SURGICAL TREATMENT AND OUTCOME OF EXTRACRANIAL GERM CELL TUMORS IN CHILDHOOD

Chirurgische behandeling en follow-up van
extracraniële kiemceltumoren bij kinderen

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Promotor:	Prof.dr. F.W.J. Hazebroek
Overige leden:	Prof.dr. D. Tibboel
	Prof.dr. R. Pieters
	Prof.dr. G. Delvaux

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Chapter 1

Introduction

Germ cell tumors (GCTs) are a very heterogeneous group of benign or malignant neoplasms that can occur at every age – from newborn to old age. They are extremely rare in childhood. The tumors may be located in the gonads (ovary and testes), but in children extragonadal sites (brain, neck, mediastinum, retroperitoneal space and sacrococcygeal region) are as frequent. The common denominator of all these tumors is presumed to be their originating cell, namely the primordial germ cell. The huge variety, the rarity and the confusing nomenclature make germ cell tumors an intriguing and challenging subject. By way of an introduction this chapter deals with several general aspects of these tumors; specific items related to each location will be treated in the following chapters.

MILESTONES IN THE HISTORY OF GERM CELL TUMORS

Ancient references to germ cell tumors almost uniquely concern sacrococcygeal teratoma, the commonest and oldest known subtype. The oldest picture resembling a child with possibly a sacrococcygeal teratoma is found on a Babylonian cuneiform papyrus dating back some 4,000 years.[1] In Antiquity, the Greek writer Pausanias (150 AD) and the Roman writer Pliny the Elder (23 - 79 AD) in his work "Naturalis Historia", reported on beings with coccygeal 'tails', which could also have been sacrococcygeal teratomas. The first unquestionable description reportedly came from the seventeenth-century French obstetrician Ph. Peu.[1]

A first breakthrough in knowledge on these tumors occurred in the nineteenth century. In his dissertation "Die krankhaften Geschwülste" (1863), Rudolph Virchow (1821-1902), the founder of modern pathology, precisely described the case of a newborn girl with sacrococcygeal teratoma.[2]

The designation of these tumors as dermoids and teratomas dates from 1858 and 1875 with Lebert and Leblanc.[1] The word 'teratoma', derived from the Greek 'terato', meaning "monster", and 'onkoma', meaning "swelling, mass", must have come into usage around that time period. Middeldorpf in 1885 was the first to give an explanation of the origin of the tumor; sacrococcygeal teratoma therefore has long been designated as Middeldorpf's tumor.[3]

In 1891, Walter Schiller and Mathias-Marie Duval described what is now known as Schiller-Duval bodies that are characteristic for yolk sac tumor (endodermal sinus tumor): structures resembling fetal glomeruli composed of a central blood vessel surrounded by embryonic cells lying within a space also lined by embryonic cells.[4]

Several theories trying to explain the origin of the tumor were developed in the first half of the twentieth century. G. Teilum was the first to propose the germ cell origin of the gonadal type. He also published on the yolk sac tumor, which therefore first became known as Teilum's endodermal sinus tumor, emphasizing their ability to secrete α-fetoprotein.[5-9]

"In dem Augenblick, wo ich dies für den Druck vorbereite, erhalte ich von Hrn. Dr. Edel in Stolp ein neues Präparat von congenitaler Steissgeschwulst, welches die nervöse Natur der betreffenden Theile in ausgezeichneter Weise erkennen lässt. Bei einem neugebornen Mädchen, dessen Becken innen ganz normal ist, wölbt sich aussen und zwar wesentlich auf der rechten Hinterbacke ein über zwei Mannsfäuste grosser Tumor hervor. Die Untersuchung zeigt, dass derselbe mit dem Filum terminale und dem Wirbelkanal in Verbindung steht und eine sehr zusammengesetzte Beschaffenheit besitzt. Neben grossen, mit Flüssigkeit gefüllten, ziemlich dickwandigen, hie und da mit telangiektatischen Papillen besetzten Säcken, die jedoch in keiner offenen Communikation mit dem Wirbelkanal stehen, finden sich festere Klumpen aus sehnigem Bindegewebe, Fett und Knorpeln, dicht am Kreuzbein. In dieser Gegend kommen auch multiloculäre Cysten-Geschwülste vor, in denen Flimmerepithel enthalten ist. Besonders interessant ist aber ein längsovaler, von festen Bindegewebszügen umgrenzter Knoten von 6 Cent. Länge und 3 Cent. Dicke, der angeschnitten eine Menge von (wahrscheinlich künstlich zerdrückter) Marksubstanz ausfliessen liess; nach der Entleerung derselben blieb im ganzen Umfange des Knotens eine zusammenhängende, 3-4 Millim. Dicke Rindenschicht stehen, welche ganz das Aussehen und die Zusammensetzung von Hirnsubstanz darbot und sich nur dadurch unterschied, dass sie nach aussen unmittelbar in die umhüllende Bindegewebslage überging. Letztere war übrigens noch von einer festeren Schicht umgeben, die überaus reich an elastischen Elementen war. Ein zweiter, noch grösserer, aber schon bei der Geburt entleerter Sack schien gleichfalls Hirnsubstanz enthalten zu haben. Beide waren jedoch in keiner directen Continuität mit dem Filum terminale. Das Rückenmark selbst verhielt sich nicht abweichend."

Source: "Die krankhaften Geschwülste" (1863), Rudolph Virchow (1821-1902)

In 1973, Peter Altman conducted a survey of the membership of the Surgical Section of the American Academy of Pediatrics on their experience with sacrococcygeal teratoma; based on the results Altman distinguished four types of sacrococcygeal teratoma. These Altman types are still in use for classification purposes (*Fig 1*).[10]

A next important contribution came in 1980 from F. Gonzalez-Crussi with the publication of his pathological atlas on extragonadal teratomas.[11]

From a therapeutic viewpoint, the introduction of cisplatin in the early to mid-eighties may rightly be considered the most important milestone for those with malignant germ cell tumors. Important in this respect as well is the creation of cooperative study groups such as MAKEI-MAHO (Maligne Keimzelltumoren - Maligne Hodentumoren of the German Association of Pediatric Oncology), POG/CCG (Pediatric Oncology Group, Children's Cancer Group) in the USA, UKCCSG (United Kingdom Children's Cancer Study Group) and SFOP (Société Française d'Oncologie Pédiatrique)/SIOP (Société Internationale d'Oncologie Pédiatrique.[12]

In the most recent years we have also witnessed remarkable progress in the molecular biology and genetic analysis of these tumors, nicely summarized in the paper by Oosterhuis and Looijenga.[13]

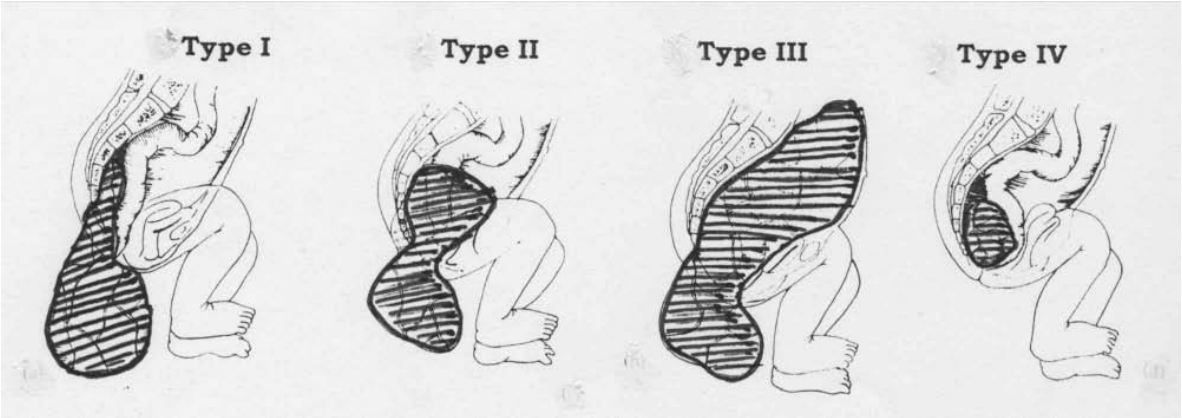

Figure 1 *Altman classification of sacrococcygeal teratoma*

INCIDENCE

Germ cell tumors in infancy and childhood are very rare. It is probably due to the heterogeneity of these tumors and the confusing nomenclature that precise data are hard to find. The most exact data are probably available for the malignant types, as many countries have developed a Cancer Registry during the past decade(s).

The Netherlands Cancer Registry reported for the years 1989-1997 a mean of 385 cases of malignant cancer (all types) per annum in children, including 15 cases of malignant germ cell tumors. For a pediatric population (0 - 14 years) of 2,899,422 in 1998 this comes down to an incidence of 5.2 in one million children < 15 years. It thus can be deduced that only 4% of all pediatric malignancies are germ cell tumors.[14]
Comparable data have been reported for Belgium. For a pediatric population (0 - 14 years) of 1,828,816 in 1994, 255 cancers (all types) were registered, including 10 germ cell tumors, which also is consistent with 4% of total cancers being germ cell tumors, corresponding with an incidence of 5.4 in one million children < 15 years.[15,16]

In a German study, the population-based incidence of malignant germ cell tumors was determined at 4.0 in one million children under 15 years.[17]
Similarly in the UK, with a pediatric population of 11 million, the incidence was reported to be between 3 and 5 in one million.[18]
Estimations for the USA (approx. 60 million children < 15 years) arrive at around 300 cases per year. In another American study including seven metropolitan areas and two states (5,151,699 children under 15 years in 1970), 1925 cases of cancer were diagnosed over a 3-year span, including 42 cases of malignant germ cell tumors. From these figures only 2.2% of all malignant tumors in children under 15

years appear to be of germ cell origin, with the incidence of malignant germ cell tumors around 2.7 in one million children < 15 years.[19]

Thus, in comparison with Germany and the US, higher figures are reported from the Netherlands and Belgium.

Considering that benign germ cell tumors are not included in cancer registries, but account for 50 - 70% of all GCT, the incidence of germ cell tumors (all types and histologies, also including intracranial types) would roughly amount to between 1 and 1.5 in 100,000, corresponding to around 30 - 40 new cases in the Netherlands and 20 - 25 in Belgium every year. Seeing that in the past decade we have treated a mean of 10 patients with germ cell tumor yearly (all locations, benign as well as malignant) in the Sophia Children's Hospital in Rotterdam, the above-mentioned incidence figures appear realistic.

The literature consistently reports an incidence of 1 in 40,000 live births for sacrococcygeal teratoma, which is the most studied subtype of germ cell tumors, and predominantly benign. However, in one of the studies presented in this thesis (chapter 9), we found evidence for a higher incidence in our countries. Indeed, between 5 and 10 patients with sacrococcygeal teratoma (mean: 7) have yearly been treated in the six centers for pediatric surgery over the past decade, indicating an incidence figure closer to 1 in 30,000 live births.

THEORIES OF ORIGIN - ETIOLOGY

The bizarre and unusual aspect of teratomas has not failed to elicit the curiosity of many investigators. Consequently, a large number of theories have tried to explain the development of these tumors. For some theories, substantial evidence already exists. Others, highly speculative or bizarre as the tumors they tried to explain, are now of purely historical interest. It was once believed for instance that a germ cell tumor was the result of frustrated development of a conjoined twin, the so-called incomplete twinning theory.[11] Monozygotic twins are formed when the embryo divides completely at the blastula stage. If at this point complete separation does not occur, the twins instead grow as a fused pair of individuals (Siamese twins); in these instances, fusion usually at the head, chest, abdomen or sacrum is observed. It has been postulated therefore that germ cell tumors may represent an instance of further derangement of the twinning process whereby only very few cells separate at the blastula stage to form an incomplete embryo. This theory's attractiveness was due to the fact that the most frequent germ cell tumors of early infancy (sacrococcygeal region, mediastinum, abdomen and brain) are located at the sites at which Siamese twins are linked. However, it is unlikely that germ cell tumors of the gonads can be explained in this manner. This theory, although very amusing, now belongs to history.

In 1965, Teilum was the first to report on the germ cell origin of these tumors, and from then on the name germ cell tumors became in use.[20] In this theory, all germ cell tumors are presumed to share a common cell of origin, namely the *primordial germ cell*. Primordial germ cells are the precursors of the sperm and egg cells of the gonads. In humans, these cells first become evident in the wall of the extra-embryonic yolk sac by the 4th week of gestation. At the same time, the gonads begin to develop in the embryo as a pair of longitudinal structures, the gonadal (or genital) ridges, on each side of the midline. During the fifth week, the primordial germ cells migrate from the yolk sac along the dorsal mesentery of the hindgut to the level of the genital ridges. At this stage of development, the genital ridges extend from the cervical to the lumbar levels of the developing vertebral column. By the sixth week of development, the primordial germ cells invade the gonadal ridges. The gonad further develops in this position and subsequently descends to its final position in the scrotum or pelvis. It is widely believed that the occurrence of germ cell tumors at extragonadal midline sites can be explained by aberrant patterns of migration. Germ cells, arrested in aberrant locations, as well as those cells that reach their final destination in the ovary or the testis, could give rise to germ cell neoplasms at any of these sites.

