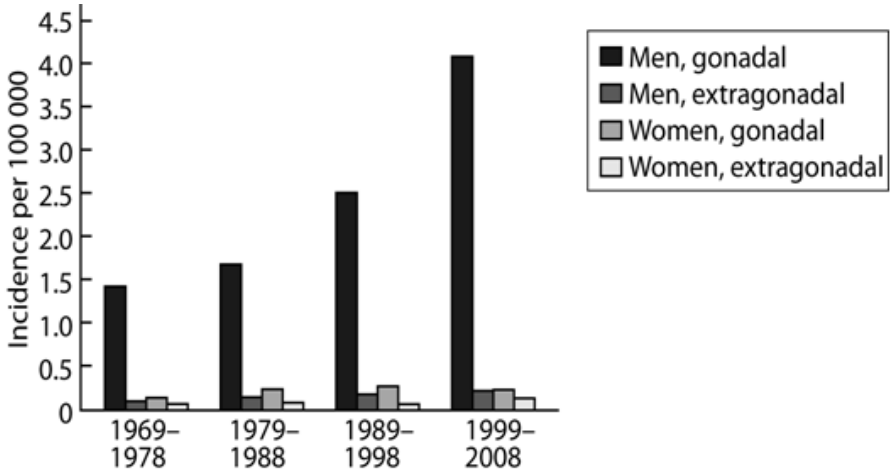

Figure 4. Ten-year average incidence rates of malignant germ cell tumors in gonadal and extragonadal locations in Finland, 1969-2008.

Men

The incidence of malignant GCTs increased significantly over the 40-year time period the increase peaking among those aged 15-44 years (Figure 4).Furthermore, we saw a trend towards an increase in both seminomas and non-seminomas, and by histology in all non-seminoma subgroups. One half of all malignant GCTs were seminomas, and only 6% of all cases (children included) were found in extragonadal locations. Intracranial germinomas were the most common extragonadal location, accounting for one third of all extragonadal cases.

Women

The incidence of malignant GCTs (including children) remained stable during the study period, being 0.34 per 100,000 person years (see Figure 2 in II). The only increase was seen in ovarian non-dysgerminomas. All ages included, the ovary was the most common location. The only subgroup in which female cases outnumbered male was extragonadal GCTs at ages 15 years or less, mainly explained by the higher number of SCTs (discussed in greater detail in 4.2.3). Teratomas and dysgerminomas were the two most common histologies in females.

Children and adolescents

Among children and adolescents (ages 0-19 years), a total of 334 malignant GCTs were found in Finland between 1969 and 2008, 225 in boys and 109 in girls. Of all malignancies in this age group, the proportion of GCTs increased from 3 to 9.7% in boys but remained stable in girls (3%) during the study period. The overall incidence in this age group during the 40-year time period was 0.6 per 100 000, with a significant increase in the proportion of GCTs among all malignancies in boys aged 15-19 years (from 3.8 to 16.3%). In girls and boys 10-19 years old, no such increase was seen.

We saw two age peaks in testicular tumors the in age groups 0-3 years and >15 years. In girls, there was a peak in extragonadal GCTs in the age group 0-1 years, mainly explained by sacrococcygeal tumors (Figure 5). Again in girls, a moderate peak was seen in malignant ovarian GCTs in the age group 11-16 years. Only 3% (n=9) of all cases (both sexes) were seen in the age group 5-9 years throughout the study period.

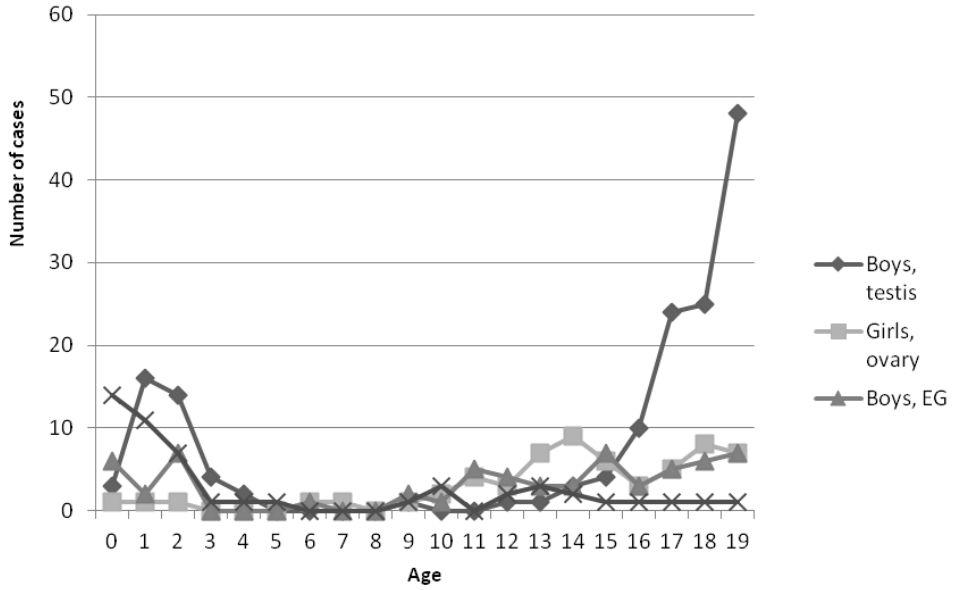

Figure 5. Malignant gonadal (testis and ovary) and extragonadal (EG) germ cell tumors in 0-19-year-olds in Finland 1969-2008.

Histologically, 23% were germinomatous tumors (including seminoma, dysgerminoma and CNS germinoma) and 77% non-germinomas, malignant teratoma/ teratocarcinoma being the most common in both sexes (39% of all cases). Two thirds of all GCTs were found in gonads, and one half of all extragonadal cases were intracranial. Malignant sacrococcygeal tumors were slightly more common in girls than boys (m: f, 1:1.6). Tumors in other locations were rare (n= 19).

Of all cases with stage reported, 57% were stage 1 tumors (local) and 27% were stage 3-4 (spread to distant lymph nodes or to adjacent tissue). The contribution of stage 3-4 disease was slightly higher during the first two study decades (30% vs. 25% respectively). Again when the two time periods were compared, the overall 5-year survival improved from 64% to 91%.

3.3 Tumor markers in the long-term follow-up of SCT

In analysis of serum tumor markers in children with no clinical recurrence during the follow-up, we found an elevated AFP in one third. However, none of these had more than one elevated value, and all were detected during the first 18 months of life. CA 19-9 was elevated in only one without recurrence. CA 125 was not elevated in SCT cases without recurrence.

In the 8 cases involving recurrence (in six children), elevated tumor markers were detected in 5/8 cases prior to recurrence (Table 7). Elevated S-AFP indicated a recurrence in three children. In another case, AFP remained elevated after the first operation and decreased gradually, being normal prior to the recurrence (detected and operated at 2 years 4 months of age). In this particular case, however, CA 125 became elevated prior to the recurrence.

Table 7. Elevated (+) and normal (-) tumor marker values prior to a recurrence of sacrococcygeal teratoma. Children´s Hospital, Helsinki 1985-2006.

Primary tumor	Sex	Age at primary operation	Age at recurrence	Histology of recurrence	AFP	CA125	CA 19-9
MT	F	10 d	8 mo	YST	+	-	-
MT	M	5 d	3y 5 mo	MT	-	+	-
MT	F	0 d	2y 4 mo	MT	-	+	-
MT	F	0 d	9 mo	adenocarcinoma	+	-	-
IT	F	3 d	6 mo	IT	+	+	-
IT	F	1 d	8 mo	IT	-	(+ *)	(+ *)

MT= mature teratoma, IT= immature teratoma, YST= yolk sac tumor
* abnormal value at birth, no other marker values available

The AFP values in relation to the recurrences in the 4 children are shown in Figure 6.

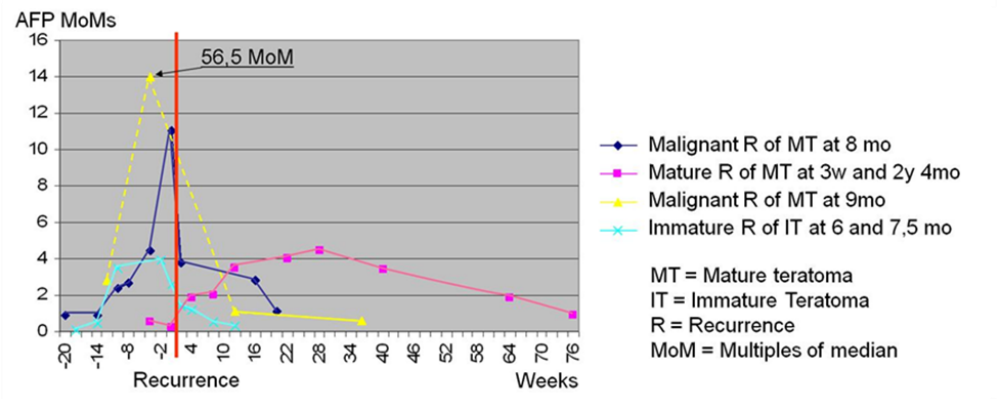

Figure 6. Serum AFP in relation to SCT recurrences. Children´s Hospital, Helsinki 1985–2006.

Only one of the neonatally detected SCT cases had elevated values of both serum AFP and CA 125 prior to a recurrence (see Table 7). Furthermore, in the late-presenting SCT cases only one recurrence was detected, with no marker values available for analysis.

4 Discussion

4.1 Sacrococcygeal teratoma

4.1.1 Determining the prevalence of SCTs: challenges and trends

The frequency of SCTs in a given population remains difficult to establish. Studies reporting the frequency are often based on single-center data, and do not thus necessarily represent the whole of the respective population. Our study used a unique population- and registry-based nationwide data including those succumbing to the disease, and thus enabled us to determine the prevalence of SCT, demonstrating it to be more common than previously reported.

This notwithstandign, SCT lacks a specific diagnostic ICD code, making it difficult to track cases born with the disease. In the present study, we found several different ICD codes in cases reported to the FRCM. In Finland, cases with Q-codes representing congenital malformations are automatically reported by clinicians, whereas others, i.e. D-codes (benign tumors) are not. The strength of the FRCM is that information is received from multiple data sources such as hospitals and cytogenetic laboratories, but also from other well-established Finnish national registers, including the Medical Birth Register, the Register on Induced Abortions and the Care Register for Health Care (HILMO). Thus, FRCM provides reliable and up-to-date information on congenital malformations, as has been ascertained in several studies (Pakkasjarvi et al. 2006, Leoncini et al. 2010).

Another problem in reporting in this context is lack of uniform terminology. The term "incidence" should not be used in SCT or other, congenital malformations occurring during the fetal period since the population at risk is impossible to define with the impact of spontaneous abortions of affected fetuses. Excluding these would result in underestimation of the frequency (Mason et al. 2005). The term "prevalence", in contrast, uses a specific time point or period, and can thus be compared to the population at risk (e.g. live births, stillbirths and all births). The historically used and even currently commonly referred low "incidence" numbers (1:35 000 to 1:40 000) (Pantoja, Lopez 1978, Isaacs 1997,

Skinner 1997) cannot be directly compared to the more recently used "prevalence" numbers. It is thus fair to assume that the old "incidence" rates, if reported as prevalence, would also be higher.