The route of primordial germ cell migration can nevertheless only explain the anatomic locations at which germ cell tumors develop; but the events that explain neoplastic alteration of the cells are still poorly understood. The precise cascade leading to the genesis of a germ cell tumor is unknown, but a general explanation in terms of differentiation pathway of the germ cell can be given (*Fig. 2*); if the differentiation of the germ cell is unipotential, and committed to form gonadal precursors of the gametes, malignant transformation results in the undifferentiated germinoma – called seminoma in the testis, dysgerminoma in the ovary, and germinoma when occurring at other sites). Another possibility is differentiation towards embryonic tissues, leading to teratoma, or towards extra-embryonic structures, leading to yolk sac tumor or choriocarcinoma.

Recent advances in molecular genetics and biology shed a new light on the oncogenetic mechanisms of the development of germ cell tumors. A recent publication by Oosterhuis and Looijenga nicely summarizes this knowledge.[13] Based on epidemiology, clinical presentation, phenotypic characterization, chromosomal constitution and genomic imprinting, five different types of GCT are now recognized. The originating cells are not only primordial germ cells but also, in some tumors, embryonic stem cells.

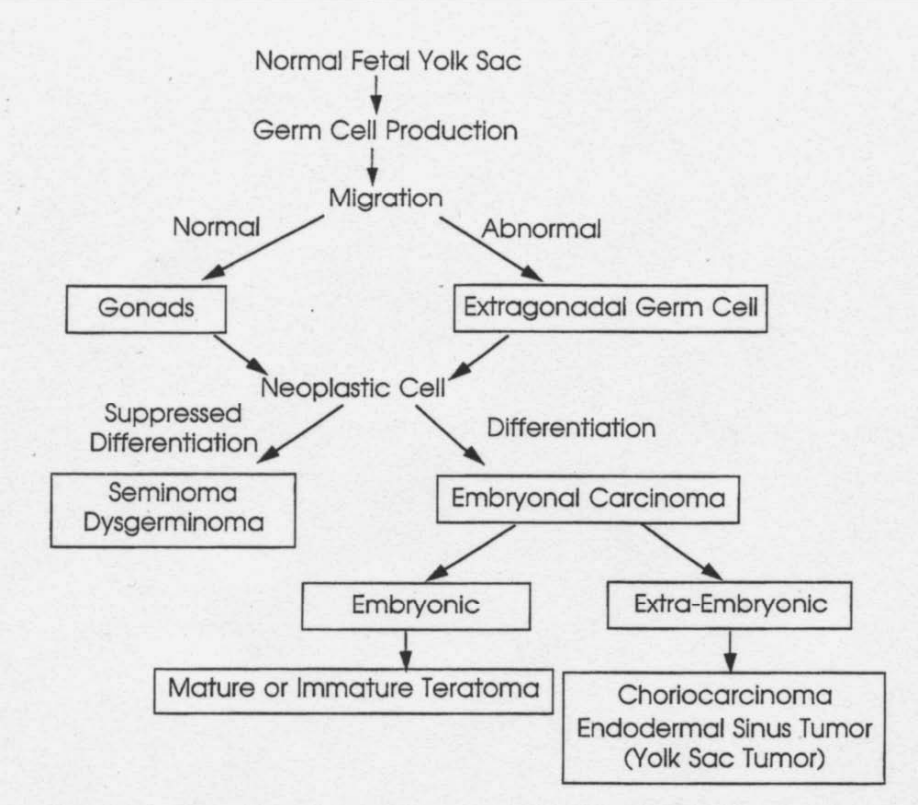

Figure 2 *Diagram of the histogenetic relationship and degree of differentiation among the various tumors of germ cell origin*

Three of the five types are observed in children: types I, II and IV. *Type I* are the teratomas and yolk sac tumors in newborns and children (all sites); their originating cell is an early primordial germ cell. Most type I teratomas have a normal chromosomal complement. The type I yolk sac tumors, on the other hand, are aneuploid with recurrent chromosomal changes such as loss of part 1p, 4, 6q, and gains of parts of 1q, 12p, 20Q and 22. These chromosomal changes are found in all anatomical sites, supporting a common pathogenesis. *Type II*, extremely rare in childhood, and occurring in the ovary, mediastinum and brain, is subdivided into the seminomatous type (called dysgerminoma when occurring in the ovary or dysgenetic gonads, and germinoma when occurring in the brain) and the non-seminomatous type. The precursor cell is the primitive germ cell or gonocyte. *Type IV* includes the dermoid cysts of the ovary that occur in children as well as in adults. The originating cell is the oogonia/oocyte. The ongoing intensive research into this domain is expected to improve understanding on how and why these tumors develop.

Little is known about the etiology of childhood germ cell tumors. Risk factors that have been examined include maternal exogenous hormone use, radiation exposure (preconception, prenatal), infection during pregnancy, parental occupational exposure and childhood virus infection (mumps, herpes virus). As smoking and alcohol consumption have been associated with alterations in endogenous estrogen levels, and as estrogen has been implicated in the possible pathogenesis of germ

cell tumors, a recent large-scale epidemiologic study analyzed this association.[21] However, no evidence was found that childhood GCT was related to prenatal exposure to parental cigarette smoking, alcohol drinking or maternal passive smoking.

HISTOPATHOLOGICAL CLASSIFICATION

Histopathological classifications have been developed for testicular and ovarian germ cell tumors. The diverse views on their histogenesis and the wide range of their histological appearances are reflected in the various classifications that have been proposed. The latter, in turn, have led to confusing nomenclature. Classification still lacks uniformity, with two systems currently in widespread use, one formulated by the World Health Organization (WHO) and the other proposed by the British Testicular Tumour Panel (BTTP). The WHO classification largely builds on the work of Melicow[22] and of Mostofi and Price.[23] It assumes that the different morphologic types of GCT are all derived from neoplastic germ cells that differentiate along various pathways. The BTTP classification system represents a modification of that originally proposed in 1964 by Collins and Pugh.[24]

The classification most widely adopted in Belgium and in the Netherlands, is the WHO classification, of which the newest version was published in 2004.[25] It distinguishes seven categories (*Table 1*).

Table 1 WHO-based classification of pediatric germ cell tumors

1	**Germinoma**		(referred to as seminoma in testis, dysgerminoma in ovary, and germinoma at other sites)
2	**Teratoma**		
	Mature		
	Immature	Grade 1	
		Grade 2	
		Grade 3	
3	**Embryonic carcinoma**		(Malignant Teratoma Undifferentiated)
4	**Yolk sac tumor**		(endodermal sinus tumor)
5	**Choriocarcinoma**		
6	**Gonadoblastoma**		
7	**Mixed malignant germ cell tumor**		

HISTOLOGICAL APPEARANCES

The description that follows intends no more than to provide a brief summary of the various histological variants of germ cell tumors. For more detailed description and illustrations, we refer to textbooks on the subject.[26]

Germinoma
This tumor, called *seminoma* when occurring in the testis and *dysgerminoma* when occurring in the ovary, is macroscopically usually well circumscribed and homogeneous. Under the microscope, the proliferating germ cells have a monotonous appearance with a polygonal shape, abundant pale cytoplasm and uniform nuclei. They aggregate in cords and clumps. The stroma, often reduced, always contains variable amounts of chronic inflammatory infiltrate, mainly composed of T lymphocytes and macrophages.

Teratoma
*Mature teratoma*s are generally well-circumscribed masses, nodular and firm. The cut surfaces are heterogeneous with solid and cystic areas. Cartilage, bone and pigmented areas may be recognizable. The well-differentiated mature (adult) tissue types (derived from all three cell layers) consist of keratinizing squamous epithelium, neural and glandular tissue. Organoid structures are not uncommon, particularly in children: skin, respiratory, gastrointestinal and genitourinary tract. Muscular tissue is the most common of the mesodermal components. Virtually, any other tissue type can be seen.

*Immature teratoma*s contain a variable amount of immature, embryonic-type tissue, mostly in the form of neuroectodermal rosettes and tubules admixed with mature tissue. Immature mesenchyme in the form of loose, myxoid stroma with focal differentiation into immature cartilage, fat, osteoid and rhabdomyoblasts is often present. Immature endodermal structures including hepatic tissue, intestinal-type epithelium and embryonic renal tissue resembling Wilms' tumor are encountered less frequently. Immature vascular structures are sometimes prominent. Immature teratomas are divided further into 3 grades, according to the quantity of immature neuroepithelial component. Grade I are those tumors with rather rare foci of immature neuroepithelial tissue that occupy less than one low power field (40x) in any slide, Grade II those occupying 1 to 3 low power fields in any slide, and Grade III those tumors with large amount of immature neuroepithelial tissue occupying more than 3 low power fields (40x) in any slide.

Older classifications also included m*alignant teratoma*, a rare tumor composed of a teratoma with a malignant non-germ cell tumor.

Embryonal carcinoma
This tumor is composed of large polygonal undifferentiated epithelial cells resembling those of the embryonic disc and growing into one or more of several patterns, glandular, tubular, papillary and solid. Macroscopically, the tumor is soft and granular, grey or whitish to pink often with foci of hemorrhage and necrosis. The tumor is often not well demarcated from the surrounding tissue. Microscopically, multiple mitoses are prominent. Syncitiotrophoblastic cells may occur scattered among the tumor cells. Cells at the periphery of the tumor may appear degenerated, smudged or apoptotic.

Yolk sac tumor
This is a tumor characterized by numerous patterns that recapitulate the yolk sac, allantois and extra embryonic mesenchyme. Macroscopically, they are solid, soft with a grey-white, sometimes gelatinous or mucoid cut surface. Hemorrhage and necrosis may be seen in larger

tumors. Tumors composed entirely of a single histological pattern are rare. Several different patterns are usually admixed within one tumor. Microcystic or reticular, macrocystic, solid, glandular-alveolar, endodermal sinus, papillary, myxomatous, polyvesicular vitelline, hepatoid and enteric patterns are observed. The reticular pattern is most characteristic: a loose, basophilic, myxoid stroma harboring a meshwork of microcystic, labyrinthine spaces lined by clear or flattened epithelial cells with various degrees of atypia. One of the other patterns, namely the endodermal sinus pattern, after which this tumor is called in certain classifications, merits special consideration. This pattern consists of structures composed of a stalk of connective tissue containing a thin walled blood vessel and lined on the surface by a layer of cuboidal cells with clear cytoplasm and prominent nuclei. These structures are known as Schiller-Duval bodies that are considered a hallmark of YST. They are seen scattered within the tumor in varying numbers. The tumor secretes α-fetoprotein.

Choriocarcinoma
This rare GCT is composed of cytotrophoblast, syncytiotrophoblast and extravillous trophoblast. Macroscopically, tumors are large and hemorrhagic. Histologically, there are fenestrated or plexiform sheets or pseudopapillae of cytotrophoblast and extravillous trophoblast admixed with numerous syncytiotrophoblasts. Vascular invasion is frequent. This tumor secretes β-HCG.

Gonadoblastoma
According to some classifications, gonadoblastoma belongs to the group of germ cell tumors, according to other classifications not. It is a benign ovarian tumor composed of germ cells and sex cord-stromal derivatives, resembling immature granulosa, and Sertoli cells. They occur in dysgenetic gonads of phenotypic female subjects who have at least a portion of the Y chromosome. These tumors usually are small, soft to firm, gray-tan to brown and slightly lobulated. Multifocal microcalcifications are responsible for the gritty feel on cut sections. Microscopically, both germ cells and sex cord cells proliferate.

Mixed malignant germ cell tumors
This category includes GCT composed of two or more types. This can be embryonic carcinoma and teratoma, teratoma and germinoma, choriocarcinoma and teratoma/embryonic carcinoma, etc.

Polyembryoma is an extremely rare neoplasm of the ovary composed exclusively of embryoid bodies in which embryonic carcinoma and yolk sac tumor components, sometimes with teratoma, are arranged in a pattern resembling the presomite embryo. It is more often, however, associated with other germ cell tumor components, especially yolk sac tumor and teratoma. The tumor is solid, soft and somewhat edematous; cystic areas suggest an associated terotomatous component. At low magnification there are numerous embryoid bodies surrounded by loose myxomatous mesenchymal tissue.

TUMOR MARKERS

The role of tumor markers in the diagnosis and follow up of patients with germ cell tumor is well established.

Alpha-fetoprotein (AFP), a α_1-globulin, is the earliest serum-binding protein in the fetus, produced in the yolk sac and in the embryonic liver and gastrointestinal tract. Its peak serum concentration is reached at 12 to 14 weeks' gestation; thereafter it gradually falls to reach an adult normal level of less than 10 ng per dL

by the age of 1 year. As AFP levels begin to decline in fetal development, albumin becomes the principal serum-binding protein. In 1974, an association between raised AFP levels in serum and the presence of yolk sac elements in a germ cell tumor was described. AFP therefore was found to be a useful and sensitive tumor marker when a germ cell tumor contains yolk sac cells.[7-9] AFP is also used for immunohistochemical staining of germ cell tumor. Elevated serum levels of AFP or positive immunohistochemical staining of germ cell tumor for AFP indicate the presence of malignant components, specifically yolk sac or embryonic carcinoma. The serum half-life of AFP is 5 to 7 days. However, as levels at birth and at different ages within the first year of life may widely vary, interpreting decay of serum AFP could be difficult. Therefore, although AFP at large is a very reliable tumor marker, it should be very cautiously used as an indicator of residual or recurrent tumor in the first ± 8 months of life. The use of normograms may be helpful.[27,28]

The β-subunit of Human Chorionic Gonadotropin (β-HCG) is another important tumor marker for germ cell tumors. This glycoprotein is normally synthesized during pregnancy by syncytiotrophoblasts of the placenta to maintain viability of the corpus luteum. Serum half-life is 24 - 36 hours. Only minute amounts are normally detected in the serum of adults. Assays for β-HCG will be positive when syncytiotrophoblasts are present in the tumor. This will be the case in choriocarcinoma and, to a lesser extent, in embryonic carcinoma and yolk sac tumor.[29]
Evidence is lacking for the clinical usefulness of carcinoembryonal antigen (CEA), CA-125 and CA-19-9 for patients with germ cell tumor.