In the current study we demonstrated the prevalence of SCT in Finland to be higher than elsewhere (Forrester, Merz 2006, Swamy et al. 2008). It can, however, possibly be even higher. Since our prevalence study reporting from clinics to the FRCM has further improved on the national level, and some additional cases have already been found in the register and verified as SCTs from hospital records (Annukka Ritvanen, personal communication). Inclusion of SCT in its different forms in future editions of the WHO ICD system would be of key importance, and would greatly facilitate further epidemiologic research.

4.1.2 Pregnancy outcome: impact of prenatal diagnostics and histopathological features

Given the obvious features of SCT the diagnosis should be made prenatally. Provision of a two-step prenatal screening system has been mandatory in Finland since 2010. The screening consists of a first-trimester US (between 10+0 and 11+6 weeks of pregnancy) and a second for the detection of severe anomalies (between weeks 18+0 and 21+6 or optionally, after 24+0 weeks). These screening scans are currently performed by a variety of health care professionals, for example general practitioners, midwives and gynecologists in a variety of units (health centers, obstetrics clinics in central and university hospitals and private clinics).

Variation in data obtained by the FRCM from clinicians account for some limitations to our study. Some hospital records included data on prenatal diagnostics while others did not. Hence, the actual prenatal detection rate may be higher than that reported. We did, however, see a trend towards an increase in the detection rate during the study period.

Another handicap from the researchers' point of view was encountered in reporting histopathological findings as mature or immature cellular features were reported in only a minority of the cases. We could thus draw no conclusions as to the impact of histology on pregnancy outcome. However, it has recently been reported that immature histology at the time of primary surgery is associated with a significantly higher mortality (Yoneda et al. 2013). In this study reporting the histological type of 84 prenatally detected SCT cases immature teratomas were significantly larger in size at delivery and more rapidly growing, necessitating

cesarean section more often. Again, solid component-dominant tumors are more likely to be immature (Yoneda et al. 2013). In the same study, immature histology was also related to a higher rate of perinatal complications (lower Apgar scores, greater blood loss during surgery, more need for cardiac resuscitation, more postoperative DIC and IC hemorrhage).

4.1.3 Factors related to survival and challenges in prenatal counseling

The rate of terminations on fetal indications in cases with SCT in Finland is surprisingly high, and the corresponding data from elsewhere are largely lacking. Finnish law on induced abortion allows the termination of pregnancy for severe or significant fetal abnormality up to 24+0 weeks of gestation. Even though the law is restrictive, interpretation is liberal. During the study period 1986-2008, one third of all antenatally diagnosed cases were terminated with SCT as the only prenatally detected anomaly in 68%. Nonetheless, 28% of the remainder were either stillborn or succumbed perinatally.

Only 5-6 SCT cases are detected in Finland annually, and identifying those with a high risk of poor outcome remains challenging. Thus, all cases detected should be centralized to tertiary facilities with sufficient means for prenatal diagnostics and counseling. According to the current literature, elective cesarean section after 36 weeks of pregnancy is recommended for low-risk cases (Vrecenak, Flake 2013). However, high-risk cases (active preterm labor, maternal mirror syndrome or placentomegaly) may require an early delivery by emergency caesarean (> 27 weeks) (Vrecenak, Flake 2013). In one large study of prenatally detected SCTs in Japan, 38% of cases had an emergency cesarean (Usui et al. 2012). Thus, the hospital should also have the means for an emergency operation on newborns. Early delivery with an EXIT procedure (see 2.1.5) may be a treatment option should there be no maternal or placental compromise (Vrecenak, Flake 2013).

In most tertiary centers in Europe and Finland, pediatric surgeons are giving antenatal counseling to families with a suspected SCT pregnancy. Optimally, the family should always meet the surgeon before the decision on a possible termination is made. Fetal surgery is currently not being performed on a clinical scale in any European pediatric surgical center, this in view of associated high mortality and morbidity, nor is it likely to be a treatment option in Finland in the near future.

4.2 Malignant germ cell tumors

4.2.1 Histological classification and locations of GCTs

The distribution of GCTs in different topographical locations in this study is in line with the current literature in this field, in both the pediatric and adult populations (Schneider et al. 2004). As discussed in the present and previous original publications, minor differences can be explained by differences in registration and methodology (e.g. inclusion or exclusion of placenta as location). Again, the classification of "mixed-type" GCTs was not similar in all cases studied, and can thus lead to misinterpretation between populations. In the WHO classification, the histology "teratocarcinoma" is defined as a mixture of embryonal carcinoma and teratoma, and "mixed germ cell tumor" includes mixed teratoma and seminoma. It is, however, likely that in clinical use the term "mixed GCT" is applied more liberally.

Gonads (testis and ovary) were the most common locations in both sexes. In the pediatric population, there were distinct differences by age in tumor location and histology. Intracranial GCTS were the most common in teenagers and young adults.

Table 8 summarizes the typical histologies and locations of malignant GCTs in different age groups in males and females, based on the findings of a recent large population-based study from England (Arora et al. 2012) and on our study material.

Table 8. Summary of typical locations and histologies of malignant germ cell tumors according to register-based studies in England (1979-2003, Arora 2012) and Finland (1969-2008, publications II and IV).

Age group	Sex	Common locations	Common histologies	Specific comments
Neonates and children <10 years	Boys	Testicular 77%	(Non-seminomas) Teratomas Yolk sac tumors	Extremely rare at ages 5 to 9 years No GCTs in CNS (#)
	Girls	Extragonadal 80% (mainly sacrococcygeal)		
Teenagers 10-20 years	Boys	Testis CNS	CNS germinomas more common than non-germinomas	Typical age group for CNS GCTs
	Girls	Ovary CNS	Non-dysgerminoma Germinoma	
Adults, 20-50 years	Men	Testis CNS Mediastinum	Seminoma 50 % (#) Germinoma	
	Women	Ovary (CNS *)		No GCTs in CNS (#)
All ages	Men	Testis > 90%	Seminoma 56% Non-seminoma 30% Other	
	Women	Ovary >80%	Non-dysgerminoma 64% Dysgerminoma 33%	
YST= yolk sac tumor; CNS= central nervous system; GCT= germ cell tumor Data on the English (*) and Finnish (#) populations				

4.2.2 Incidence and time trends in malignant GCTs

Epidemiological data on malignant GCTs remain limited and based on only a few published reports. Thus, our population-based nationwide study, including essentially all cases of malignant GCTs in Finland over four decades, adds significantly to the data. The results of our epidemiological studies on malignant GCTs were in line with those published in Germany (Gobel et al. 2000), and more recently in England (Arora et al. 2012). However, there were dissimilarities, possibly explained by differences in registration and classification. For example in Germany has no nationwide register covering all cases with cancer and all age groups (like the Finnish Cancer Registry), and furthermore, some children are treated by urologists rather than pediatric surgeons (Gobel et al. 2000). Such patients are not automatically reported to pediatric cancer registries. Thus, our nationwide material, even if limited in numbers, gives valuable information even from an international perspective.

The incidence of malignant TGCTs has been studied intensively during the last few years. The incidence is high and on the increase, particularly in Northern Europe. Men in Scandinavia (especially Denmark and Norway) seem to have 5-10 time higher incidences than populations in Africa and Asia (McGlynn, Cook 2009). While the incidence in Finland has in fact been lower than in the other Nordic countries, Finland seems to be "catching up". The reasons for these trends are largely unknown. Nevertheless, simultaneous and rapidly increasing trends in both testicular germ cell tumors and impaired semen quality suggest the underlying causes to be of environmental and thus preventable origin. Hence, further research to detect and eliminate possible causative environmental factors is warranted. The increase in malignant GCTs can already be demonstrated in the adolescent population, and the proportion among all malignancies is increasing in both the pediatric and adolescent population.

The increase in the incidence of testicular cancer has been suggested to be a birth cohort phenomenon (Bergstrom et al. 1996). A birth cohort comprises all people born at the same, specified time period, e.g. one year. The lengthy history of cancer registration in the Nordic countries enables the use of more advanced statistical methodology. When age, period and birth cohort are all taken into account (the so-called age-period-cohort-model), more detailed information can be obtained than by comparing simple time trends (Clayton, Schifflers 1987a, Clayton,

Schifflers 1987b). It has been shown in several countries in Northern Europe that birth cohort is a more important determinant in testicular cancer incidence than time period (Bergstrom et al. 1996, Verhoeven et al. 2008, Myrup et al. 2010). In Australia, the birth cohort effect has been shown in non-seminomas (Baade et al. 2008). Here, we found a birth cohort effect in testicular cancer but not in other GCT groups, numbers being too small for birth cohort analyses. In the future, these findings can help in identifying possible underlying causes, e.g. environmental exposures responsible.

Several pre-and postnatal risk factors have been postulated to be associated with GCTs, mainly testicular cancer (McGlynn, Cook 2009). In our population-based study, decreasing parity is the only pregnancy-related risk factor seemingly linked to the increasing TGCTs at population level.

Malignant GCTs in ovarian and extragonadal locations and children in general are rare, making clinical research on childhood GCTs difficult. As the Nordic countries have high-quality cancer registers, inter-state collaboration to study trends in incidence in GCT subgroups (e.g. pediatric) could possibly promote understanding of the possible etiological factors of these rare tumors

4.3 Following up SCT cases using prognostic tumor markers: opportunities and limitations

The possible risk of recurrence makes the follow-up of these patients important. Serum markers should be determined before surgery as reference for future follow-up, including cases with a delayed diagnosis (late presentation, intrapelvic cases). The recommendations suggest that patients with SCT be systematically followed-up for at least the first three years of life (Hawkins et al. 1993, De Corti et al. 2012). Among the present neonatally detected treated cases, 6 out of 8 recurrences were detected during the first year of life. However, one child in our series had a recurrence at 3 years 5 months of age, and recurrences even up to teenage have been found (Professor Risto Rintala, personal communication). Again, long-term functional sequelae (mainly urological and anorectal) have been described in 30-50% of cases (Derikx et al. 2007) Again, scar and appearance-related issues may require attention and even evaluation by a plastic surgeon. Thus, for the above-mentioned reasons, annual follow-up visits to a pediatric surgical outpatient clinic up to teenage years (until the end of growth) are recommended.

In addition to the clinical findings and imaging, tumor markers have been used to detect possible recurrences or residual tumors (Laberge et al. 2010). Elevated marker values noted during follow-up visits should raise a suspicion of recurrence, justifying a more judicious follow-up and/or imaging (i.e. MRI imaging).

The reported use of AFP in the follow-up of SCT (Lahdenne et al. 1991c, Lahdenne, Heikinheimo 2002, Mann et al. 2008) was also deemed beneficial in the present context. In addition to this, we found that CA 125 can be a useful adjunct to AFP. Serum CA 19-9, in contrast, was not found useful.

This notwithstanding, our tumor marker study had some limitations. The main drawback was the small number of cases and, in particular, the low rate of recurrences. Again, changes in methodology over the study period were unexpected and caused difficulties in analyses.

The reported recommendations for the follow-up of SCT and malignant SC tumors include only AFP, mainly for early detection of a yolk sac recurrence (Mann et al. 2008). In light of our limited experience, we would recommend CA 125 in addition to AFP during all out-patient clinic visits.

Summary and conclusions

This study constitutes a comprehensive analysis of germ cell tumors (mainly SCTs and malignant GCTs), including the prevalence, biological, clinical and epidemiological features of these rare neoplasms.

Our register-based study (III) showed the prevalence of SCT in Finland to be markedly higher than that reported for other countries. Nearly one third of cases have concomitant abnormalities, most commonly in the urinary tract and also various syndromes. The antenatal detection rate has increased during the last 20 years. Nevertheless, early detection of SCT, especially cases with a poor prognosis, along with appropriate management, remains challenging. The high mortality detected has an impact on the counseling of families and planning of deliveries.

In the epidemiological study (II) we demonstrated that malignant GCTs in Finland are 7.6 times more common in males than in females. Specifically, a constant and significant increase was seen in men between 15 and 44 years of age over a 40-year time period. In contrast, we saw no change in the incidence of gonadal GCTs in boys under 15 years and men over 45 years of age. In women, no such change was seen. The distribution of morphologies differed between males and females. The differences noted in the GCT incidence between men and women suggest that the risk factors differ between the sexes.

Focusing on malignant GCTs in the pediatric and adolescent population (IV), we described the histological and gender distribution and distribution into gonadal and extragonadal tumors at different ages. Despite being a rare group among all malignancies, the relative frequency of GCTs has increased during the last four decades, mainly due to an increasing number of TGCTs in teenagers, this possibly attributable to a host of environmental exposures. The overall survival improved from 64% to 91% during the study period, reflecting positive developments in surgery, chemotherapy and supportive care.

Finally, our tumor marker study (I) showed the role of multiple markers in the follow-up of SCT to be limited. The role of AFP in detection of GCT recurrences is well established, and this was also demonstrated in our study. Additionally, we detected elevated serum CA 125 values indicating non-malignant SCT recurrences. Hence, we now routinely monitor both AFP and CA 125 during follow-up.

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Appendix

Appendix 1. Germ Cell and Trophoblastic Neoplasms. ICD-O-3, WHO 2000.

906-909 GERM CELL NEOPLASMS
9060/3 Dysgerminoma
9061/3 Seminoma, NOS (C62._)
9062/3 Seminoma, anaplastic (C62._)
Seminoma with high mitotic index (C62._)
9063/3 Spermatocytic seminoma (C62._)
Spermatocytoma (C62._)
9064/2 Intratubular malignant germ cells (C62._)
Intratubular germ cell neoplasia (C62._)
9064/3 Germinoma
Germ cell tumor, NOS
9065/3 Germ cell tumor, nonseminomatous (C62._)
9070/3 Embryonal carcinoma, NOS
Embryonal adenocarcinoma
9071/3 Yolk sac tumor
Endodermal sinus tumor
Polyvesicular vitelline tumor
Orchioblastoma (C62._)
Embryonal carcinoma, infantile
Hepatoid yolk sac tumor
9072/3 Polyembryoma
Embryonal carcinoma, polyembryonal type
9073/1 Gonadoblastoma
Gonocytoma
9080/0 Teratoma, benign
Adult cystic teratoma
Adult teratoma, NOS
Cystic teratoma, NOS
Teratoma, differentiated
Mature teratoma
9080/1 Teratoma, NOS
Solid teratoma
9080/3 Teratoma, malignant, NOS

Embryonal teratoma
Teratoblastoma, malignant
Immature teratoma, malignant
Immature teratoma, NOS
9081/3 Teratocarcinoma
Mixed embryonal carcinoma and teratoma
9082/3 Malignant teratoma, undifferentiated
Malignant teratoma, anaplastic
9083/3 Malignant teratoma, intermediate
9084/0 Dermoid cyst, NOS
Dermoid, NOS
9084/3 Teratoma with malignant transformation
Dermoid cyst with malignant transformation (C56.9)
Dermoid cyst with secondary tumor
9085/3 Mixed germ cell tumor
Mixed teratoma and seminoma
9090/0 Struma ovarii, NOS (C56.9)
9090/3 Struma ovarii, malignant (C56.9)
9091/1 Strumal carcinoid (C56.9)
Struma ovarii and carcinoid (C56.9)

910 TROPHOBLASTIC NEOPLASMS
9100/0 Hydatidiform mole, NOS (C58.9)
Hydatid mole (C58.9)
Complete hydatidiform mole (C58.9)
9100/1 Invasive hydatidiform mole (C58.9)
Chorioadenoma destruens (C58.9)
Chorioadenoma (C58.9)
Invasive mole, NOS (C58.9)
Malignant hydatidiform mole (C58.9)
9100/3 Choriocarcinoma, NOS
Chorionepithelioma
Chorioepithelioma
9101/3 Choriocarcinoma combined with other germ cell elements
Choriocarcinoma combined with teratoma
Choriocarcinoma combined with
embryonal carcinoma
9102/3 Malignant teratoma, trophoblastic
9103/0 Partial hydatidiform mole (C58.9)
9104/1 Placental site trophoblastic tumor (C58.9)
9105/3 Trophoblastic tumor, epithelioid

Appendix 2

HYKS Lastenklinikka; SAKROKOKKYGEAALISET TERATOMAT- SEURANTAOHJELMA

Seuraava seurantaohjelma on luotu koska vastasyntyneen benigneissä sakrokokkygeaalisissa teratoomissa on n. 5-10 % malignisoitumisriski. Maligniteetti (yolk sac-tuumori) esiintyy pakaroiden/lantion alueella. Tiedossa olevat malignisoitumiset ovat tapahtuneet 10 kk – 1v 8 kk iässä

Tilaus-numero		0 (oper)	1	2	3	4	6	8	12	18	24
	Kliininen tutkimus	X	X	X	X	X	X	jne.			
1040	**S-AFP** (HY, Sero-bakteriologian laitos tai mm. KYS, OYKS) A: ennenaikaiset (<35 gv) *viitealue (µg/l)* B: täysiaikaiset	X A:<335000 B:<44000	X <66000 <4000	X <37000 <400	X <10000 <240	X <620 <130	X <170 <70	jne. <80 <35	<33 <17	<10 <10	jne jne.
4235	**S-HCG-Beta** *viitealue (µg/l)*	X <5	X <5	X <5	X <5	X <5	X <5	jne. <5 jne.		**Seuranta jatkuu 24 kk jälkeen 6 kk välein 4 v ikään, ja sen jälkeen 1-2 v:n välein lastenkir pkl:lla**	
3412 3414	**S-CA 19-9** *viitealue (µg/l)* **S-CA 125** *viitealue (µg/l)*	X	X	X	X	X	X	jne.			
	1-2 ml seerumia syväjäähän (Heikinheimo)										
	Vatsan ja lantion alueen UÄ		X			X		X	X	X	x

* Mikäli jokin parametri viitealueen ulkopuolella, konsultoidaan ao. yliopistosairaalan lastenhematologia/ Tiedustelut myös Markku Heikinheimo, HYKS, Lastenklinikka, puh. 90–4711 tai Stenbäckinkatu 11, 00290 Helsinki (AFP:n kohdalla U/ml-arvo saadaan jakamalla µg/l-arvo 1.09:llä)

5/86 MH/JR/MS/IL
12/89 MH/PL/MS//RR/HIL

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RESEARCH ARTICLE

Tumor markers AFP, CA 125, and CA 19-9 in the long-term follow-up of sacrococcygeal teratomas in infancy and childhood

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Abstract Given the tendency of a proportion of sacrococcygeal teratomas (SCT) to recur, we evaluated whether serial tumor marker measurements are helpful in the management of these children. Between 1985 and 2006, 32 children with SCT were followed up for 1–15 years, and a total of 344, 197, and 193 serial samples for serum alpha-fetoprotein (AFP), CA 125, and CA 19-9 were analyzed, respectively. Six children with neonatal SCT developed eight recurrences. Serum AFP was elevated in two of two children prior to diagnosis of malignant recurrences (yolk sac tumor and adenocarcinoma), and CA 125 was elevated in one third of mature and one third of immature recurrences. CA 19-9 remained within reference values in relation to recurrences of neonatal SCT. Taken together, serum CA 125 measurements may complement the use of serum AFP in the follow-up of SCT.

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Keywords Tumor markers · AFP · CA 125 · and CA 19-9

Introduction

Sacrococcygeal teratoma (SCT) is the most common neonatal tumor (1:35,000 to 40,000 live births) [1, 2]. Recurrent tumors occur in 4%–21% of SCTs, at least 50% of them being malignant yolk sac tumors [3]. Malignant SCTs in older infants and toddlers tend to be more subtle in presentation with predominantly presacral location prior to recognition of the tumor, and most have advanced-stage disease at diagnosis [4].

Tumor markers are developmentally regulated proteins or carbohydrate molecules that can be produced in low quantities by normal cells but which are secreted in larger quantities into the bloodstream by certain tumors or by the host in response to cancer [5]. Alpha-fetoprotein (AFP) has been used as a tumor marker for malignant germ cell tumors and malignant relapses of SCT (reviewed in [5]) in children. Serum CA 125 and CA 19-9 are elevated in a variety of malignancies in adults [6–8], but only little is known of their biology during infancy. They have, however, been suggested to be useful adjuncts in the follow-up of immature teratomas (IT) [9].

Tumor markers are potentially helpful in screening, determining diagnosis and prognosis, assessing response to therapy, and monitoring cancer recurrence. However, it has not been critically evaluated whether a long-term follow-up including serial tumor marker measurements is helpful in the management of SCT patients, and especially in detecting recurrences. We therefore instituted a follow-up program (with regular physical examinations, serum tumor marker measurements, and ultrasound up to a minimum of

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5 years from the diagnosis including essentially all SCT cases in a tertiary pediatric surgical center covering a population of over 1 million. Considering that an earlier study from our hospital suggested that serum CA 125 and CA 19-9 may be useful in the follow-up of immature teratomas [9] and that AFP is a known marker for malignant yolk sac tumor, the most common malignant recurrence in childhood SCT (reviewed in [5]), we serially measured serum CA 125, CA 19-9, and AFP in SCT patients.

Patients and methods

Thirty-three children underwent treatment for SCT at our institution between 1985 and 2006 and are included in this study. We divided them into two subgroups according to the age at diagnosis:

1. *Neonates* (diagnosis made antenatally or at birth), $n=25$.

Of these, 18 of 25 were mature teratomas (MT); and 6 of 25, ITs. One child had a malignant tumor (Wilms' tumor) within an MT. These children underwent our follow-up scheme with clinical evaluation and tumor marker samples (at 1, 2, 4, 6, 8, 12, 18, and 24 months, thereafter annually). If either the clinical evaluation or marker values suggested a recurrence, an ultrasound followed by computed tomography or magnetic resonance imaging (MRI), when indicated, were performed. Six children (five girls and one boy) developed eight recurrences (two malignant, three mature, and three immature). The mean length of follow-up was 7 years (range, 1–15 years).