SYMPTOMS – DIAGNOSIS – STAGING SYSTEMS

Symptoms, signs and diagnostic methods are specific to each tumor site; they will extensively be described in chapters 3 - 8, and the dominant symptoms will be schematized in the general discussion.

Various staging systems are in use. Specific staging systems have been developed for gonadal germ cell tumors, such as the International Federation of Gynecology and Obstetrics (FIGO) classification for ovarian types, based on clinical, surgical and pathologic findings. The Pediatric Oncology Group and the Children's Cancer Group further refined the FIGO classification (see chapter 3).[29] These groups developed a staging system for testicular germ cell tumors that accounts for tumor markers and also less-than-ideal transscrotal surgery to these tumors (see chapter 4).[29]

A 'universal' staging system for malignant germ cell tumors for all extracranial sites (ovary, testis, other extragonadal) is the Pinkerton classification (see chapter 2).[30] Of course, the TNM (tumor-node-metastasis) classification is another valid staging system.[31]

AN OVERVIEW OF TREATMENT MODALITIES AND PRINCIPLES

The heterogeneity of pediatric germ cell tumors relative to histological type, site of origin, age and stage demands an individualized, multimodality treatment plan. Details of treatment strategy including surgical considerations for each site of occurrence will be addressed in the following chapters and in the discussion and summary chapters. This section just goes into some generalities of treatment in the historical context.

Principles of surgery. Complete surgical resection is the (sole) therapy of choice for benign germ cell tumors. For malignant tumors, surgical removal is indicated as well, but given the availability of effective chemotherapy, resection should not be mutilating anymore, as it was until some 30 - 40 years ago. In this situation, only debulking or biopsy is appropriate. After chemotherapy, resection of remaining tumor serves to assist in achieving complete response.

Principles of chemotherapy. The outcome for patients with malignant germ cell tumors was poor before the use of systemic chemotherapy with 3-year survival rates around 20%.[32,33] The introduction of cyclophosphamide-based therapy improved the outcome for patients with localized tumors, but patients with advanced disease continued to do poorly.[34-37] For example, in a series of 57 patients with malignant germ cell tumors treated between 1962 and 1979, Kaplan Meier survival at 3, 5 and 10 years was only 42%.[37] The introduction of Einhorn's multidrug regimen (PVB) combining cisplatin, vinblastine and bleomycin, developed in 1977 for adults with testicular germ cell tumor , dramatically improved the prognosis for these patients.[38,39] This was the start of modern multiagent chemotherapy for germ cell tumors at other sites as well, also in children. From then on, several regimens have been in use: PVB, PEB, JEB, PEI, combining vinblastine (V), bleomycin (B), cisplatin (P), carboplatin (J), ifosfamide (I) and etoposide (E)[29,40] Similarly, the organizations listed in the history section (and many more) were created, organizing multigroup studies which in turn have optimized treatment regimens. All this has resulted in steadily improving survival rates, as was nicely illustrated in a paper from the American Pediatric Oncology Group published in 1986 (*Fig. 3*).[41]

Nowadays, survival rates of 80 - 90% in series of children with malignant germ cell tumor are not unusual anymore.[42] In recent years, the focus has been on reducing toxicity while maintaining the highest efficacy. The next challenge will be to define those patients who have low probability of survival with the present therapeutic strategies. This would enable us to administer dose-intensification schemes only in this subpopulation. It would not be reasonable to attempt to improve survival rates by a generalized intensification of chemotherapy, as many of those who do not need more intense chemotherapy will then suffer from side effects.

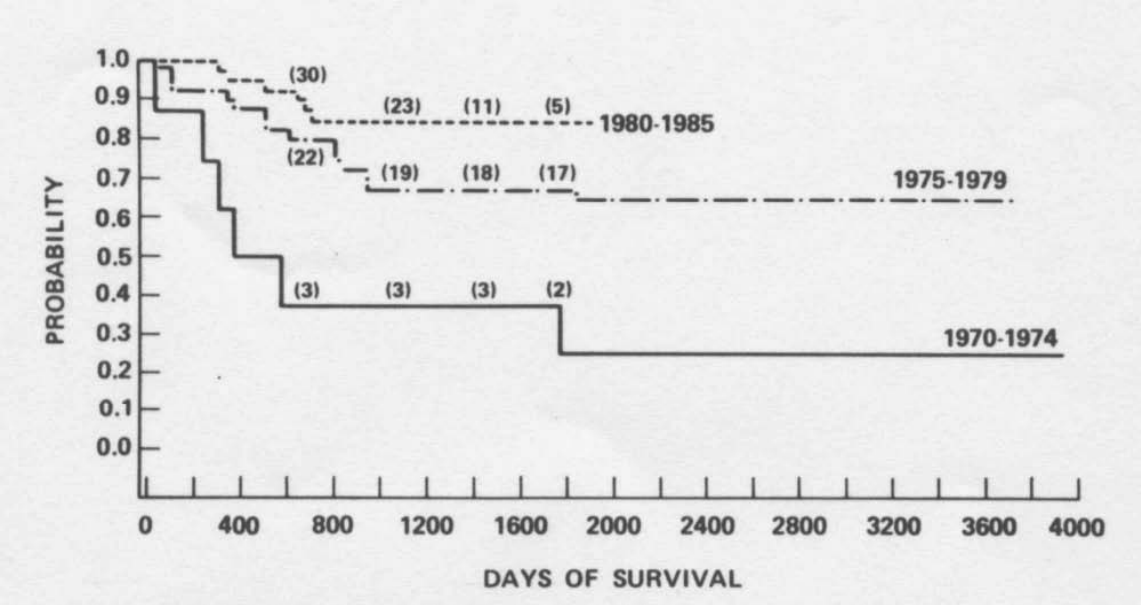

Figure 3 *Comparison of survival by date of diagnosis in a series of 89 patients with malignant nongerminomatous GCT. Overall survival probability was 0.25 in the patients treated between 1970 - 1974 (n = 8), was 0.65 in the patients treated between 1975 - 1979 (n = 30) and 0.85 in the patients treated between 1980 - 1985 (n = 49). This graph nicely shows the improved survival during the seventies and eighties. Hawkins EP, et al. Cancer 1986;58:2579 - 2584. Reprinted with permission*

Radiotherapy. The only indication for radiotherapy is for intracranial germ cell tumors, which are not included in our study. Nowadays, there is hardly any place, if any, for radiotherapy in the treatment of extra-cranial GCT – except perhaps in malignant local recurrences of sacrococcygeal teratoma.[43]

AIMS AND OUTLINE OF THE THESIS

Germ cell tumors, in particular those occurring during infancy and childhood, are extremely rare tumors. As a consequence, numbers of patients with such condition treated, even in the largest centers of pediatric surgery, are very small. The pediatric literature on this entity therefore is mainly built up of smaller series and of case reports. Furthermore, some pediatric cases have been included in series of predominantly adult patients; the characteristics of the pediatric patients are difficult to single out. The only prospective studies on pediatric germ cell tumors are those conducted by multicenter groups studying chemotherapy protocols for malignant ones. Thus there seems to be room for more large retrospective institutional studies that shed more light onto epidemiology, clinical aspects, treatment modalities and results. The large numbers of children with germ cell tumors treated in the Erasmus MC-Sophia Children's Hospital in Rotterdam never were the subject of a study so far, and neither were those treated in the Children's Hospital of the Free University in Brussels.

We therefore retrospectively studied the hospital records of in total 193 infants and children with extracranial germ cell tumors treated between 1960 and 2003 in Rotterdam and from 1987 (opening of the hospital) till 2003 in Brussels. In addition we conducted a multicenter, retrospective study of 173 patients with sacrococcygeal teratoma treated between 1970 and 2003 in all academic centers in the Netherlands, and of 18 patients treated between 1992 and 1996 in Belgium and Luxembourg. The results of these studies are presented in this thesis.

The aims of this thesis are:

- to get insight into complaints and symptoms, results of diagnostic tests, treatment modalities, pitfalls in surgical therapy, histology and outcomes (in terms of mortality and morbidity) concerning extracranial germ cell tumors and to compare results from the above two hospitals with those of other centers, for each site of occurrence. Moreover, the database thus created should also serve as a basis for further prospective long-term follow-up studies.
- to define risk factors with respect to overall prognosis in all patients with germ cell tumors.
- to study factors associated with recurrence in patients with sacrococcygeal teratoma
- to assess functional sequelae and health-related quality of life in patients with sacrococcygeal teratoma.

Outline

In Chapter 2, we will briefly present the 193 patients from Rotterdam and Brussels, focusing on the influence of tumor site and of histology on long-term survival. In Chapters 3 and 4, germ cell tumors occurring in the gonads are analyzed. The clinical data of 66 girls with ovarian GCT and 20 boys with a testicular GCT will be presented. The remaining chapters are on extra-gonadal GCT. Chapter 5 deals with cervical germ cell tumors. These tumors, although mostly benign, carry a high mortality rate. We have therefore summarized recent data from the literature and added these to our practical experience, and propose a well-structured approach for treatment. High mortality rates have been observed as well in children with mediastinal germ cell tumors. In Chapter 6, we investigated the reasons for death in our patient series. Chapter 7 concerns children with retroperitoneal teratoma who suffer a high number of intra-operative complications. We have analyzed the complications encountered in our patients and those reported by others, and explore how they might be avoided. Chapters 8 - 11 discuss patients with sacrococcygeal teratomas. Recurrence is a major issue in this patient population. In Chapters 8 and 9, we analyzed the factors that are associated with recurrence in series of 70 patients from Rotterdam, as well as in a Dutch multicenter series of 173 patients. Chapter 10 presents a smaller series of 18 patients from Belgium and Luxembourg, with a focus on obstetrical data and quality of treatment. In Chapter 11, we studied functional sequelae (fecal and urinary incontinence) in the Dutch multicenter patient series and analyzed the

influence of these sequelae on patients' quality of life. Chapter 12 presents a general discussion and conclusions about the treatment of infants and children with germ cell tumors, as well as some ideas for future investigations.

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2 Chapter

Influence of Tumor Site and Histology on Long-Term Survival in 193 Children with Extracranial Germ Cell Tumors Treated between 1960 - 2003

Antoine De Backer
Gerard C. Madern
Rob Pieters
Patrick Haentjens
Friederike G.A.J. Hakvoort-Cammel
J. Wolter Oosterhuis
Frans W.J. Hazebroek

Submitted

ABSTRACT

Background
Although germ cell tumors (GCT) supposedly share the same cell type of origin, their clinical course may differ considerably, resulting in widely ranging outcomes depending upon tumor site, histology, etc. The aim of this work was to study long-term survival stratified for tumor site and tumor histology.

Methods
Retrospective analysis of medical records of 193 consecutive infants and children (140 girls, 53 boys, median age 1 year) with extracranial GCT treated between 1960 - 2003. The GCT arose in the following anatomical sites: sacrococcygeal region (n = 70), ovary (n = 66), testis (n = 20), retroperitoneum (n = 12), neck (n = 8), mediastinum (n = 7), and miscellaneous (n = 10). Histological analysis revealed 152 teratomas (mature: 115, immature: 37), 27 yolk sac tumors, 8 mixed tumors, 2 dysgerminomas, 2 gonadoblastomas, 1 choriocarcinoma and 1 embryonal carcinoma.

Results
For the whole patient group, overall survival (OS) probability was 0.91 ± 0.02 and event-free survival (EFS) probability was 0.88 ± 0.02 at ten years (Kaplan-Meier estimates ± standard error). Statistically significant differences in EFS were observed between tumor sites and between histologies. Patients with gonadal GCT had statistically significant higher probability of OS than those with extragonadal GCT (P = 0.029). Patients with tumors in the neck and the mediastinum had statistically significant lower probability of EFS than those with gonadal, retroperitoneal or sacrococcygeal GCT (P = 0.018). Patients with choriocarcinoma, embryonal carcinoma, immature teratoma, YST and mixed GCT had lower probability of EFS than patients with mature teratoma or gonadoblastoma ($P < 0.001$).

Conclusions
Overall, germ cell tumors in childhood carry an excellent prognosis. The prognosis for gonadal GCT (regardless of histology) is better than that for those tumors at extragonadal sites. GCTs in the neck or mediastinum (regardless of histology) or a histologic diagnosis of choriocarcinoma, embryonal carcinoma or immature teratoma (regardless of site), are associated with less favorable outcome than GCTs at other sites or with other histologies. Mortality is not only dictated by malignant histology, but also, as in the case of mature teratoma, by occurrence at certain sites.

INTRODUCTION

Germ cell tumors are a heterogeneous group of very rare tumors, benign or malignant, which can occur from newborn to old age. They are thought to arise from primordial germ cells and are found in a variety of sites, either in the gonads or, following aberrant germ cell migration, in (mostly midline) extragonadal sites from the brain to the sacrococcygeal region. Those primordial germ cells can give rise to either germinoma (seminoma/dysgerminoma) or to tumors that have differentiated towards embryonal (teratoma) or extra-embryonal (yolk sac tumor, choriocarcinoma) cells.[1-5] Although GCT are supposed to originate from the same cell type, the clinical course and outcome of patients with GCT differ considerably, depending upon tumor site, histology, and other factors.[6] The few institutional publications on large numbers of patients with GCT, published in the past 20 years, were descriptive and did not contain detailed survival analyses.[7-10] Survival data were almost exclusively reported by multicenter cooperative study groups for malignant GCTs.[11-14] Mortality in patients with GCT, however, is not exclusively associated with tumor malignancy.[15] We undertook a retrospective study in patients with GCT treated in our hospitals with follow-up as long as 44 years, aiming at assessing the factors that influenced survival.

PATIENTS AND METHODS

Patients

We reviewed the medical records of the patients < 16 years of age with extracranial GCT treated either in the Erasmus MC-Sophia Children's Hospital, Rotterdam, the Netherlands between January 1960 and December 2003 or in the Academic Hospital of the Free University of Brussels, Belgium between its opening in 1987 and December 2003. During this 44-year period, a total of 193 patients were treated, the vast majority (173) in Rotterdam. Over the study period, numbers of patients almost doubled every 11-year time period: 1960 - 1970 (13 patients), 1971 - 1981 (23 patients), 1982 - 1992 (57 patients) and 1993 - 2003 (100 patients). Patients referred from other centers for second opinion or for histological confirmation of diagnosis, were excluded from this report. All relevant clinical data were entered into a Filemaker Pro database. We used the World Health Organization (WHO) classification for classifying germ cell neoplasms into 7 histologic categories: germinoma, teratoma (mature, immature), embryonal carcinoma, yolk sac tumor, choriocarcinoma, gonadoblastoma and mixed malignant GCT.[16,17] Immature teratomas were graded according to the Norris classification.[18] For the subgroup of patients with mature and immature teratomas, the "completeness of resection" was determined. All surgical protocols were reviewed according to the recommendations by Göbel.[15] Complete tumor resection was defined as a resection of all parts containing tumor tissue. In coccygeal teratomas a resection of the tumor and the os coccyx in one bloc was mandatory and in ovarian teratoma resection should include the ovary and fallopian tube. Peritoneal implants originating from ovarian primaries less than 1 cm in diameter

were not considered for complete or incomplete resection. Microsurgical excision of the tumor alone with preservation of the affected ovary was registered as incomplete resection. In the testicular site, semicastration by high inguinal dissection of the funiculus spermaticus was the treatment of choice. If all these criteria were fulfilled and no visible tumor was left, the resection was defined as complete. Incomplete resection was assumed, if 1) the tumor capsule was ruptured; 2) an infiltration of the tumor into the surrounding tissue was detected or adherent tumor parts were observed and a complete removal in one piece was not possible; 3) in coccygeal site: if the tumor was not resected en-bloc with the whole of coccyx. The tumor stages were determined retrospectively according to a staging system for malignant GCT in childhood for all extracranial sites, as proposed by Pinkerton.[2] In this classification, Stage I is defined as complete resection of primary tumor with subsequent fall of markers and no nodal involvement, Stage II as microscopic residual disease at surgical margins, and for testicular tumors transscrotal resection or biopsy, Stage III as tumors with gross residual disease, or biopsy only, nodes positive on imaging, contiguous visceral involvement in the case of ovary (omentum, intestine, bladder), diffuse tumor spill at surgery and Stage IV as those tumors with distant metastases to liver, lung, bone, bone marrow, distant nodes or brain. This staging system also allowed the classification of benign tumors into 3 stages (Stage I – III).

Statistical analysis

Overall survival (OS) and event-free survival (EFS) were estimated according to the Kaplan-Meier method. OS was defined as all-cause mortality and EFS as the time from diagnosis to the first relapse or death from any cause.[12] The remaining patients were censored at the time of the last reported examination. The univariate influence of each potential prognostic factor on OS and EFS was analyzed with the log-rank test. The following potential prognostic factors were investigated: year of diagnosis, age at diagnosis, gender, tumor site and tumor histology. *P* values < 0.05 were considered significant. Multivariate (Cox) regression analyses were conducted to investigate which factors had independent prognostic value. A subgroup univariate analysis restricted to the patients with teratomas was also performed to test the influence of complete resection on survival. All data analyses were performed using SPSS version 12.0 (SPSS, Inc., Chicago IL).

RESULTS

Sex and age

With 53 boys (27.5%) and 140 girls (72.5%), the male: female ratio was 1:2.6. Half of the patients (n = 96) were one year old or younger at the time of diagnosis. After this sharp peak in the first year of life, age at time of diagnosis was more or less equally distributed, except for a smaller and broader peak during the second half of childhood.

Tumor site

Table 1 shows histologic diagnoses, recurrences and mortality rate per tumor site. In 86 patients (45%), the tumor was located in the gonads and in 107 patients (55%) at extragonadal sites. The most frequent location was the sacrococcygeal region (36%), followed by the ovary (34%), testis (10%), retroperitoneum (6%), neck (4%) and mediastinum (4%). Rare locations included the female genital tract (uterus & vagina) (3 patients), face (eye & orbit) (2 patients), urinary bladder (2 patients), spinal cord in association with myelomeningocele (2 patients) and nasopharynx (1 patient).

Tumor histology

Histologic examination evidenced 115 mature teratomas, 37 immature teratomas, 27 yolk sac tumors, 8 combined (mixed) tumors, 2 dysgerminomas, 2 gonadoblastomas, 1 choriocarcinoma and 1 embryonal carcinoma.

Tumor Stage

Table 2 shows the stage distributions among tumor sites and histologies. In the subgroup of malignant tumors (i.e. yolk sac tumor, mixed malignant histology, dysgerminoma, choriocarcinoma and embryonal carcinoma (n = 39), 43.6% were Stage I, 5.1% Stage II, 33.3% Stage III and 18% were Stage IV.

Treatment

Surgical extirpation of the tumor was the cornerstone of treatment for most of the patients. Of all 152 teratomas, complete resection was achieved in 114 patients whereas in 34, resection was scored as incomplete according to Göbel's criteria (4 patients had not been operated upon). Patients with malignant histology as well as those with Grade III immature teratoma of ovary were given multi-agent chemotherapy using cisplatin (P), carboplatin (J), etoposide (E), ifosfamide (I), bleomycin (B) or other in combinations such as PEI, PEB or JEB and according to the international multicenter protocols of MAHO/MAKEI, SIOP and others.[11]

Recurrence

With 13 recurrences in 193 patients, the overall recurrence rate was 6.7%. Recurrence was rare in patients with mature teratoma (3.5%), higher in patients with immature teratoma (10.8%) and YST (11.1%), and was 100% in patients with choriocarcinoma and embryonal carcinoma. The latter two diagnoses, however, were each encountered in one patient only, which disallows solid conclusions to be made. Recurrences were not observed in patients with mixed histology, and in those with dysgerminoma and gonadoblastoma. Patients with immature teratoma showed a strikingly high recurrence rate (10.8%), equally high as yolk sac tumor. As to site, recurrence was rare in ovarian (4.5%), testicular (5%) and, to a lesser extent sacrococcygeal (8.6%) GCT, and was high in mediastinal GCT (28.6%). No recurrences at all were observed in retroperitoneal and cervical GCT. (*Table 1*)

Table 1 Schematic presentation of a series of 193 patients with extracranial Germ Cell Tumors

	Gonadal		Extragonadal							
	Ovary	**Testis**	**Neck**	**Mediastinum**	**Retroperitoneal**	**Sacrococcygeal**	**Miscellaneous**	**Total**	**Recurrence (%)**	**Mortality (%)**
Mature Teratoma	42 (0)	7 (0)	5 (0)	4 (0)	4 (0)	48 (3)	5 (1)	115	4 (3.5%)	5 (4.3%)
Immature Teratoma	9 (2)	4 (0)	3 (0)	1 (1)	6 (0)	12 (1)	2 (0)	37	4 (10.8%)	6 (16.2%)
Yolk Sac Tumor	3 (0)	9 (1)		1 (0)	2 (0)	9 (2)	3 (0)	27	3 (11.1%)	2 (7.4%)
Mixed Histology	7 (0)					1 (0)		8	0	1 (12.5%)
Dysgerminoma	2 (0)							2	0	0
Gonadoblastoma	2 (0)							2	0	0
Choriocarcinoma				1 (1)				1	1 (100%)	1 (100%)
Embryonal Carcinoma	1 (1)							1	1 (100%)	1 (100%)
Total	66	20	8	7	12	70	10	**193**		
Recurrence (%)	3 (4.5%)	1 (5%)	0	2 (28.6%)	0	6 (8.6%)	1 (10%)		**13 (6,7%)**	
Mortality (%)	2 (3%)	1 (5%)	3 (37.5%)	2 (28.6%)	1 (8.3%)	6 (8.6%)	1 (10%)			**16 (8.3%)**

The histologic diagnosis is plotted against tumor site.
Recurrence and mortality rates are calculated for the total series, for each tumor site and for every histologic diagnosis.
Numbers between brackets indicate patients who developed recurrence.

Table 2 Repartition of clinical Stages for the various tumor sites and histologies

	STAGE				Patients not operated upon
	I	II	III	IV	
Ovarium	56 (1)	2	7 (1)	1	
Testis	14 (1)	3	2	1	
Neck	5 (1)		1		2 (2)
Mediastinum	4		2 (1)	1 (1)	
Retroperitoneal space	7	2	1	1	1 (1)
Sacrococcygeal region	48 (3)	11 (1)	8 (1)	2	1 (1)
Miscellaneous	4		5 (1)	1	
Teratoma, mature	96 (2)	9	7	Not applicable	3 (3)
Teratoma, immature	24 (2)	7 (1)	5 (2)	Not applicable	1 (1)
Yolk Sac Tumor	9 (1)	2	10 (1)	6	
Mixed Histology	7 (1)		1		
Dysgerminoma	1		1		
Gonadoblastoma	1		1		
Choriocarcinoma				1 (1)	
Embryonal Carcinoma			1 (1)		
TOTAL	**138 (6)**	**18 (1)**	**26 (4)**	**7 (1)**	**4 (4)**

Numbers between brackets represent deaths

Mortality

Sixteen patients died, of whom 6 after recurrence, resulting in a mortality rate of 8.3%. The mortality causes were: impossibility to obtain an airway in the case of huge cervical teratoma (2), intraoperative bleeding in a huge retroperitoneal teratoma (1), postoperative septicaemia (1), postoperative pneumothorax and intraventricular hemorrhage (1), complications of chemotherapy (bleomycin alveolitis (1), second T-cell ALL (1)), uncontrollable tumor progression (8). Moreover, treatment was intentionally withheld in one patient with sacrococcygeal teratoma plus severe associated malformations. Tumor sites in the patients that died were: sacrococcygeal (6 patients), neck (3 patients), mediastinum and ovary (2 patients each) and testis, retroperitoneal space and nasopharynx (1 patient each). The initial histological diagnoses in the patients who died from uncontrollable tumor progression were mature teratoma (1 patient), immature teratoma (3 patients), YST (2 patients), choriocarcinoma (1 patient) and embryonal carcinoma (1 patient).

The single patient in our series with embryonal carcinoma and the other with choriocarcinoma, both died. Mortality in the patients with immature teratoma was 16.2%, with mixed tumors 12.5%, with yolk sac tumor 7.4% and with mature teratoma 4.3%. Mortality was particularly high for tumors in the neck (37.5%), and in the mediastinum (28.6%). Sacrococcygeal and retroperitoneal tumors had a mortality rate of 8.6 and 8.3%, respectively. Lowest mortality was observed for GCT in the gonads (ovary: 3%, testis: 5%). As one group, gonadal GCTs (mortality rate 3/86 = 3.5%) carried a better prognosis than extra-gonadal GCTs

(mortality rate 13/107 = 12.1%). (*Table 1*) Mortality has remained stable over the first three 11-year periods (15%, 12.5% and 13%, respectively); only during the last 11-year period a reduction in mortality rate (2.5%) could be observed.

Factors predictive of overall survival (OS) and event-free survival (EFS)
Overall survival (OS)(0.91 ± 0.2) and EFS (0.88 ± 0.02) curves for the complete series of patients at ten years (Kaplan-Meier probability estimate ± standard error) are depicted in *Fig. 1*. Univariate Kaplan-Meier analyses demonstrated a statistically significant difference in EFS when stratified for tumor site (*Fig.2*) (P = 0.018) and for tumor histology (*Fig.3*) (P < 0.001). (*Table3*) Probability of survival at 10 years for gonadal and extragonadal GCT was 96.3% and 87.6%, respectively (P = 0.029). The 10-year OS and EFS did not differ between boys and girls and did also not differ between patients treated before or after 1989. Age at diagnosis did not influence OS or EFS. A subgroup analysis restricted to the 152 patients with mature and immature teratoma, testing the influence of either complete or incomplete resection according to the criteria of Göbel on survival, did not show a statistical difference (P = 0.198).