2. *Late occurrences* (diagnosis made between 4 months and 14 years of age), n=8.

Seven of these were MTs, and one was IT. Six of these eight children were diagnosed to have Currarino syndrome including presacral teratoma, funnel anus, and sacral defects [10]. Only one child with primary MT at 14 years of age had a mature recurrence (3 years postoperatively). The mean length of follow-up was 8 years (range, 3–14 years).

Serum samples and tumor marker measurements

During the first 5 years of follow-up serum AFP (S-AFP), CA 125, and CA 19-9 were measured in an average of 81%, 64%, and 65% of the patients at each visit.

The average amount obtained from each child for S-AFP analyses was 16 samples (range, 1–56) and, for CA 125 and CA 19-9, 10 samples (range, 1–21). S-AFP was evaluated with immunofluorometry throughout the study period. The evaluation methods for CA 125 and CA 19-9 were, before 1995, immunoradiometric assay; in 1995–2005, Immuno-1 assay; and from 2006 onwards, immunoluminometry (Abbott i2000 Architect, Illinois, USA). For comparison of the values of CA 125 and CA 19-9 that were obtained with the different methods, the values were transformed according to our laboratory's instructions based on comparisons between the methods.

We used the reference values for children determined earlier in the same laboratory [9, 10]. Values higher than the normal 90% (AFP) and 95% (CA 125 and CA 19-9) confidence interval (CI) were found in 25%, 15%, and 10% of all the values, respectively. Thus, for AFP, a cutoff value of 2.5 multiples of median (MoM) was chosen as this has been used in previous studies [11, 12]. Given that median values were not available for CA 125 and CA 19-9 and that values only slightly above the upper limit of 95% CI could not be considered truly pathological, we analyzed these values with the aid of multiples of the upper limits of 95% CI. Values higher than 1.5 times 95% CI were regarded elevated.

Results

Neonates, without recurrence

AFP was elevated (mean, 3.3 MoM; range, 2.8–5.5) in one third (33%) of all children without recurrence (5/14 of MTs and 1/4 of ITs) during the first 3–18 months of life (Table 1). None of these children had any abnormal values after 18 months of age. CA 19-9 values were elevated (mean, 5.2 times the upper 95% CI) in only one child with a giant IT without recurrence, between 1.5 and 3 years of age. CA 125 was not elevated in any of these children. The only child with malignant primary tumor (Wilms' tumor within a mature teratoma) had normal serum AFP, CA 125, and CA 19-9 values and no recurrence during the 4-year follow-up.

Neonates with recurrence

Recurrences of primary MT

Serum AFP was clearly increased in two of two SCT patients with malignant recurrences of primary MT (yolk sac tumor, 2.8–56.5 MoM and adenocarcinoma, 2.6–11.0 MoM). The first elevation was detected at 3 and 2 months prior to the diagnosis of the recurrence, respectively.

One child with two mature recurrences (at 3 weeks and 2 years 4 months) of MT had elevated serum CA 125 6 months and 2 weeks before the second reoperation. The other child with a mature recurrence (at 3 years 5 months) of MT was lost to follow-up.

Table 1 Normal versus elevated tumor marker values in neonates with SCT and no recurrence

Histology	Sex	Age at operation	Follow-up (years)	Elevated/all samples		
	F/M			AFP	CA 125	CA 19-9
Mature teratoma (MT)						
1	M	1 day	8.5	0/7	0/4	0/4
2	F	6 days	4	0/13	0/11	0/11
3	F	2 weeks	4	0/12	0/11	0/11
4	M	3 days	6	1/14	0/12	0/11
5	F	1 day	15	0/10	0/4	0/3
6	M	1 day	9	0/18	0/17	0/15
7	F	12 days	14	1/36	0/2	0/2
8	M	0 day	7	0/15	0/12	0/11
9	F	1 day	2.5	1/12	0/10	0/10
10	M	0 day	7	0/3	0/3	0/3
11	F	6 days	3	1/11	0/12	0/12
12	F	4 days	0.7	0/6	0/6	0/6
13	F	4 days	7	0/19	0/15	0/15
14	F	1 week	2	1/11	0/9	0/9
MT: patients with elevated values/all patients (%)				5/14 (36%)	0/14	0/14
MT: elevated values/all samples (%)				5/187 (2.7%)	0/128	0/123
Immature teratoma (IT)						
15	F	3 days	10.5	0/7	0/4	4/21
16	F	1 day	2.5	1/11	0/10	0/9
15	M	0 day	2.5	0/11	0/10	0/10
18	F	1 day	8	0/12	0/8	0/9
IT: patients with elevated values/all patients (%)				1/4 (25%)	0/18	1/18
IT: elevated values/all samples (%)				1/41 (2.4%)	0/50	4/67

AFP: values > 2.5 MoM (multiples of median) are regarded elevated. CA 125 and CA 19-9: values > 1.5 times 95% CI are regarded elevated

Recurrences of primary IT

One neonate with an immature recurrence of IT (at 8 months) had elevated serum CA 19-9 and CA 125 at birth, all other values being normal. The other child with two immature recurrences (at 6 and 7.5 months) of IT had an elevated AFP (3.5 MoM) 2 months and elevated CA 125 1 week prior to the diagnosis of the first recurrence, but there were no values available between 6 and 7.5 months.

Late presentations

Due to the fact that 6 of 8 of the late occurring SCT's were diagnosed after 1 year of age, most of these children lacked systematic tumor marker follow-up. Only 1 of 8 had a recurrence (primary MT at 14 years and mature recurrence at 17 year). However, the only marker values from this patient are post-recurrence AFPs that were normal. One child with Currarino syndrome and MT (4 months) had elevated CA 19-9 preoperatively (4.5 times 95% CI), all other values being normal. Another child with IT (diagnosis at 11 months) had two marginally elevated (two times 95% CI) CA 19-9 values postoperatively.

Discussion

The need for careful follow-up of the SCT patients has been emphasized based on the tendency of SCTs to recur. Especially immature teratomas have increased incidence of local recurrence and malignant degeneration. Recurrences are often malignant [13]. Even though long-term follow-up studies in the management of SCT have been reported [14, 15], experience in tumor marker follow-up has been limited to the use of serum AFP [10, 16]. However, several other potential serum markers have been recognized [5]. We therefore instituted a long-term follow-up including serial measurements of serum tumor markers CA 125, CA 19-9, and AFP.

Our results revealed that serum AFP was elevated in two of two SCT patients with malignant recurrences at 2 and 3 months prior to the diagnosis of recurrence. Both of these children had primary MT. Although we found elevated S-AFP values in one third of children without recurrence during the early follow-up, only 2.5% of all AFP values in this group were abnormal when the entire follow-up period was taken into account. None of these children had more than one elevated value, and they were all detected during

the first 18 months of age. This may be related to the relatively wide reference range of S-AFP during the first year of life.

In addition to the traditional yolk sac tumor marker AFP, we wanted to evaluate the usefulness of two other known tumor markers, serum CA 125 and CA 19-9, in the follow-up of SCT. These carbohydrate markers are recognized by monoclonal antibodies and are present in elevated concentrations in several malignant and non-malignant conditions [6–8]. CA 19-9 is a widely used tumor marker in adult gastrointestinal cancer [8], but its use in pediatric patients is limited. CA 125 antigen is most consistently present in epithelial ovarian cancer, but this marker can be expressed in a number of other gynecologic (endometrial, fallopian tube, and ovarian germ cell) and non-gynecologic (pancreatic, breast, colon, and lung) cancers as well as in non-malignant conditions such as endometriosis [6, 7, 17]. In clinical practice, serum CA 125 assays are most of all used in monitoring ovarian cancer [6, 7]. In children, serum CA 125 levels are often elevated in children with veno-occlusive disease after bone marrow transplantation [18]. Our earlier results encouraged us now to evaluate the usefulness of serum CA 125 as well as CA 19-9 in the follow-up of children with sacrococcygeal teratomas [9]. In the present study, we found that CA 125 level was elevated in one of three of the mature and one of three of the immature recurrences. Notably, only one of these cases was associated with elevated serum AFP levels. Therefore, CA 125 may offer an additional tool for the detection of non-malignant recurrences of neonatal SCT. Serum CA 19-9 was not elevated in relation to any of the recurrences except in one case with a late presentation and is unlikely to help in neonatal SCT follow-up.

There are no reports on the use of MRI or ultrasound as to their ability to detect SCT recurrences, although both methods are to our understanding applied in the follow-up of children with SCT. We used ultrasound follow-up as a routine method, and S-CA 125 elevations were seen at a point when ultrasound did not reveal abnormal findings. These results have to be, however, interpreted with caution given the low number of recurrences in our patients. If future studies confirm that elevated S-CA 125 is a sensitive and early indicator of a SCT recurrence, the more expensive imaging studies during the follow-up of SCT may be unnecessary.

Our follow-up program covered a single institution series of virtually all patients during more than 20 years, and an advantage in our study is this long follow-up time with many serial samples. Given that SCT is an uncommon tumor, the number of cases remains, however, limited. SCT recurrences remain a clinical challenge and more cases with recurrences should be analyzed to establish the value of new serum markers, such as CA 125, in their management (Table 2).

Table 2 Tumor marker values in relation to SCT recurrences

Primary tumor	Sex	Age at primary operation	Age at recurrence	Histology of recurrence	Values pre/post recurrence	Elevated/all samples		
						AFP	CA 125	CA 19-9
MT	F	10 days	8 months	Malignant; yolk sac	Pre	2/2	–	–
					Post	0/54	0/8	0/6
MT	M	5 days	3 years 5 months	MT	Pre	0/7	1/1	–
					Post	–	–	–
MT	F	0 day	3 weeks	MT	Pre	0/1	0/0	0/1
			2 years 4 months	MT	Pre	5/10	3/10	0/10
					Post	0/16	0/11	0/11
MT	F	0 day	9 months	Malignant; adenocarcinoma	Pre	2/2	0/0	0/0
					post	0/19	0/7	0/9
IT	F	3 days	6 months	IT	Pre	2/5	1/3	0/3
			7.5 months	IT	Pre	0/1	–	–
					Post	0/28	0/17	0/18
IT	F	1 day	8 months	IT	Pre	0/1	1/1[a]	1/1[a]
					Post	0/12	0/11	0/11
Recurrences: patients with elevated values/all patients						4/6	4/6	1/6
Recurrences: elevated values/all samples (%)						13/157	6/69	1/70

For AFP, values>2.5 MoM (multiples of median) are regarded elevated CA 125, and for CA 19-9, values > 1.5 times 95% CI are regarded elevated

[a] Abnormal value at birth

In conclusion, the value of multiple serum markers in the follow-up of SCT is limited. Serial serum AFP samples at follow-up visits are, however, recommended to detect malignant recurrences. In addition, elevated serum CA 125 may indicate non-malignant recurrences. Therefore, we have adopted a routine to monitor these two markers during the SCT follow-up up to 5 years from diagnosis.