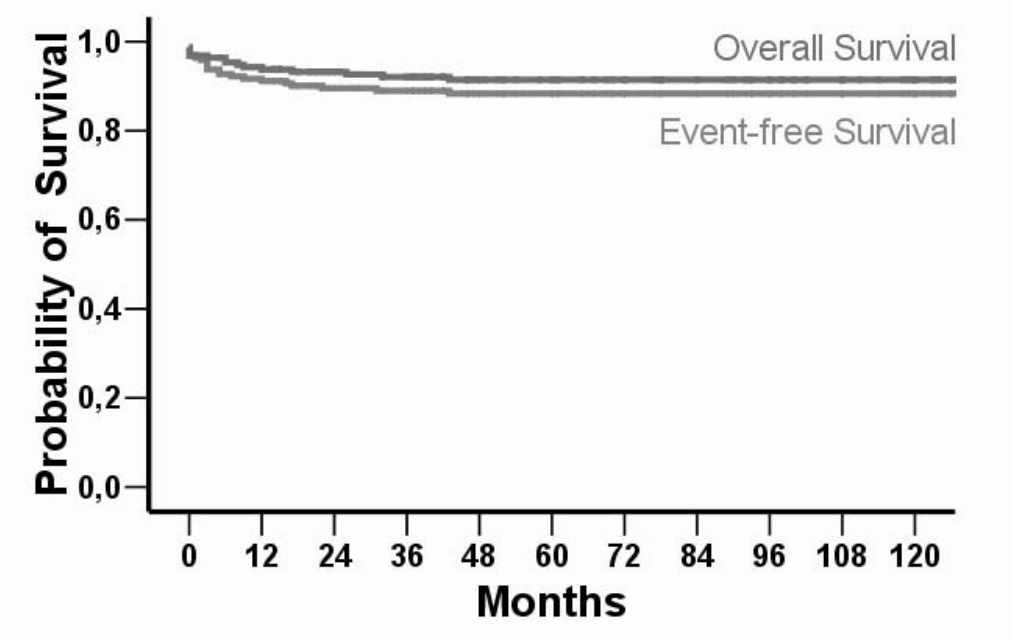

Figure 1 *Overall survival (91.4 ± 2.1%) and event-free survival (88.3 ± 2.3%) in 193 infants and children with extracranial germ cell tumor operated upon between 1960 and 2003 (Kaplan- Meier estimate at 10 years, probability ± standard error, expressed as a percentage)*

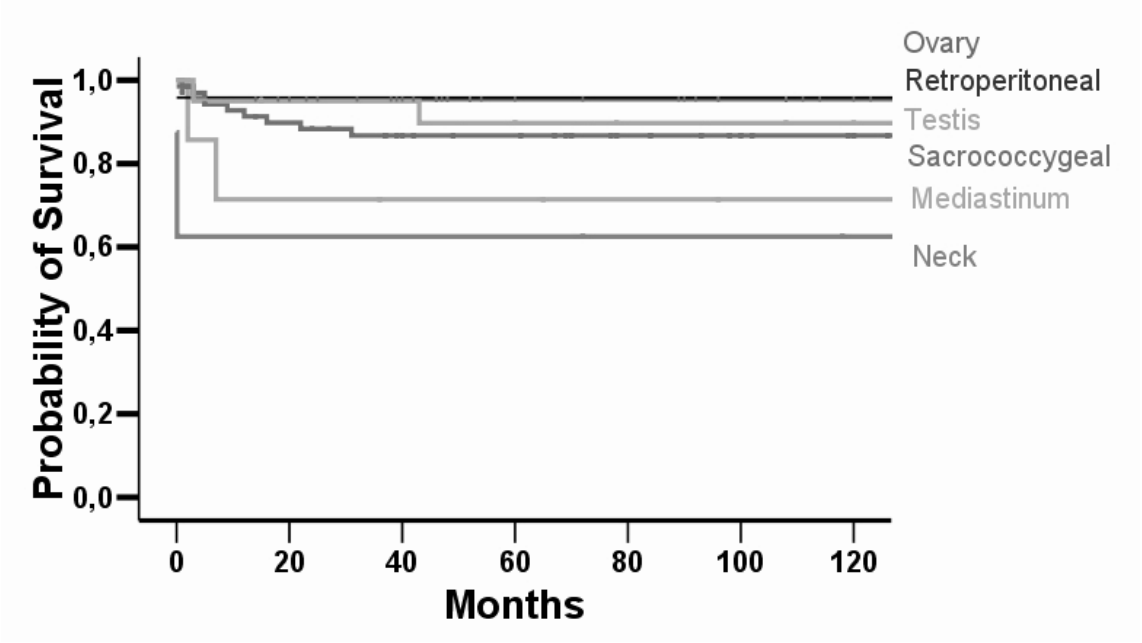

Figure 2 *Event-free survival according to the primary site of tumor. Very rare tumor sites (< 5 patients) have been left out: female genital tract, spinal cord, bladder and prostate, eye and orbit, nasopharynx. Both gonadal locations showed excellent survival rates (Kaplan-Meier estimate at 10 years: ovary: 95.5 ± 2.6, testis: 89.7 ± 6.9). Likewise good event-free survival rates were achieved in retroperitoneal GCT (91.7 ± 7.9), and sacrococcygeal GCT (86.7 ± 4.1). Survival for mediastinal (71.4 ± 17.1) and cervical (62.5. ± 17.1) GCT was significantly lower. The curves for ovarian and retroperitoneal GCT are almost identical and overlap each other in this figure.*

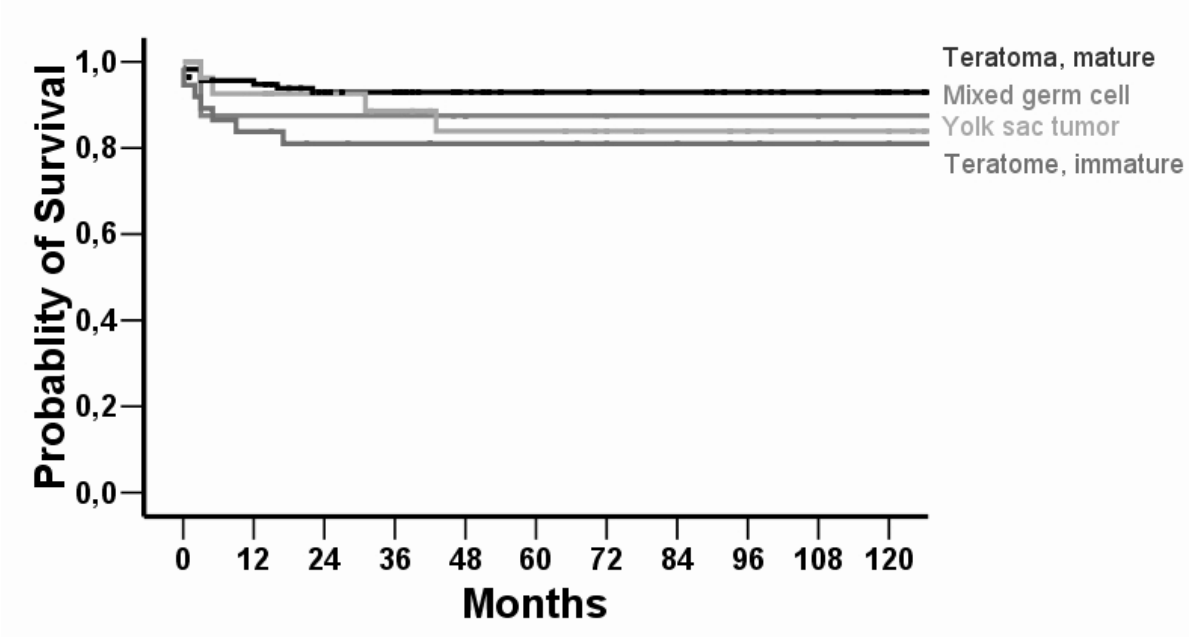

Figure 3 *Event-free survival according to the histological diagnosis. Very rare histologic diagnoses (<5 patients) have been left out, i.e.choriocarcinoma, gonadoblastoma, embryonal carcinoma and dysgerminoma. Mature teratomas had the best prognosis (Kaplan-Meier percentage estimate at 10 years: 92.3 ± 2.5), but mixed tumors had good EFS as well (87.5 ± 11.7). Percentages of event-free survival were similar for immature teratoma (80.1 ± 6.5) and for YST (83.9 ± 7.4).*

Table 3 Kaplan-Meier estimates of overall and event-free survival at 10 years in 193 patients with GCT, according to tumor site and histological diagnosis

		Number of Patients	Overall Survival	Event-free Survival
Tumor site	Sacrococcygeal	70	91.1 (3.5)	86.7 (4.1)
	Ovary	66	96.9 (2.1)	95.5 (2.6)
	Testis	20	94.7 (5.1)	89.7 (6.9)
	Retroperitoneal	12	91.7 (7.9)	91.7 (7.9)
	Neck	8	62.5 (17.1)	62.5 (17.1)
	Mediastinum	7	71.4 (17.1)	71.4 (17.1)
	Female genital tract	3	/*	/*
	Spinal Cord	2	/*	/*
	Bladder and prostate	1	/*	/*
	Other	4	75.0 (21.6)	50.0 (25.0)
Histology	Teratoma, mature	115	95.6 (1.9)	92.2 (2.5)
	Teratoma, immature	37	83.2 (6.3)	80.1 (6.5)
	Yolk Sac Tumor	27	91.7 (5.6)	83.9 (7.5)
	Dysgerminoma	2	/*	/*
	Mixed histology	8	87.5 (11.6)	87.5 (11.7)
	Choriocarcinoma	1	0 (0)	0 (0)
	Gonadoblastoma	2	/*	/*
	Embryonal Carcinoma	1	0 (0)	0 (0)

Numbers between brackets represent standard error
/ survival estimates cannot be computed since all observations are censored.*

Multivariate (Cox) regression analysis of the impact of several factors on survival

Multivariate (Cox) regression analyses were used to estimate adjusted effects of potential prognostic factors on OS and EFS. Potential prognostic factors were included in regression models if there was statistical evidence of, or a theoretical basis for, a relationship to OS and EFS. Two significant predictors of poor EFS were identified: tumor site (P = 0.027) and tumor histology (P = 0.008). These factors were independently predictive of a lower probability of EFS. An association between OS/EFS and gender (P = 0.286), age at diagnosis (P = 0.218) or year of diagnosis (P = 0.363) could not be established

Discussion

This retrospective study confirms the rarity of GCT; 193 patients with extracranial GCT treated over a 44-year span is not imposing as a large series, yet it is among the largest published, apart from a recent cooperative multicenter study that included 150 centers.[4] Over the study period, numbers of patients with GCT steadily increased. Of course, concurrent advances in perinatal care have allowed for survival of children who would otherwise have died before coming to hospital. Centralization of pathology as well as better patient registration may also account for the increase in numbers of patients. Whether our data also reflect a true

increase in incidence of pediatric GCT in the Netherlands and in Belgium, cannot be proved with this study, although there is some likelihood. Indeed, a recent study reported an increasing trend in incidence for acute lymphoblastic leukemia, Hodgkin's disease and for malignant CNS tumors, but also for germ cell tumors and hepatic tumors.[19] With an overall mortality rate of 8.3%, this series compares favorably with the few other larger series published in the past 20 - 25 years, which reported mortality rates from 9 to 36%.[4,7-10] This series covers a period of major changes in the surgical-technical domain, in chemotherapy, and also in medical imaging and in supportive care. Surgery has remained the cornerstone of treatment for the majority of cases. For gonadal GCT, we have witnessed a shift from aggressive surgery (inguinal orchiectomy plus retroperitoneal lymph node dissection for testicular tumors, extended ovariectomy with omentectomy for ovarian tumors) towards orchiectomy/ovariectomy or even tumorectomy. Chemotherapy protocols have changed as well. The introduction of cisplatin and the recognition of its potency for GCT in the mid-eighties, as well as the creation of intergroup studies such as MAHO/MAKEI, SIOP, UKCCSG and POG/CCG have dramatically improved the survival rates of malignant GCT.[2,4,13,14,20] Improvements in prenatal diagnosis and perinatal care have led to delivery by sophisticated procedures such as the EXIT-procedure (ex-utero intra-partum treatment) of children who otherwise would have died in utero or during transportation to a tertiary centre.[21,22] This is especially so for newborns with huge cervical teratoma. Therefore, we had expected mortality rates to diminish gradually over time. However, only over the last decade a reduction in mortality rate could be observed. Significant associations between year (period) of diagnosis and OS/EFS could not be demonstrated, in view of the low numbers of patients. Previous survival studies in patients with malignant GCT showed high prognostic significance of tumor site, clinical tumor stage and histology, especially in the pre-cisplatinum era. In the present period, after the introduction of cisplatin, those factors appeared to have partly lost their prognostic relevance, and completeness of tumor resection has emerged as a new, highly relevant prognostic factor.[11] The present study, which also includes histologically benign GCT, confirms the importance of tumor site as a prognostic parameter. Indeed, GCTs in the gonads (3.5% mortality rate) carry a statistically significant better prognosis than extragonadal GCTs (12.1% mortality). The mere fact that these tumors/organs are much easier to remove (when compared with those in mediastinum, retroperitoneum or sacrococcygeal region for instance) might be an explanation for this finding. Notwithstanding a lower proportion of malignant histologies, the prognosis for GCT in the neck and mediastinum is worse when compared to the gonads, retroperitoneum and the sacrococcygeal area, due to non-oncological factors.