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ORIGINAL PAPER

The incidences of malignant gonadal and extragonadal germ cell tumors in males and females: a population-based study covering over 40 years in Finland

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Abstract
Purpose Germ cell tumors (GCTs) comprise a heterogeneous group of tumors derived from primordial germ cells. The incidence of malignant testicular GCTs has increased in recent decades, but little is known about possible changes in malignant female GCTs. Population-based data covering all malignant GCTs in both sexes remain limited.
Methods All cases of malignant GCTs in 1969–2008 were collected from the Finnish Cancer Registry and their age-adjusted annual incidences calculated.
Results The overall incidence of malignant GCTs was 2.56 per 100,000 person-years in males and 0.34 per 100,000 in females. The incidence of gonadal GCTs increased from 2.27 to 8.36 per 100,000 in males between 15 and 44 years of age. Moreover, the incidence of all histological subtypes of gonadal GCTs increased in males. In females, the only increase was seen in the incidence of ovarian non-dysgerminoma (from 0.07 to 0.29/100,000). The incidence of extragonadal GCTs did not change during the study period, being 0.18 and 0.10 per 100,000 in males and females, respectively.
Conclusions The incidence of gonadal GCTs in males increased significantly during the 40-year study period, whereas in females, no such change was observed. There were significant gender differences regarding the distribution of histological subtypes and patients' ages. However, the incidence of extragonadal GCTs remained low in both sexes. The differences in the incidences of gonadal GCTs derived from the same population suggest that the risk factors of these malignancies differ between the two sexes.

Keywords Extragonadal germ cell tumor · Germ cell tumor · Incidence · Malignant · Ovary · Testis

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Introduction

Germ cell tumors (GCTs) are a heterogeneous group of tumors sharing a common origin, the primordial germ cell. However, their histological, biological, and clinical presentations vary markedly. Data on malignant GCTs in children and adolescents [1], as well as on specific GCT subtypes and locations, such as the testis or ovary [2–4], have been published. These studies, however, have included only cases of a particular age group, gender, site of origin or histology. There is only one population-based report on both female and male GCTs including all locations [5] and one including

both gonadal GCTs [6]. Additionally, a recent register study concerned comparison of incidence trends of gonadal and extragonadal germ cell tumors in both sexes [7].

The overall incidence of GCTs in females is high as a result of the considerable number of benign GCTs, such as ovarian dermoid tumors and teratomas. In contrast, males have been reported to have more malignant GCTs [6]. Malignant GCTs comprise approximately 95 % of all testicular cancers, but less than 5 % of all ovarian malignancies [8]. An increasing incidence of malignant testicular GCTs has been noted during the last few decades in industrialized countries [9, 10]. In Finland, the incidence rate of GCTs has been found to increase 131 % between 1973–1977 and 1998–2002 [11]. Moreover, the annual increase in GCT incidence was 3.8 %, 1953–1990, and 4.6 %, 1990–1999 [12]. However, less is known about potential developments in the incidence of malignant ovarian GCTs [4, 13].

Cryptorchidism and contralateral testicular and familial testicular GCTs are well-established risk factors of malignant testicular GCTs [14]. Testicular cancer and other male reproductive maladies including impaired semen quality have been suggested to be linked and comprise a "testicular dysgenesis syndrome" (TDS) of fetal origin, putatively caused by environmental factors [15]. A recent study in Finland revealed a rapid adverse trend in semen quality concomitantly with an increasing incidence of testicular cancer [16]. These changes suggest the underlying causes to be of environmental origin. In addition, exposure to exogenous hormones (e.g., diethylstilbestrol) and other endocrine-disrupting chemicals, such as organochlorine pesticides and polychlorinated biphenyls [17], as well as some maternal-related characteristics including low parity [18], preterm birth [19, 20], low birth weight [21], and mother's young age [22] have been suggested as potential risk factors of testicular GCTs. However, no risk factors of malignant ovarian GCTs have been documented.

As malignant GCTs in both sexes are thought to originate from primordial germ cells, we hypothesized that the risk factors, and consequently the incidences of malignant gonadal GCTs, would share similarities in males and females in a defined population. Thus, we analyzed the incidences and histological distribution of all malignant GCTs in both sexes over the last four decades in a population-based study, using the data of the national Finnish Cancer Registry, which covers all malignancies diagnosed in Finland since 1953.

Materials and methods

This study was approved by the Ethics Committees of Helsinki University Central Hospital (DNRO 398/E9/07, 13.12.2007) and the National Institute for Health and Welfare (DNRO 156/5.05.00/2009). All cases of malignant GCTs in both sexes and all ages and their age-adjusted annual incidences (between 1969 and 2008) were obtained from the Finnish Cancer Registry.

The cases were classified according to the WHO International Classification of Diseases, Oncology, 3rd Edition (ICD-O-3 Behavior code 3 [malignant] tumors), and additionally, of tumors located in the central nervous system (CNS), benign and uncertain behavior codes (0 and 1) were included. The histology codes used for all germ cell tumors are shown in Table 1. The following ICD-O-3 topography codes were used (all C00-C80.9): 1. testis C62; 2. ovary C56; and 3. Extragonadal—3a, CNS C69-72, 3b, mediastinum and thorax C33-38.8, C49.3, C76.1, 3c, abdominal and pelvic C41.4, C48, C49.5-49.6, C51-55, C57, C61.9, C76.2-76.3, and 3d, other or unspecified (all other topography codes). All cases of extragonadal choriocarcinoma in women (uterus $n = 41$, other female reproductive tract $n = 3$, placenta $n = 41$, unknown origin $n = 5$) were excluded from this study as being potential gestational choriocarcinomas. Finally, spermatocytic seminoma ($n = 9$) was excluded from the analysis as it is not associated with carcinoma in situ, and thus, its relationship with other germ cell tumors is uncertain [23, 24].

The total GCT incidences were adjusted for age against the world standard population (http://www.cancerregistry.fi/atlasweb/source/t/t_worldstandardpop.htm) for each 10-year period. Relative changes in incidence (with 95 % confidence intervals) were also calculated. Confidence intervals were calculated by using a Poisson distribution [25]. In addition, age–period–cohort analyses were performed to assess the birth cohort influence on male gonadal GCT incidences. This was done using goodness-of-fit analysis [26, 27] using apc.fit function in Epi package for R (Software environment for statistical computing and graphics, version 2.13.0, The R Foundation for Statistical Computing). As regards to male extragonadal GCTs and all female GCTs, the numbers were insufficiently low for solid age-cohort analyses.

Results

A total of 3,015 malignant germ cell tumors were diagnosed in Finland between 1969 and 2008, 2,714 in males and 301 in females. These accounted for 0.7 % of all malignant tumors diagnosed in males and 0.08 % in females.

Distribution of GCTs

The gonads were the most prevalent sites of GCTs in both sexes. All ages included; there were totals of 157 (6 % of all) extragonadal GCTs (EGCTs) in males and 69 (23 % of

Table 1 Extragonadal germ cell tumors and their most common histologies

Location	Men $n = 157$ (%)	Women $n = 69$* (%)
Intracranial	61 (38.9 %)	18 (26.1 %)
Germinoma	42 (69 %)	13 (72 %)
Teratoma	13 (21 %)	3 (17 %)
Other	6 (10 %)	2 (11 %)
Mediastinum	43 (27.4 %)	5 (7.2 %)
Teratoma/Teratocarcinoma	5 (12 %)	3 (60 %)
Seminoma	16 (37 %)	–
Embryonal carcinoma	9 (21 %)	1 (20 %)
Other	13 (30 %)	1 (20 %)
Abdomen/pelvis	36 (22.9 %)	40 (58.0 %)
Teratoma/teratocarcinoma	17 (47 %)	27 (67.5 %)
Yolk sac tumor	7 (20 %)	11 (27.5 %)
Other	12 (33 %)	2 (5 %)
Other or unspecified	17 (10.8 %)	6 (8.7 %)
Choriocarcinoma	6 (35 %)	–
Embryonal carcinoma	4 (24 %)	–
Other	7 (41 %)	6 (100 %)

Finland 1969–2008

* Choriocarcinomas in placenta, uterus, and other female tract ($n = 85$) excluded as potential gestational germ cell tumors

all) in females. Table 1 summarizes the distribution of EGCTs and their most common histologies in men and in women.

Histological distribution of GCTs

The main difference in the histological distribution of all GCTs between males and females was the significantly higher rate of teratomas in females (41 % of all GCTs). The second most common type of female GCT was dysgerminoma (31 %). In males, 50 % of all the malignant GCTs were seminomas.

The distribution of the different histological types of malignant GCTs in the gonads is shown in Table 2. Of these, testicular seminoma (51 %) and ovarian dysgerminoma (38 %) were the most common histological types. Malignant teratomas and yolk sac tumors were more common in the ovary, whereas embryonal carcinomas were more common in the testis.

Regarding extragonadal locations, the most common histological subtype in males was germinoma ($n = 50$; 32 %), followed by teratoma or teratocarcinoma ($n = 41$; 26 %), and embryonal carcinoma ($n = 21$; 13 %). In females, more than half of the extragonadal cases were teratomas or teratocarcinomas ($n = 36$; 52 %), with germinomas accounting for 20 % of the cases ($n = 14$).

Age and sex distribution and gonadal and extragonadal GCTs

Male predominance was found in all age groups in gonadal GCTs, the male–female ratio being most pronounced (34:1) in group 25–29 years in 1969–1978. During the last study decade (1999–2008), the male–female ratio was highest in age groups 30–34 and 40–44 years (31:1 in both). In extragonadal GCTs, there was a slight male predominance in all except age group <15 years in which male–female rate was 1:5, 1:1.4, and 1:1.6 during the last three decades, respectively. Additionally, in age group 40–44 years, the male–female ratio in EGCTs was 1:1 in periods 1969–1978 and 1989–1999.

Age distribution regarding gonadal GCTs varied between the two sexes. Only 1 % of all testicular GCT patients ($n = 42$) but 12 % ($n = 27$) of female gonadal GCT patients were under 15 years of age. In addition, the proportion of extragonadal germ cell tumors among those of less than 15 years of age was higher in females (67 %) than in males (22 %). There were also other significant differences between the two sexes. For example, extragonadal yolk sac tumors were found almost exclusively in 0- to 3-year-old girls (90 %), whereas in males, these tumors were more widely distributed (age range 2–37) and 72 % were found in men older than 20 years. CNS tumors were most common among 10- to 30-year-old males and 10- to 20-year-old females.

Incidence of malignant germ cell tumors in Finland

The overall world standard-adjusted incidence of all GCTs during the whole study period was 2.56 per 100,000 person-years in males and 0.34 per 100,000 person-years in females. In males, the incidence increased 2.8-fold, from 1.56 per 100,000 person-years in 1969–1978 to 4.32 per 100,000 person-years in 2000–2008. In females, the increase was 1.8-fold, from 0.23 to 0.40 per 100,000 person-years during the same time period. However, in females, the overall incidence of GCTs during the last three ten-year periods remained essentially stable (i.e., 0.36, 0.38, and 0.40 per 100,000 person-years).

Regarding gonadal locations, the incidence of testicular GCTs in the whole study period was 2.39 per 100,000 person-years. During the study period, this incidence increased from 1.44 to 4.09 per 100,000 person-years. We found a significant birth cohort effect together with age and period effects when these variables were studied one by one in separate models. The full age–period–cohort model had a better fit compared with the age-period model indicating that cohort has a significant independent effect. However, the age–period–cohort model fit did not differ significantly from the age–cohort model indicating that the independent period effect might be

Table 2 Distribution of malignant gonadal germ cell tumors (according to ICD-O-3) in males and females (all ages) according to morphology in Finland between 1969 and 2008

Morphology M9060-9090/3, 9100-9101/3	Men (testis, C62) $n = 2{,}557$	Women (ovary, C56) $n = 232$
Seminoma 9061-M9062/3*, 9064/3	1,310 (51.2 %)	–
Dysgerminoma 9060/3	–	87 (37.5 %)
Embryonal carcinoma 9070/3	486 (19.0 %)	11 (4.7 %)
Yolk sac tumor 9071/3	64 (2.5 %)	38 (16.4 %)
Malignant teratomas and teratocarcinomas 9080-84/3	414 (16.2 %)	84 (36.2 %)
Mixed-type GCT 9085/3	221 (8.6 %)	4 (1.7 %)
Choriocarcinoma 9100-9101/3	62 (2.4 %)	8 (3.4 %)

* Spermatocytic seminoma (9063/3) excluded

very small and/or cohort effect explains the majority of the period changes. The overall incidence of ovarian GCTs was 0.23 per 100,000 person-years. The incidence increased modestly, that is, from 0.16 to 0.25 per 100,000 person-years during the study period.

Extragonadal tumors were rare in both males and females, with incidence rates of 0.18 and 0.10 per 100,000 person-years, respectively. Thus, a male and gonadal predominance in the incidence of GCTs was evident (Fig. 1).

The greatest increase in the incidence of malignant GCTs during the past 40 years has been in males aged 15–44 years

The age-specific incidence rates of GCTs rose constantly over time among males aged 15–44 years (Fig. 2). The increase varied from a minimum of a 2.1-fold increase (from 2.39 to 5.04 per 100,000 person-years) among those aged 40–44 years to a maximum of a 7.6-fold increase (0.48–3.66 per 100,000 person-years) among those aged 15–19 years. However, no such change was seen in boys younger than 15 or men older than 44 years.

The incidence rates of malignant GCTs in the gonads (ages 15–44 years) is shown in Table 3. We found consistent and significant increases in the incidence rates of both testicular seminoma (3.3-fold increase between the first and last study decade) and non-seminoma (4.1-fold increase). Of the non-seminomas, increases were found in embryonal carcinomas (2.9-fold increase), teratomas (4.1-fold increase) and mixed-type GCTs (6.3-fold increase). In females, non-dysgerminoma showed a consistently increasing incidence (4.1-fold increase), whereas between the first and the last study decade, the incidence of dysgerminoma was not increased (from 0.15 to 0.10 per 100,000 person-years).

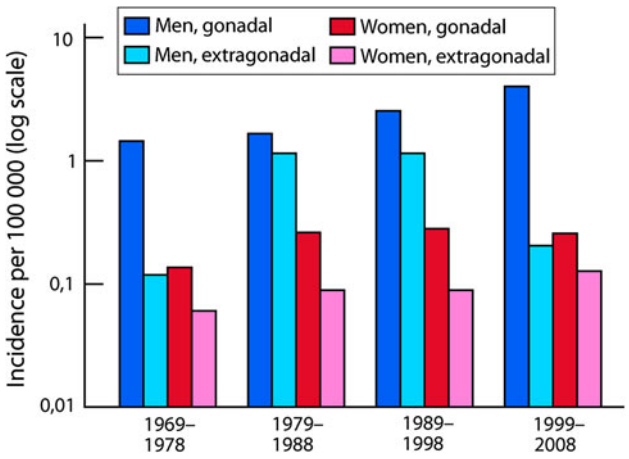

Fig. 1 Ten-year average incidence rates of malignant germ cell tumors in Finland, 1969–2008. Gonadal versus extragonadal locations

Discussion

Our population-based study covers all locations and histological subtypes of malignant GCTs in both males and females of all ages in Finland, with a population of 5.3 million in 2008. Given the recently published UK study on more than 33,000 patients [5], this is the second population-based report on all malignant GCTs. Thus, this report adds to the limited data on the incidence trends of these rare tumors. The present data show that during a 40-year period in Finland, the male-to-female ratio in GCT incidence was 7.6–1. The overall age-adjusted incidence of male GCTs increased significantly, whereas in women, no corresponding change was seen. Although the increase in male GCTs was mainly due to a significant increase in the incidence of seminomas, we also found significant increases in the incidence of non-seminomas, including testicular embryonal carcinomas, teratomas, and mixed-type GCTs.

The classification "mixed-type GCT" was introduced in the late 1980s. Thus, declines in the incidence rates of embryonal carcinomas, teratomas, and choriocarcinomas have been reported together with an increase in the incidence of mixed-type GCTs [30]. However, in our study, the incidence rates of embryonal carcinomas and teratomas increased together with the incidence of mixed-type GCTs.

The Finnish Cancer Registry was established in 1953, and notification to the Registry of all diagnosed cancer cases, including patient information, histological type and location of the malignancy has been mandatory since 1961 (www.cancerregistry.fi) [27]. In 2005, the old diagnostic codes were translated to ICD-O-3 back to the year 1953. According to the Finnish Cancer Registry, for the major histological types, the translation was possible since the early 1970s, and an exact translation for all histologies was possible from 1979 on. Thus, the Registry provides reliable

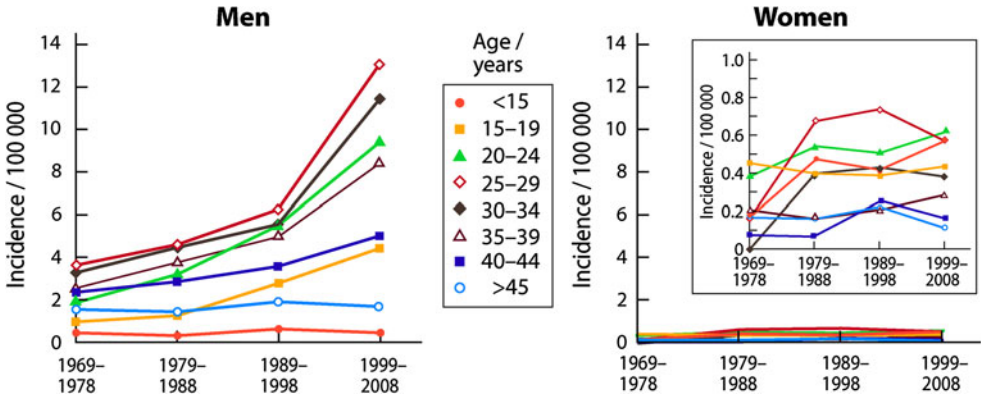

Fig. 2 Ten-year average incidence rates of all malignant GCTs by age at diagnosis; all locations. Finland 1969–2008

Table 3 Malignant gonadal germ cell tumor (GCT) incidence, ages 15–44 years (Finnish Cancer Registry 1969–2008)

Time period	Ten-year average incidence per 100,000 person-years (95 % confidence interval)					
	Males			Females		
	All	Seminoma	Non-seminoma	All	Dysgerminoma	Non-dysgerminoma
1969–1978	2.27	1.09	1.18	0.22	0.15	0.07
	(2.00–2.57)	(0.91–1.31)	(0.98–1.40)	(0.14–0.34)	(0.09–0.25)	(0.03–0.14)
	$n = 250$	$n = 120$	$n = 130$	$n = 23$	$n = 16$	$n = 7$
1979–1988	3.06	1.22	1.85	0.41	0.23	0.18
	(2.76–3.39)	(1.03–1.42)	(1.61–2.11)	(0.30–0.55)	(0.14–0.34)	(0.11–0.27)
	$n = 376$	$n = 158$	$n = 218$	$n = 43$	$n = 23$	$n = 20$
1989–1998	4.43	1.82	2.61	0.43	0.20	0.22
	(4.05–4.83)	(1.59–2.07)	(2.31–2.93)	(0.31–0.58)	(0.12–0.31)	(0.14–0.33)
	$n = 507$	$n = 229$	$n = 278$	$n = 43$	$n = 20$	$n = 23$
1999–2008	8.36	3.59	4.77	0.40	0.10	0.29
	(7.81–8.93)	(3.25–3.96)	(4.35–5.22)	(0.29–0.55)	(0.05–0.19)	(0.19–0.42)
	$n = 874$	$n = 406$	$n = 468$	$n = 38$	$n = 9$	$n = 29$

and detailed information on the histological distribution of malignant GCTs in all age groups. Consequently, our material includes essentially all cases of GCTs diagnosed in Finland during the study period and allows analysis of time trends in their incidence. However, as the Registry data are based on reports from various pathology units, the diagnostic criteria may vary between different laboratories and time periods. However, it is unlikely that such variations could explain the changes observed.

Several groups of investigators worldwide have reported on the increasing incidence of testicular cancer over the last 30 years [2, 7, 11, 12, 30, 31]. A recent register study from the United States revealed a significantly increased incidence of testicular GCTs in both white and black males. However, the incidence was much higher among whites. Because of small numbers, other ethnic origins were excluded from the study [7]. Previously, McGlynn et al. reported the incidence of testicular seminoma to have increased between 1973 and 1998 in the United States but this rate to slowly have declined. Additionally, they found that non-seminoma rates plateaued among whites and increased in blacks more modestly than seminoma rates [2]. Similarly, we found that the incidence rates of several histological subtypes of testicular GCTs have increased over the last four decades in Finland. Thus, our findings are in line with the previous studies. Yet, this ongoing trend was only seen in men aged 15–44 years.

In comparison with testicular GCTs, the overall incidence of malignant ovarian GCTs was not increased among Finnish females. Even though we found a significant increase in the incidence rate of ovarian non-dysgerminomas in the age group of 15–44 years between the first and the last study decade, this incidence has remained stable during the last three decades. Similarly, in a study on ovarian cancer incidence by histological type carried out in Osaka, Japan 1975–1998, Ioka et al. [13] reported that the incidence of ovarian GCTs had remained stable. However, in England, the incidence of ovarian GCTs has increased slightly along with the increasing incidence rate of testicular GCTs [6]. In contrast, in a study covering more than

1,200 cases of malignant ovarian GCTs in the United States, it was concluded that incidence rates have declined over the last 30 years, with the decrease being nearly 30 % as regards dysgerminomas [4]. (The investigators classified ovarian GCTs as dysgerminomas, malignant teratomas, and mixed-type GCTs.) Similarly, a more recent study carried out in the US demonstrated a slight decrease in the incidence of ovarian germ cell tumors in both black and white women [7]. Thus, the incidence of ovarian GCTs has not been shown to have increased along with that of testicular GCTs in industrialized countries.