In this series, we could not find evidence for the completeness of resection as being of prognostic significance in patients with mature or immature teratomas, as was documented earlier by Göbel.[15] The percentage of patients with incomplete resection in our series (23%) compares remarkably well with Göbel's series (24%).

Although numbers of patients still are relatively small (152 and 270, respectively), this probably cannot represent a bias for the discrepancy between both studies. Complete resection must of course be pursued in every patient. In our experience, the cases where a sacrococcygeal teratoma was not resected in one bloc with the coccyx, but separately, had not necessarily a bad prognosis. Similarly, absence of removal of the fallopian tube in patients with ovarian teratoma in whom histologically complete tumorectomy has been achieved, do probably not represent a higher risk for recurrence or for impaired outcome. Further studies are recommended to shed more light on this important issue.

The one patient with embryonal carcinoma and the one with choriocarcinoma in this series died. These latter histologies are associated with 50% survival rates in other studies.[13] The 4.3% mortality rate in patients with mature teratoma in this series might seem incomprehensible. However, death was the result of tumor progression in one patient only (initially mature teratoma, recurrence as grade IV Yolk sac tumor), the remaining being the result of the impossibility to obtain an airway in 2, of septicemia, and of the decision to withhold from treatment in a baby with severe associated malformations. Similar mortality rates in patients with mature teratoma were reported by others as well.[11]

A striking finding in this series was a mortality rate of 16.2 % in patients with immature teratoma (all grades), which was twice that for YST (7.4%). Only patients with grade III immature teratoma had received chemotherapy.

Age at diagnosis in our series was not a predictor of outcome. Another series with malignant GCT only, however, found a favorable prognosis in those infants aged less than 1 year.[13] Of course, a specific histology may bear a different prognosis depending on the site of the tumor. Due to their similar origin, GCTs are often considered as one group of tumors. This study however underlined again that each specific histology at each specific location is a separate, specific entity with its own characteristics and prognosis.

Nowadays, most patients with GCT have excellent prognosis, provided a diagnosis is obtained without delay. For patients with e.g. sacrococcygeal, cervical and retroperitoneal teratoma, this means a correct antenatal diagnosis allowing to opt for the best timing (at term, before term) and method (vaginal, caesarean section, EXIT-procedure, OOPS-procedure) of delivery and even for experimental fetal procedures such as stapling of the exophytic part of sacrococcygeal teratoma in children with a hyperdynamic state which represents a threat of hydrops. For newborns with cervical teratoma, for instance, the EXIT–procedure has resulted in improved survival.[22,23]

Thanks to the multicenter grouping of patients into protocols, it has been possible to establish ideal treatment protocols that nevertheless are still being refined and updated in order to achieve even better survival rates, but also to diminish the

complications of therapy. Indeed, prevention of the functional sequelae associated with GCT at specific sites – fertility for gonadal GCT, neurogenic bladder and fecal incontinence in children with SCT – will be one of the main challenges for the future.

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Chapter 3

OVARIAN GERM CELL TUMORS IN CHILDREN: A CLINICAL STUDY OF 66 PATIENTS

Antoine De Backer
Gerard C. Madern
J. Wolter Oosterhuis
Friederike G.A.J. Hakvoort-Cammel
Frans W.J. Hazebroek

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ABSTRACT

Background
Ovarian germ cell tumors are rare in childhood. The aim of this study is to review clinical presentation, management, and outcome in a two-center series of girls with ovarian germ cell tumor.

Procedure
The records of 66 patients (median age 9 years) with histologically proven ovarian germ cell tumor (either benign or malignant), treated over a 44-year-span, were reviewed.

Results
Pain and an abdominal mass were the most frequent symptoms. The tumors were right-sided in 35, left-sided in 28, and bilateral in 3. Most patients (52) were stage I, 4 were stage II, 6 stage III, and 1, with liver metastases, stage IV. Sixteen patients had an emergency operation for tumor torsion. Unilateral salpingo-oophorectomy was the most frequently performed procedure (n = 46), and ovarian-sparing tumorectomy was performed in 9 patients (one bilaterally). Histologically, teratomas were found most frequently (mature: 45, immature: 9), followed by mixed tumors (n = 7), yolk sac tumors (n = 3), dysgerminoma (n = 2), gonadoblastoma (n = 2), and embryonal carcinoma (n = 1). Surgical removal of the tumor with or without the ovary and/or adnex was the sole treatment in 55 patients, chemotherapy was administered in 10 and radiotherapy + chemotherapy in one. Intra-operative spillage of tumoral fluid occurred in six; this did not influence outcome in five. Recurrence was observed in three patients. Two patients, with malignant disease, died. The 64 survivors are now between 8 months and 44 years after treatment.

Conclusions
With a recurrence rate of 4.5% and a mortality rate of 3%, this series confirms the excellent prognosis for girls with ovarian germ cell tumor (GCT).

INTRODUCTION

Ovarian tumors are uncommon in children. Their incidence is estimated to be approximately 2.6 cases per 100,000 girls per year.[1] About one third of all childhood ovarian neoplasms are reported to be malignant. Malignant ovarian neoplasms make up about 1% of all childhood cancers.[2] Histologically, germ cell tumors (GCT) are more frequent than epithelial and sex cord-stromal tumors. Their etiology is unknown.[3] Although good results of treatment are generally reported, even with malignant GCT, several questions on diagnosis and treatment remain. The objective of this study, therefore, is to review clinical presentation, treatment, and outcome in our two-center series of girls with ovarian GCT. This might broaden the knowledge on this rare childhood tumor.

PATIENTS AND METHODS

The medical records of all 66 patients with histologically proven ovarian GCT treated in Erasmus MC-Sophia Children's Hospital, Rotterdam, The Netherlands between January 1960 and December 2003 (n = 60) and in the Hospital of the Free University of Brussels, Belgium between its opening in 1987 and December 2003 (n = 6), were reviewed. Ovarian GCT appeared to constitute 31% of all GCT (all locations) treated in these institutions over this 44-year-span. This makes the ovary the second location for GCT after the sacrococcygeal region.

We recorded symptoms that led to further investigation and to diagnosis, age at diagnosis, the radiological and biochemical methods employed in the diagnosis, methods of treatment, and complications. Clinical staging was according to the Children's Oncology Group staging, a modification of the FIGO (International Federation of Gynecology and Obstetrics staging for ovarian tumors) classification.[4] This classification defines Stage I as a tumor limited to the ovary, stage II as a tumor with pelvic extension, microscopic residual or positive lymph nodes < 2 cm, stage III as a tumor with gross residual or biopsy only, contiguous visceral involvement, lymph nodes with malignant metastatic nodules > 2 cm, and stage IV as a tumor with distant metastases, including liver. The histopathologic records of all patients were studied in detail, and the tumors were typed according to the WHO classification.[5-7] Immature teratomas were graded according to the Norris classification.[8]

RESULTS

Age

Age at diagnosis ranged from 3 months till 15 years (mean and median: 9 years). The age distribution showed that tumors were diagnosed at every age, with a slight predominance between ages 8 and 14 years.

Symptoms

In two patients, the diagnosis had been made antenatally by routine ultrasound; they appeared to be asymptomatic after birth and during the first weeks of life. The other 64 patients presented with altogether 131 symptoms, predominantly pain and an abdominal/pelvic mass. Abdominal pain, either acute, chronic, or both was reported for 47 patients (71%). The second most frequent symptom, major abdominal distension by the abdominal or pelvic mass, was noted for 36 patients (55%), associated with pain in 21 and painless in 15. A mass was reported for 21 of the 47 girls with abdominal pain. A third important symptom was constipation, reported for 21% of the patients. Nausea and vomiting was reported for 11%, and urinary symptoms for 9% of the patients. Four girls (6%) showed endocrine symptoms: isosexual precocious puberty in two, precocious pseudopuberty in one, and hypogonadotropic hypogonadism with delay of puberty in one. Fever, fatigue, and anorexia were rare. In three patients, the diagnosis resulted from the school physician noting an abdominal tumor at routine clinical examination.

Imaging

Various imaging studies were used for the work-up of these patients over the years, except in those with an acute abdomen. In the sixties and seventies, plain abdominal X-rays combined with "indirect" imaging using intravenous pyelography, barium enema, arteriography, etc. were used to confirm the diagnosis, whereas in more recent years abdominal ultrasound, and abdominal CT or MRI were performed. Thus, calcifications were observed in 40 patients. The space-occupying lesion was reported to be purely cystic in 6, purely solid in 3, and mixed cystic-solid in 44 patients. In the other 13 patients, the radiology report did not permit a classification. Tumor dimensions ranged from 2.5 x 1.5 x 1.5 cm till 24 cm in diameter, with corresponding volumes from 3 cm^3 till 7,230 cm^3 (mean 950 cm^3).

Tumor markers

Alpha-feto-protein levels were elevated in eight patients (three with pure yolk sac tumor, three with mixed tumor with yolk sac component, two with immature teratoma (Gr II and III)), and were normal in all others. Beta HCG levels were normal in all patients.

Tumor side and stage

The tumors were right-sided in 35, left-sided in 28, and bilateral in 3. Sixty-three patients could be staged retrospectively according to the Children's Oncology Group staging of ovarian GCT: 52 were stage I, 4 were stage II, 6 stage III, and 1 stage IV.

Histology

The histologic diagnosis of the 69 tumors is summarized in *Table 1*. Mature teratomas were the commonest tumors (n = 45), followed by immature teratomas (n = 9), combined (mixed) malignant tumors (n = 7), yolk sac tumors (n = 3), dysgerminoma (n = 2), gonadoblastoma (n = 2), and embryonal carcinoma (n = 1). The distribution of benign or malignant GCT by age groups is shown in *Table 2*.

Table 1 Histopathologic diagnosis in 66 patients with altogether 69 ovarian germ cell tumors

Teratoma	54
Mature	45
Immature	9
Grade I	5
Grade II	3
Grade III	1
Combined (mixed)	7
Dysgerminoma + gonadoblastoma	1
Dysgerminoma + mature teratoma	1
Polyembryoma + mature teratoma + low-grade angiosarcoma	1
Yolk sac tumor + immature teratoma	2
Embryonal carcinoma + mature teratoma + immature teratoma + yolk sac components	1
Mixed germ cell-sex cord stroma tumor and sex cord tumor with annular tubules	1
Yolk sac tumor	3
Dysgerminoma	2
Gonadoblastoma	2
Embryonal carcinoma	1

Table 2 Distribution of benign/malignant GCT by age groups

Age (years)	Total GCT	Benign	Malignant (% of total)
0 - 5	16	13	3 (19%)
6 - 10	29	25	4 (14%)
11 - 15	24	16	8 (33%)

Treatment

Surgery was considered the sole treatment necessary in 55 patients, surgery + chemotherapy in 10 other patients, and surgery + chemotherapy + radiotherapy in 1. Two of the patients initially treated with surgery alone showed tumor recurrence after 5 and 3 months, respectively, and were subsequently treated with chemotherapy. The multi-agent chemotherapy regimens administered were according to the international protocols of SIOP and MAKEI through the years (VAC, VAPB, PVB, PEB, JVB, PEI).

Seventeen patients with acute symptomatology had undergone emergency surgery: 16 for torsion of the tumor, one for apparent tumor rupture. The others had been operated upon electively. Only one stage IV patient with a secreting tumor and liver metastasis had chemotherapy first, followed by surgery.

Various surgical approaches have been used over the years: median (21) or transverse (18) laparotomy, Pfannenstiel laparotomy (14), Mc Burney laparotomy (2), laparoscopy followed by open surgery (5) or laparoscopic surgery (2). In four of the oldest patients, the operative report did not mention the exact approach. The procedures consisted of unilateral salpingo-oophorectomy (n = 46), unilateral

oophorectomy (n = 9), unilateral ovarian-sparing tumorectomy (n = 10), and bilateral salpingo-oophorectomy (n = 1). The contralateral ovary was always inspected and palpated very carefully in every patient; a suspect lesion was biopsied in five patients. Bivalving of the contralateral ovary was never performed. Frozen sections histology was performed to rule out peritoneal malignant inplants in two patients; the diagnosis of peritoneal gliomatosis was made correctly with this technique. The tumors themselves were not subjected to frozen sections histology. Ascites was sent for cytologic analysis when present, and did not reveal malignant cells in any of the patients, of whom one had malignant recurrence.

Intraoperative rupture of the tumor was reported in six patients (*Table 3*). In one patient with mature teratoma (patient 5), a cyst rupture resulted in spillage of the operative region with a clear fluid. This patient did not show recurrence. Rupture of the tumoral capsule occurred in three other patients with malignant tumors (patients 3, 4, and 6) and in one with an immature grade II teratoma (patient 2). All received adjuvant chemotherapy resulting in remission for a median of 8 years. Only one patient with embryonal carcinoma (patient 1), treated over 30 years ago, who had intraoperative tumor rupture, never went into remission, and died.

Postoperatively, one patient developed a wound abscess, and three a mechanical small intestinal obstruction by adhesions. In one patient, the obstruction subsided with conservative measures, in the two others surgical adhesiolysis was necessary to relieve the obstruction.

Recurrence (*Table 4*) was observed in three girls (4.5%), two of whom had similar clinical courses. The first is an 11-year-old (patient 8) who ultimately died from alveolitis after one course of bleomycin. The second is a 7-year-old (patient 9) who underwent salpingo-oophorectomy with omentectomy (the omentum adhered to the tumor) for an immature teratoma grade II (stage III) of the left ovary with gliomatosis peritonei. We initially did not administer chemotherapy. Three months later, she showed inguinal metastasis in the right groin. The histologic diagnosis was immature teratoma. Chemotherapy (PEI) was started, but then she developed a right-sided subdiaphragmatic recurrent tumor, which continued to grow under treatment. This tumor was removed and characterized histologically as immature teratoma. She was treated with temozolamide in compassionate use, and is now in remission since 1 year. A third patient with immature grade III teratoma treated with chemotherapy (patient 7) developed a recurrent intrapelvic tumor. Histologically, this tumor was entirely benign, however, and was excised completely. This patient shows no evidence of disease 15 years after treatment.

Table 3 Survey of the six patients whose operation was complicated by intra-operative tumor spill

Patient	Year of treatment	Age at diagnosis	Histology	Adjuvant treatment	Recurrence?	Final outcome
1	1974	13	Embryonal carcinoma	VAC + radiotherapy	Tumor control never achieved	Died 6 months after diagnosis
2	1995	14	Immature teratoma grade II	PEB	No	NED 8.5 years
3	1995	14	Mixed tumor (YST + immat. T.)	JVB	No	NED 9 years
4	1996	10	Mixed tumor (YST + immat. T.)	PEB	Yes	NED 8 years
5	2000	14	Mature teratoma	None	No	NED 3.5 years
6	2002	12	YST	PEI	No	NED 2 years

NED *no evidence of disease*

Table 4 Survey of three patients who developed recurrence

Patient	Year of treatment	Age at diagnosis	Initial histology	Treatment	Time elapsed till recurrence	Histology of recurrent tumor	Treatment	Final outcome
7	1988	11	Immature teratoma grade III	Complete surgical excision, chemotherapy	6 months	Ganglioneuroblastoma, benign	Complete surgical excision	No evidence of disease, 15 years after treatment
8	1990	11	Immature teratoma grade I	Complete surgical excision	5 months	Immature teratoma	Surgical biopsy, chemotherapy	Died from bleomycin alveolitis, 4 months after start of chemotherapy
9	2003	7	Immature teratoma grade II	Complete surgical excision	3 months	Immature teratoma	Chemotherapy + surgical excision	In remission for 1 year

Outcome

Two patients (3%) died. One is a 12-year-old with embryonal carcinoma in the left ovary with contiguous visceral involvement of sigmoid colon, uterus, bladder, pelvic peritoneum, and omentum. Tumor spillage had occurred during attempt at removal. Despite chemotherapy (in 1974 consisting of VAC (vincristine, actinomycin-D, and cyclophosphamide)) and radiotherapy (3,000 rad) she never experienced remission, and died 5 months after diagnosis. The second is an 11-year-old with immature teratoma grade I, stage I, who showed a picture of carcinomatosis peritonei (histologically proven recurrence of multiple immature teratoma in the omentum, cavum Douglasi and peritoneum) with ascites, 5 months after the initial operation. Chemotherapy was started (in 1990 VAPB (vinblastine, actinomycin-D, cisplatin, bleomycin). She died from bleomycin alveolitis 4 months after start of chemotherapy, 9 months after the initial diagnosis.

The 64 surviving patients are now aged between 3.5 and 56 years, and are between 8 months and 44 years after onset of treatment. Fifteen patients are being followed regularly, 12 with benign disease, and 3 with malignant tumors who have been in remission for 3 months, 1.5, and 2.5 years respectively.

DISCUSSION

Ovarian pathology in general, and ovarian germ cell tumors in particular, are rare in childhood. Sixty-six ovarian GCTs over a 44-year-period do not really constitute a large series, yet it is the second largest of its kind reported in the past decade.[1,9-13] The literature shows a discrepancy in age distribution for malignant tumors. Malignancy was stated to occur far more frequently at lower ages.[9] The assertion that 80% of the ovarian neoplasms in girls aged 9 years or less were malignant,[11] was cause for great concern and definitely influenced the extent of surgery in former years. However, these findings sharply contradict those from our study (*Table 2*). We found a much more equal distribution of malignancy over the ages, even an increase with increasing age: 19% malignancy in the age group 0 - 5 years, 14% in the group 6 - 10 years, and 33% in the group 11 - 15 years. Only one other study reports a similar trend, although with much lower incidence in the youngest age group.[10] Thus, from our study and from Brown's study,[10] we might conclude that teenagers are at higher risk for malignancy than are younger infants. We cannot explain the discrepancy between the various series, except by referral patterns and the small numbers of patients reported.

Twenty-five percent of our patients had acute symptomatology requiring urgent surgical exploration, and were found to have torsion. Seemingly high, this proportion was reported by others too.[13] Bilaterality was observed in only 5% of cases, a proportion falling between those reported by Van Winter (6%) and Cass (2.8%).[11,13] All these figures are lower than the 10% usually reported.

This series confirms the excellent over-all results that can be achieved in children with ovarian GCTs. Obviously, a 100% survival with low morbidity is now the rule for benign ovarian neoplasms. The introduction of platinum compounds in the multi-agent chemotherapy regimens in the mid-eighties has resulted in high survival rates for malignant ovarian GCT as well. Moreover, recent protocols focus at reducing the complication rates of chemotherapy. One of the two non-survivors in our series was treated in 1974, long before cisplatin became available. Of course, we do not know for certain whether she would have survived with cisplatin chemotherapy. Yet there is every likelihood that she would have survived, seeing that the most recently published intergroup study on children with malignant ovarian germ cell tumors reports 6-year survival rates between 93% and 97%![14,15] The second patient died from bleomycin alveolitis; bleomycin has now been excluded from some recent chemotherapy regimens, and is used at lower doses in other regimens.[15]

An important issue is the extent of surgical therapy. The vast majority of the patients in our series underwent unilateral salpingo-oophorectomy (70%) or oophorectomy (14%). In 15% of cases, unilateral ovarium-sparing tumorectomy had been performed. Ovarian-sparing surgery was certainly not the standard policy in our departments, as the literature still reports salpingo-oophorectomy to be the traditional management procedure.[16] But with the increasing concern for the fertility potential, and the rise of minimally invasive surgical procedures, one may wonder if salpingo-oophorectomy is really necessary in cases that impose as benign (well-circumscribed tumor, no evidence of distant disease, no ascites, no elevated tumor markers). Nine girls in our series underwent 10 ovarium-sparing procedures with favorable outcome, and have never showed evidence of recurrence. They are now between 1 and 21 years after surgery (mean and median: 10 years). This outcome, albeit in very few patients, suggests that conservative surgery might be justified in selected cases. This attitude was taken up long ago already in treating young adult women, and has been proposed for pediatric patients in bilateral disease.[17] Although there is frequently no apparent residual ovarian tissue to salvage or to reconstruct, salvaging the hilar capsula and reconstructing the "ovary" as we do for pure ovarian cysts, seems a worthwhile procedure.[18] Beiner reported no recurrences in eight patients with immature teratoma treated by cystectomy, and followed in five by adjuvant chemotherapy.[19] Silva reported a similar result.[20] As bilaterality in GCTs may occur asynchronously, we must proceed with extreme caution in view of the fertility potential. Ultrasound may aid in the selection of those with apparently benign disease, the predictive value of a nonmalignant diagnosis being reported as high as 95.6%.[21]

Regarding the approach, several reports in adults propagate the laparoscopic technique for benign teratomas.[22,23] Skills in pediatric laparoscopic surgery have increased over the past decade as well.[16,24] Smaller tumors may certainly be dealt with laparoscopically. Nevertheless, GCTs in childhood are often very large, rendering laparoscopic removal less advantageous when compared with adults.

Moreover, intraoperative tumor rupture and spillage of tumor into the peritoneum need to be avoided at all cost, because they have been associated with recurrence. Perioperative tumor spillage, reported in 9% in our series, fortunately did not lead to recurrence, except in the patient treated 30 years ago in the era before platinum-based chemotherapy. Reported spillage rates in laparoscopic excision of dermoid cysts range considerably. In a series of 340 adult women aged 15 - 70 years, laparoscopic enucleation of the dermoid cyst without rupture was successful in 7% only.[22] Spillage occurred in 52% in a pediatric series, but without subsequent peritonitis or recurrence.[16] On the other hand, spillage rates with laparoscopy close resemble those reported with laparotomy; in Shalev's series.[23] the spillage rate was 13%, for example.

We conclude that ovarian germ cell tumors in children have an excellent prognosis even when malignant. Apparently benign tumors (non-secreting, no ascites, no lymph nodes or distant tumors, no ingrowth of tumor) can probably be treated safely with a more conservative surgical procedure (ovarium-sparing tumorectomy rather than oophorectomy or salpingo-oophorectomy), in order to conserve the fertility potential to its fullest. This statement, however, needs to be confirmed by studies in larger numbers of patients. The fate of remaining with a single ovary does not imply a reduced fertility potential to conceive.[25] However, women have no compensatory mechanism for the loss of one ovary and, as the number of primordial follicles in the ovary is finite, these women may have a shorter reproductive life span. The manner in which chemotherapy influences fertility is still a matter of dispute with fertility being reported either to be seriously compromised[26] or not at all.[27,28] More work is needed to shed more light on this issue.

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4 Chapter

TESTICULAR GERM CELL TUMORS IN CHILDREN: MANAGEMENT AND OUTCOME IN A SERIES OF 20 PATIENTS

A. De Backer
G.C. Madern
K.P. Wolffenbuttel
J.W. Oosterhuis
F.G.A.J. Hakvoort-Cammel
F.W.J. Hazebroek

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ABSTRACT

Testicular germ cell tumors occurring during childhood are extremely rare. This study reports the clinical presentation, pathological diagnosis, treatment methods and outcome in a series of 20 boys, aged between 3.5 months and 16 years (median: 1.5 years; 19 were prepubertal), who were treated between 1963 and 2003. Histologically, mature teratoma was present in seven, immature teratoma in four and yolk sac tumor in nine. Nineteen patients were stage I; only one patient was stage IV. Of the 11 teratomas, 10 were treated by orchiectomy and one by testis-sparing tumor excision only. All 11 patients have survived and show no evidence of disease between 10 and 28 years after surgery. The nine patients with yolk sac tumor were managed by orchiectomy, in two plus retroperitoneal lymphadenectomy, and in eight plus chemotherapy. One patient is in remission for 10 months, seven are alive with no evidence of disease for 5.5 - 23 years, and one patient died from a T-cell acute lymphoblastic leukemia, 2 years after the end of treatment of the testicular tumor. A gradual switch towards less invasive treatment has been observed over the years. This study confirms the excellent cure rates obtained in children with testicular germ cell tumor, provided diagnosis is prompt and treatment accurate.

INTRODUCTION

In contrast to adults, in infants and children testicular tumors are extremely rare. Their annual incidence is estimated to be between 0.5 and 2 per 100 000 children.[1] Only 1% of all pediatric solid tumors are testicular in origin. Of all true intra-testicular tumors, 77 - 82% are germ cell tumors (GCTs).[1,2] Consequently, reports on this subject are rare as well. This retrospective study was undertaken to study the clinical behavior of testicular GCTs in a series of pediatric patients, with the intention of improving understanding of this rare tumor.

MATERIALS AND METHODS

We analyzed the records of 20 patients with testicular GCT treated between 1963 and 2003 in the Erasmus MC-Sophia Children's Hospital in Rotterdam, The Netherlands, and in the Children's Hospital of the Free University of Brussels, Belgium. As the total number of children with GCT (all locations) treated during the period 1960 - 2003 in our institutions was 212, the proportion of testicular GCT was 9.5%, making the testis the third most frequent location after the sacrococcygeal region (33%) and the ovary (31%).

For every patient, age at presentation, symptoms and methods for diagnosis were recorded. The operation charts were analyzed in depth as well as the pathology reports. The patients were retrospectively staged according to the Pediatric Oncology Group/Children's Cancer Group Staging of Testicular Tumors,[3] defining stage I as a tumor limited to the testis, completely resected, with no spill, no evidence of disease beyond the testes and normalization of tumor markers, stage II as a tumor removed trans-scrotally with gross spill of tumor, microscopic scrotal residual, retroperitoneal lymph node involvement $\leq$ 2 cm, and increased tumor marker, stage III as patients with retroperitoneal lymph node involvement > 2 cm, and stage IV as distant metastases, including liver. Finally, the hospital follow-up reports were summarized. We have a strict follow-up protocol for all the patients with testicular GCT (including teratomas). The protocol includes regular control visits with clinical examination, determinations of α-fetoprotein and β-HCG and testicular US; patients are seen every 3 months during the 1st year, every 4 months during the 2nd year, every 6 months during the 3rd year, and finally at 4 and 5 years after treatment. Only one boy in this series died of a second malignancy; namely a T-cell acute lymphoblastic leukemia 2 years after the end of chemotherapy for his testicular yolk sac tumor.