We found that the proportion of cases of extragonadal GCTs in Finnish males was similar to that recently reported in the US [7]. In females, however, the percentage of EGCT cases was somewhat higher in the US than in Finland (39 vs. 23 %). This may be explained by the significant amount of placental and uterine GCTs, and thus, probable gestational tumors included in the US study [7]. Moreover, geographical variation in the incidence rates of extragonadal GCTs in Europe, with a somewhat higher incidence rate in Northern European countries (0.17 per 100,000 person-years), has recently been reported [32]. Thus, the low incidence rate of extragonadal tumors (0.1 per 100,000 person-years) in our study is in line with the results of previous studies [5, 28].

The reason(s) for the increasing incidence of testicular germ cell tumors remain(s) an enigma. Several pregnancy-related factors, such as low parity [18], young maternal age [21], preterm birth [19, 20], and low birth weight, have been postulated as risk factors of testicular GCTs. However, apart from parity, the prevalence of these proposed risk factors has either declined or remained stable in Finland over the last few decades [29]. In contrast, between 1975 and 2008, the overall mean maternal age increased from 26 to 30 years and that of primiparous mothers from 25 to 28 years. Moreover, the percentage of parturients younger than 20 decreased from 8 to 2 %. The percentage of low-birth-weight newborns and the percentage of cases of preterm birth remained low and stable at 4 and 5 %, respectively [33]. Thus, of these proposed pregnancy-related risk factors, only decreasing parity may be linked to the increasing incidence of testicular GCTs at the population level. Moreover, one of the proposed endocrine disruptors associated with testicular cancer, diethylstilbestrol, has never been used in Finland for prevention of miscarriage. We speculate that the etiological agent(s) behind the increasing incidence of testicular GCTs in Finland may be of environmental origin.

The key finding in our study is the different evolution of the incidence of malignant testicular versus ovarian GCTs over the past few decades. As the data are derived from the same population, with a uniform genetic background and with similar exposure to various environmental factors, they further suggest that the risk factors associated with these tumors differ between the sexes. Alternatively, varying sensitivity of testicular and ovarian primordial germ cells to potential environmental factors may also play a role.

Conclusions

There are significant differences in both the incidence and histological distribution of germ cell tumors between males and females. The incidence of malignant GCTs is nearly eightfold higher in males than in females. The incidences of several histological subtypes of testicular GCTs have increased consistently and significantly over several decades. In females, such incidences have remained low, with no significant increase in either gonadal or extragonadal germ cell tumors. The differences in germ cell tumor incidence between males and females also suggest that the risk factors of these tumors are dissimilar in the two sexes.

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Conflict of interest The authors declare that they have no conflict of interest.

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REGULAR ARTICLE

High Prevalence of Sacrococcygeal Teratoma in Finland – A Nationwide Population-Based Study

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Keywords
Associated anomalies, Prenatal diagnosis, Prevalence, Sacrococcygeal teratoma

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ABSTRACT

Aim: The birth prevalence of sacrococcygeal teratoma (SCT) has been reported to range from 1:27 000 to 1:40 000. We assessed the population-based prevalence and clinical presentation of SCT over 22 years.

Methods: We identified all cases of SCT, including live births, stillbirths and terminations of pregnancy (TOPs), in the Finnish Register of Congenital Malformations, covering 1987–2008. Data on prenatal diagnoses, pregnancy outcomes, infant deaths and associated anomalies were collected.

Results: One hundred and twenty four SCT cases were identified among 1 331 699 pregnancies. There were 89 (72%) live births, 13 (10%) stillbirths and 22 (18%) TOPs. The total prevalence of SCT was 1:10 700. Tumours were detected *in utero* in 55% of the pregnancies with SCT. The proportion of perinatal deaths among all SCT births was 28%. Thirty percentage of the cases had associated abnormalities (mainly of the urinary tract and various syndromes).

Conclusion: This nationwide, population-based study on SCT shows that the total and birth prevalence of SCT in Finland is markedly higher than previously reported. This may reflect true differences between populations, but may also be explained by accurate nationwide registration of SCTs. The high perinatal mortality rate has an impact on counselling of families and planning of deliveries.

AIM

Sacrococcygeal teratoma (SCT) is the most common foetal and neonatal neoplasm (1). The typical presentation is a large sacral mass clearly discernible at birth. SCTs are composed of multiple tissues, often derived from all three embryonic layers. The origin is presumably a totipotent primordial germ cell giving rise to teratomas located anywhere between the brain and the sacrococcygeal area, usually in the midline (2). A female preponderance of 3:1 has been reported for SCT (1,3).

Sacrococcygeal teratomas diagnosed postnatally have been associated with an excellent prognosis (4–8). However, with improved antenatal imaging techniques, SCT is commonly detected as early as during the second trimester of pregnancy. Antenatally diagnosed SCTs have been associated with risks of perinatal complications and death (9–11). The presence of a solid tumour with abundant vascularization usually causes foetal heart failure with the consequent development of polyhydramnios, placentomegaly and foetal

Abbreviations
FRCM, the Finnish Register of Congenital Malformations; NIHW, National Institute for Health and Welfare; SCT, sacrococcygeal teratoma,; TOP, termination of pregnancy.

Key notes
- The birth prevalence of sacrococcygeal teratoma in Finland is much higher than previously reported.
- One third of the cases have associated abnormalities.
- The high mortality rate observed and the rate of associated anomalies have an impact on counseling affected families, follow-up of the pregnancies and planning of deliveries.

hydrops, all of which have been reported as predictors of a poor outcome, mainly due to prematurity (9).

The live birth prevalence of SCT has been reported to lie at 1:35 000–1:40 000 (1,12). However, most studies have involved case series from single tertiary centres. A live birth prevalence of 1:27 000 and 1:23 000 have been reported from northern England (13) and Hawaii (14), respectively. However, population-based reports on the nationwide prevalence of SCT are rare. We therefore evaluated the population-based prevalence and pregnancy outcome in cases of SCT in Finland over a period of 22 years, including stillbirths and terminations of pregnancy (TOPs) for foetal indications. In addition, we describe anomalies and conditions associated with SCT.

PATIENTS AND METHODS

All cases of sacrococcygeal teratoma, including live births, stillbirths and TOPs because of foetal anomalies, were identified in the Finnish Register of Congenital Malformations (FRCM) for the period 1987–2008 inclusive. This nationwide, population-based register maintained by the National Institute for Health and Welfare (NIHW) has been used to collect data on congenital anomalies, including teratomas, since 1963 (15). Data are mostly received from hospitals and clinics, health care professionals and cytogenetic laboratories, but also from other national health care registers, that is, the Medical Birth Register, the Register on Induced Abortions and the Care Register for Health Care, all maintained by the NIHW. Data on TOPs are provided by the National Supervisory Authority for Welfare and Health, and those on stillbirths and infant deaths by Cause of Death Statistics, maintained by Statistics Finland. These data are cross-linked by way of the unique personal identification number assigned at birth to all citizens and permanent residents in Finland. The diagnoses obtained from the various data sources are confirmed by the hospitals. Anomalies connected with stillbirths and infant deaths as well as TOPs are verified from autopsy reports. Although the FRCM is mainly used to collect data on anomalies for monitoring those affected, it is also used to continuously collect data on subsequently detected congenital anomalies, for statistics and research. The coverage and quality of the FRCM are considered good and have been ascertained in several studies (16,17).

Data on prenatal diagnoses, pregnancy outcomes, infant deaths and associated anomalies were collected in all cases of SCT from the FRCM and subsequently linked with data in the national Finnish Cancer Registry (18) to ascertain the inclusion of all malignant cases (n = 6) possibly detected later in childhood. All the SCT diagnoses and other anomalies received from the FRCM were confirmed by a paediatric surgeon (S.-L.P.), using hospital records.

The total numbers of all births (1 331 699) and live births (1 326 263) in Finland from 1987 to 2008 inclusive were taken from the national Medical Birth Register (19).

This retrospective, registry-based study was approved by the Ethics Committees of Helsinki University Central Hospital and the National Institute for Health and Welfare.

RESULTS

Clinical presentation and prevalence

A total of 124 cases of sacrococcygeal teratoma were identified, with a female–male ratio of 4:1. The median maternal age was 29 years (range 18–44 years) at birth or TOP. None of the women had a history of delivering a child with SCT, a stillbirth, or had undergone a TOP because of foetal anomalies, or had carried a stillbirth.

The total prevalence of SCT (including births and TOPs) was 1:10 700, the birth prevalence, 1:13 000 and the live birth prevalence, 1:14 900. When the observation period of 1987–2008 was divided into three 7-year 4-month time periods, the prevalence as well as the number of cases was found to be stable over time. When the nine cases diagnosed after the neonatal period were excluded, the live birth prevalence of SCT was 1:16 600. Four of the late diagnoses where Currarino syndromes that are likely to be of a hereditary origin. Additionally, among the terminated cases, there were SCTs associated with an anal atresia, and these cases can also be classified as Currarinos. Excluding these cases from our analyses has little effect on the total SCT prevalence numbers (1:11 300 when the Currarinos and anal atresias have been excluded, compared to 1:10 700 without exclusions). The live birth prevalence excluding these six cases was 1:15 600.

Of the 89 live births with SCT, there were 70 females (79%) and 19 males (21%). Altogether, 16 infants (18%) died perinatally (14 immediately after birth, two within 2 days). The mean gestational age of the live births was 36 + 6/7 weeks (range 28 + 2/7–41 + 2/7); it was 38 + 0/7 among the survivors and 31 + 3/7 weeks among those dying during the perinatal period. Survival among the 73 children (56 females; 82% of the live births) surviving the first days of life and undergoing surgery was high. Only one such child died, suffering a massive intraoperative haemorrhage and disseminated intravascular coagulopathy (DIC). The respective pregnancy outcomes are shown in Figure 1.

Nine of the live births (10%) presented with a presacral SCT diagnosed at 5 months to 14 years of age. Six of these were mature and three malignant (two with yolk sac and one with embryonal carcinoma components). Four of the mature cases were diagnosed with Currarino syndrome, that is, sacral defects, anorectal anomaly and presacral SCT (20). Seven of the nine with a late SCT-diagnosis were females.

Twenty-two SCT pregnancies (20 females) were terminated during the study period as a result of both SCT- and severe-associated anomalies, or SCT alone. The mean gestational age at the time of TOP was 19 + 2/7 weeks (range 13–23 weeks). Thirteen of the SCT cases (11 females) were stillbirths. The mean gestational age at the time of stillbirth was 27 + 2/7 weeks (range 22–40 weeks). When the 22 TOPs and 17 infant deaths were included, the

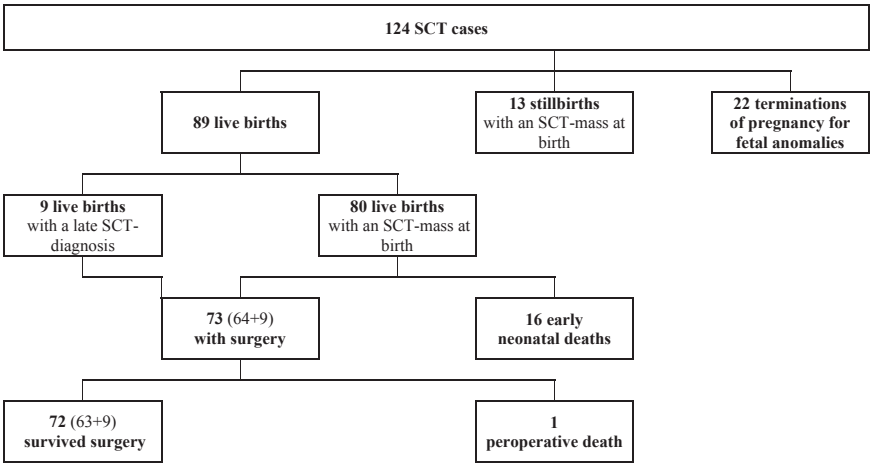

Figure 1 Outcome sacrococcygeal teratoma (SCT) in Finland 1986–2008.

total loss of foetuses and children with SCT was 42% (52/124).

Antenatal diagnostics and outcome in cases of SCT

Sacrococcygeal teratoma was diagnosed antenatally in 55% of the SCT pregnancies (68/124), 49% of the births with SCT (50/102) and 46% of the live births with SCT (in 51% of the live births when the nine children with late diagnosis are excluded). Of the 16 early neonatal deaths, six had no prenatal diagnosis of SCT. Mortality in the group with antenatal diagnosis was 54% (37/68) and it was 33% (15/46) when the terminations were excluded. Mortality in the group with no antenatal diagnosis was 21% (12/56).

When the observation period was divided into three 7-year 4-month time periods, that is, 1987–1994, 1994–2001 and 2001–2008, the antenatal detection rates were 50%, 51% and 72%, respectively.

Ten foetuses were reported to have hydrops in antenatal ultrasonographic scans. Only one of these survived. One of the pregnancies was terminated at 18 + 2/7 weeks. Four cases were stillborn (22 + 2/2–36 + 6/7 weeks) and another four died on the first day of life (gestational age 29 + 0/7–35 + 6/7 weeks). Additionally, 14 cases with SCT had associated polyhydramnion. Five of these survived (38% survival) and none of the survivors had anomalies other than SCT. Interestingly, SCT was an isolated anomaly in all of the stillbirths.

Of the 22 pregnancies terminated, SCT was the only prenatally detected anomaly in 16 cases. Five of the terminated SCT cases had additional major anomalies or conditions (Table 1).

Three cases had no prenatal diagnosis of SCT, and the termination was performed because of other foetal indications (trisomy 13, trisomy 21 and large omphalocele), with SCT detected after TOP.

Other concomitant abnormalities

Associated abnormalities (Table 1) were reported to the register in 38 cases (30%). Of these, 23 children had multiple abnormalities. Urinary tract abnormalities (hydronephrosis, hydroureter, double renal system) were the most common (16% of the cases). However, dilatation in the urinary tract with no other findings represented 65% of all the urological abnormalities.

Nine children (7%) had anomaly complexes and syndromes. We found two cases of cloacal exstrophy, commonly referred to as the omphalocele, exstrophy of the bladder, imperforate anus and spinal abnormalities (OEIS) complex. This is a rare anomaly with a prevalence of 1:250 000 live births (21). One of these cases was terminated at 11 + 2/7 weeks and the other died on the first day of life. The syndromes were Currarino syndrome (n = 4) and trisomies 13, 18 and 21 (one of each).

DISCUSSION

Our study revealed that the total and birth prevalence of SCT in Finland was significantly higher than has been reported previously from other countries. Of all the SCT cases, 42% died prior to the end of the early neonatal period or ended in TOP. Moreover, nearly a third of our cases had additional abnormalities.

The birth prevalence of SCT has been reported to be markedly lower than our data indicates, between 1:35 000 and 1:40 000 (1,12). In a recent study, an SCT live birth prevalence of 1:27 000 was reported in a population-based study involving multiple data sources in northern England (13), again lower than our result. In an epidemiological study of teratomas in Hawaii, a live birth prevalence of 1:23 000 was noted (14). However, there were only 13 SCT cases in this study. The reasons for the different prevalence rates are unclear and likely to be multifactorial. Accurate nationwide registration may explain in part the seemingly high total and birth prevalence of SCT in Finland. However, true differences in the prevalence of SCT between different populations cannot be ruled out. In our series, we had 6 cases of a probable hereditary origin (Currarinos). Excluding these cases from our analyses has little effect to our total

Table 1 Associated anomalies and conditions in foetuses and children with sacrococcygeal teratoma in Finland in 1987–2008. All individual anomalies (except those included in a syndrome or complex) are included

	Associated conditions and anomalies					
Outcome	Cardiothoracic	CNS	Genitourinary	Musculoskeletal	Syndrome/chromosomal	Other
Live birth; survivors (n = 71)	Aortic arch narrowing	MMC Hydrocephalus (2) Ventriculomegaly Tethered cord Megalencephaly	Multicystic renal dysplasia Double renal system (3) Rectovaginal fistula Hydronephrosis (10)	Clubfoot DDH (2) Scoliosis (2)	Currarino syndrome (4) Suspected Sotos syndr.	Translocation, balanced NOS
Early neonatal deaths (n = 29)	Hypoplastic lungs (5) Agenesis of diaphragm Hypoplastic thymus	Hydrocephalus	Hydronephrosis (2) Indeterminate sex Ectopic kidneys	Abducted feet Tumour of right femur	OEIS complex/Cloacal exstrophy)	Ectopic adrenal glands
TOP (n = 22)	–	Plexus chorioideus cyst Hydrocephalus	Hydronephrosis (3) Genital anomaly (2) Dilatation of urinary bladder (2)	Omphalocele (1) Micrognathia (2) Clubfoot (2)	Trisomy 18 (1) Trisomy 13 (1) Trisomy 21 (1) OEIS complex/Cloacal exstrophy	Anal atresia (2)

DDH = Developmental dysplasia of the hip (hip luxation); MMC = Myelomeningocele; OEIS = Omphalocele-exstrophy of the cloaca-imperforate anus-spinal defects; TOP = termination of pregnancy.
In all stillbirths, SCT was an isolated finding.

prevalence numbers (1:11 300 when the Currarinos and anal atresias have been excluded, compared to 1:10 700 without exclusions).

Our data are in agreement with those of Swamy et al. (13), with 50% of their cases being detected antenatally. In our material, the prenatal detection rate increased significantly with time, from 50% (1987–1994) to 72% (2001–2008). This increase may be attributed in part to increased use of prenatal ultrasonographic screening, especially during the 1990s. Since the beginning of 2010, a two-step foetal ultrasonographic protocol consisting of a mandatory scan at 10–13 weeks and a second scan at 18–21 or after 24 weeks of pregnancy has been used in Finland (22). This is likely to have increased the rate of antenatal SCT detection even further.

Foetal hydrops, a solid tumour and polyhydramnion have been found to be predictors of a poor outcome (7,8,20). Similarly, in our study, nearly all (10/11) cases with foetal hydrops succumbed and only one-third of the cases with polyhydramnion survived.

It is noteworthy that one-fourth of the stillbirths in our material did not have a prenatal diagnosis of SCT. However, there were only two stillbirths during the final 7-year 4-month period. This may be explained by improved antenatal diagnostics and a planned delivery in the high-risk SCT cases. Identification and management of cases with a poor prognosis remains challenging.

In a recent study in Japan, the overall mortality rate among prenatally diagnosed SCT cases was 26%, with a mortality rate excluding terminations of 16% (23). This cohort study, however, included data from only 15% (48 of 325) of major Japanese perinatology centres. In our series, 42% of the cases had a fatal outcome, and without terminations, the mortality rate was 29%. This may not always be apparent to paediatric surgeons, as the majority of SCT cases undergoing surgery have a good prognosis (4,5).

An association between SCT and anorectal and sacral defects (Currarino syndrome) has been described (20). Additionally, urological (24) and vertebral anomalies (25) have also been reported. Moreover, urinary tract anomalies were recently reported to be relatively common among girls with SCT (12%). However, the diagnosis of these may be delayed as late as up to puberty (26). In a previous study in the United States including 214 SCT cases, 15% had associated findings (urological anomalies and hydronephrosis included) (27). In the present study, we also found a high rate (23%) of associated abnormalities in several organ systems. Dilatation in the urinary tract was a common pre- or postnatal finding (in 12% of all cases). These are likely to be reversible findings caused by an obstructing effect of the tumour mass on the urinary tract. True urological abnormalities in postnatal ultrasonographic scans were found in 8% of the live births with SCT. These associated anomalies may explain some of the foetal deaths and TOPs. However, SCT was the only anomaly in all of the 13 stillbirths in our series. Yet, urinary obstruction may have remained undetected at the autopsy, particularly if the pathologist has not actively looked for this.

In our series, we found two cases of suspected OEIS complex. This is a rare anomaly with a prevalence of 1:250 000 live births (21). We found only one previous report of a case with OEIS complex and a sacral mass presumed to be a teratoma (28), and a second defined as a

cloacal exstrophy with an associated SCT (29). Additionally, there were two cases with omphalocele in our material. The first had absent genitals and anal atresia with omphalocele (terminated at 21 weeks) and the second had trisomy 13.

The validity of data in the Finnish Register of Congenital Malformations is considered good and has been ascertained in several studies (16,17). The coverage of SCT in the Register seems to be comprehensive, but as there is no specific diagnostic ICD code for sacrococcygeal teratoma, some of the cases may have been missed. Hence, it was impossible to cross-validate our data with that in the national Medical Birth Register, the Care Register for Health Care or hospital records of the five tertiary paediatric surgical units dealing with SCT in Finland. Moreover, there may be some underreporting of SCT cases to the FRCM, because SCT is a tumour and is not regarded as a congenital anomaly. Furthermore, some cases diagnosed beyond infancy may be missing from the register. Thus, our report may even underestimate the true prevalence of SCT. Nevertheless, the lack of a uniform diagnostic ICD code for sacrococcygeal teratoma is problematic, and we urge that it is included in future editions of the WHO International Classification of Diseases.

CONCLUSIONS

This is the largest population-based material concerning epidemiology, morbidity and mortality in cases of neonatal sacrococcygeal teratoma. The total and birth prevalence of SCT in Finland appear to be markedly higher than previously reported internationally. This may be explained in part by the accurate nationwide and population-based diagnostics and registration of SCTs. The high mortality rate observed and the rate of associated abnormalities have an impact as regards counselling of affected families, follow-up of the pregnancies and planning of deliveries, which should optimally be centralized in tertiary-care maternity hospitals with associated paediatric surgical units.

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CONFLICT OF INTEREST

None declared.

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The authors have no financial relationships relevant to this article to disclose.

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