RESULTS

A summary of the clinical data of the 20 patients is listed in *Table 1*. The median age at diagnosis was 1.5 years (range: 3.5 months to 16 years). Nineteen patients were prepubertal and were very young: eight were 1 year old or younger, 16 were

2.5 years old or younger and 19 were 5 years old or younger. The 20th patient was 16 years old.

The tumors were right-sided in 14 boys and left-sided in six. The main symptom or sign was a hard hemiscrotal swelling, painless in 18 and painful in two. In four patients, the swelling had a bluish color, which led to a false diagnosis of hydrocele. Only one patient had symptoms due to metastatic disease (abdominal pain, nausea, and weight loss). Ultrasonography of the testis and the abdomen, plain X-ray of the thorax and α-fetoprotein levels were the examinations performed preoperatively in most patients (except in the earliest years of the study when US was not yet implemented in clinical practice). The methods of treatment and the outcome will be analyzed per category, according to the histological diagnosis. In this series of patients, there were seven with mature teratoma, four with immature teratoma, and nine with yolk sac tumor.

Treatment and outcome in seven patients with mature teratoma

These seven boys, aged between 3.5 months and 5 years (median: 1 year), had stage I tumor in the right (n = 4) or left (n = 3) testis. Tumor markers were normal in all cases. Four patients (cases 3 - 5 and 7) underwent inguinal radical orchiectomy as the sole treatment. None showed recurrence, and all are free of disease between 10 and 27 years after treatment. In the patient reported as case 1, a small cystic tumor was biopsied through an inguinal incision. Once the histological diagnosis of mature teratoma was known, it was decided not to perform an orchiectomy, but to follow the patient. This patient developed a recurrent mature teratoma, which was treated with inguinal orchiectomy 5 years after the initial operation. In another patient (case 2), operated upon for a hydrocele, a small tumoral testicular lesion was detected during the operation. The tumor was biopsied. After the histological diagnosis of mature teratoma became available, an inguinal orchiectomy was performed. Both patients are now free of disease, 27 years after treatment. In the patient reported as case 6, tumorectomy of a mature teratoma was performed. Excision of the tumor was judged complete, and the patient followed. This boy did not show recurrence and it is now 11 years after his treatment.

Treatment and outcome in four patients with immature teratoma

These four patients aged between 4 months and 1 year (median: 7.5 months) were all stage I. In three patients, the tumor was situated in the right testis, in one in the left testis. α-Fetoprotein level was normal in cases 9 - 11, and was not determined in case 8 who was treated 40 years ago. In two patients (cases 8 and 10), diagnosis of a testicular tumor was made on clinical grounds, and these patients underwent inguinal radical orchiectomy. In two other patients (cases 9 and 11), the initial diagnosis was hydrocele; during surgery, it became apparent that there was a testicular swelling or localized tumor, and these tumors were biopsied. One week later, orchiectomy was performed using the inguinal route in case 9, and using a combined inguinal/transscrotal approach in case 11 (as a

consequence of adhesions and bleeding following the biopsy procedure). None of these patients showed recurrence. They are now at 41, 27, 16 and 11 years after treatment without evidence of disease.

Treatment and outcome in nine patients with yolk sac tumor

These patients were somewhat older than the patients with teratoma; they had a median age of 2.5 years (range: 1.5 - 16 years). Their tumors were predominantly right-sided (n = 7). Staging and treatment over the years have changed considerably in this series of patients. The two oldest patients underwent a staging laparotomy with retroperitoneal lymphadenectomy; the others were staged by US and by the more sophisticated imaging techniques such as CT and MRI. Eight patients were stage I, and only one patient (the oldest of this series), with metastases in the liver, lungs and supraclavicular lymph nodes, was stage IV. In two patients, data for α-fetoprotein levels were lacking; in the other patients this tumor marker was strongly elevated, except in case 17. In case 20, β-HCG levels were strongly elevated as well. Inguinal radical orchiectomy was performed as the first procedure in eight patients. In the patient who did not show elevated α-fetoprotein levels, an open biopsy was performed first, followed by inguinal orchiectomy. Surgery was followed in seven patients by chemotherapy. The regimen changed according to the protocols at the time: the oldest patient requiring chemotherapy was given VcrAC (vincristine, actinomycin-D and cyclophosphamide), from the 1980s on PVB (cisplatin, vinblastine and bleomycin) and JEB (carboplatin, etoposide and bleomycin) regimens were used, and in the most recent case TIP (taxol, ifosfamide and cisplatin) was used as salvage therapy for a mixed response. In the latter case, stem cell pheresis was performed as well. Case 17 was admitted to the emergency department 1 day after his initial cure with PVB for respiratory depression due to severe polyneuropathy. He recovered relatively well from this iatrogenic complication, but it was decided to stop chemotherapy. In two patients (cases 18 and 19) no adjuvant treatment was given; however, case 19 relapsed after 3 months (elevation of α-fetoprotein, retroperitoneal enlarged lymph nodes) and subsequently received JEB treatment. One patient (case 20) is still under treatment; in seven there has been no evidence of disease between 5.5 and 23 years after the end of chemotherapy. Only one patient died (case 16), repeat chemotherapy having induced an initial remission. The cause of death was not testicular cancer, but the development of a second malignancy, namely T-cell acute lymphoblastic leukemia, 2 years after the end of treatment for his testicular cancer.

Table 1 Summary of 20 patients with testicular germ cell tumor

Case number	Year of treatment	Age at diagnosis	Location of tumor	Clinical stage	α-Fetoprotein	Treatment	Chemotherapy	Recurrence/treatment	Outcome
(a) Patients with mature teratoma									
1	1972/1977	5 Years	Left	I	Normal	Initially only biopsy	No	Yes (5 years later)/ inguinal orchiectomy	NED - 27 years
2	1976	10 Months	Right	I	Normal	Unexpected discovery of a small lesion during cure for hydrocele; orchiectomy 1 week later	No	No	NED - 28 years
3	1977	1 Year	Left	I	Normal	Inguinal radical orchiectomy	No	No	NED - 27 years
4	1992	2 Years	Right	I	Normal	Inguinal radical orchiectomy	No	No	NED - 12 years
5	1992	11 Months	Right	I	Normal	Inguinal radical orchiectomy	No	No	NED - 12 years
6	1993	3.5 Months	Left	I	Normal	Inguinal tumorectomy	No	No	NED - 11 years
7	1994	4 Years	Right	I	Normal	Inguinal radical orchiectomy	No	No	NED - 10 years
(b) Patients with immature teratoma									
8	1963	1 Year	Right	I	Not determined	Inguinal radical orchiectomy	No	No	NED - 41 years
9	1977	6 Months	Right	I	Normal	Incidental discovery during hydrocele surgery; biopsy; orchiectomy 1 week later	No	No	NED - 27 years
10	1988	4 Months	Left	I	Normal	Inguinal radical orchiectomy	No	No	NED - 16 years
11	1993	9 Months	Right	I	Normal	Incidental discovery during hydrocele surgery; biopsy; orchiectomy (via inguinal and trans-scrotal route) 1 week later	No	No	NED - 11 years

Case number	Year of treatment	Age at diagnosis	Location of tumor	Clinical stage	α-Fetoprotein	Treatment	Chemotherapy	Recurrence/treatment	Outcome
(c) Patients with yolk sac tumor									
12	1979	5 Years	Left	I	Unknown	Inguinal radical orchiectomy + retroperitoneal lymphadenectomy	VcrAC	No	NED - 23 years
13	1984	1.5 Years	Right	I	Unknown	Inguinal radical orchiectomy + retroperitoneal lymphadenectomy	PVB	No	NED - 19 years
14	1987	2.5 Years	Right	I	Normalization 1 week postoperative	Trans-scrotal biopsy/inguinal orchiectomy	PVB	No	NED - 16 years
15	1988	2.5 Years	Right	I	Strongly elevated	Inguinal radical orchiectomy	PVB	No	NED - 16 years
16	1990	2.5 Years	Right	I	Strongly elevated	Inguinal radical orchiectomy	PVB	No	Died from T-cell ALL 2 years after end of treatment testicular tumor
17	1990	1.5 Years	Right	I	Normal	Inguinal radical orchiectomy	Incomplete PVB	No	NED - 14 years polyneuropathy
18	1998	1.5 Years	Right	I	Strongly elevated	Inguinal radical orchiectomy	No	No	NED - 5.5 years
19	1998	1.75 Years	Right	I	Strongly elevated	Inguinal radical orchiectomy	No	Yes (after 3 months)/JEB	NED - 5.5 years
20	2003	16 Years	Left	IV (metastases in lung, liver and supraclavicular lymph nodes)	Strongly elevated (β-HCG as well)	Radical orchiectomy via inguinal and trans-scrotal route)	PEB/TIP + stem cell pheresis	No	In remission since 10 months

ALL *acute lymphoblastic leukemia*
NED *no evidence of disease*
VcrAC *vincristine-actinomycinD-cyclophosphamide*
PVB *cisplatin-vinblastine-bleomycin*
TIP *taxol-ifosfamide-cisplatin*
JEB *carboplatin-etoposide-bleomycin*

DISCUSSION

The awareness that we have treated only 20 patients with a testicular GCT over a 44-year time span, as well as the very scarce literature on this subject, testifies to the extreme rarity of this tumor. Indeed, most single or two-center series published recently report each on just a few patients.[4-9] The three larger series are multicentric studies in the frame of pediatric oncology group studies.[10-12] The present study, with a survival rate of 95%, confirms the excellent prognosis for (prepubertal) children with GCT of the testis. Other recent multicentric studies produced similar results.[10-12]

Our study largely confirms several facts and trends with regard to testicular tumors in children. In our series also, the most common presentation of this condition was that of a painless scrotal mass. The preoperative diagnosis of testicular tumor was made correctly in 80% of the patients; the remaining 20% were initially diagnosed as hydrocele, which is a high incidence when compared to the 7% reported by Kay.[1] It is known that testicular tumors may induce a reactive hydrocele. Hydroceles usually are not operated upon before the age of 2 - 3 years, which explains why the presence of a hydrocele may delay diagnosis by several months, at least in the young infant. In contrast with other series, we had no cases that were initially diagnosed as inguinal hernia or acute scrotum.[12] Testicular GCTs are usually discovered in the first years of life. For the 19 prepubertal boys, the diagnosis was made between 4 months and 5 years, with a mean age of 22 months and a median age of 18 months. This figure is identical to that in Kay's series.[1] This study also confirms that nearly all patients are stage I at the time of diagnosis, which is in contrast to adults, of whom only 35% are stage I at the time of diagnosis. Histologically, we have diagnosed mature and immature teratomas as well as yolk sac tumors. Yolk sac tumors have been diagnosed at a somewhat later age (mean: 4 years; median: 2.5 years) than immature (mean and median 7.5 months) or mature (mean: 2 years; median: 1 year) teratomas. This difference, however, is not significant, and thus should not be used as a predictor of possible malignancy. α-Fetoprotein levels were good indicators of malignancy, except in one boy. This being a historical series covering a 44-year span, various treatment strategies have been used, showing a gradual switch towards less invasive treatment. This is true for chemotherapy regimens but also as far as the aggressiveness of surgery is concerned. Indeed, we have observed an evolution from radical inguinal orchiectomy to testis-sparing surgery for benign cases, and from radical inguinal orchiectomy plus retroperitoneal lymph node dissection and chemotherapy to radical inguinal orchiectomy only for stage I malignant tumors, reserving chemotherapy for more advanced stages. Trans-scrotal violation has occurred in three patients mostly because of adhesions and the large size of the tumor. As could be expected from the literature on adults, this has been without consequence for the outcome. Hemiscrotectomy, therefore, has been abandoned.[13,14] Neither is retroperitoneal lymphadenectomy recommended routinely anymore in the protocols.

Frozen section histology has been documented to be a reliable tool for discriminating between benign and malignant tumors.[15] It can thus be used whenever testis-sparing surgery is considered and should be implemented in the management strategy. For cases that immediately impose as malignant tumors (raised α-fetoprotein levels, enlarged retroperitoneal lymph nodes, eventually symptoms of metastatic disease), the surgical treatment consists of an inguinal approach with early vascular control of the testicular vessels and orchiectomy. For the other cases (α-fetoprotein levels within normal limits, no signs or symptoms of metastatic spread) as well as for those cases incidentally discovered during surgery for hydrocele, an inguinal approach with early vascular control, followed by enucleation of the tumor with frozen section histology, appears to be the treatment of choice, thereby conserving fertility potential at its fullest. Of course, the risks of (too) radical surgery must be weighed against the risks of inadequate therapy.

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Chapter 5

STRATEGY FOR MANAGEMENT OF NEWBORNS WITH CERVICAL TERATOMA

Antoine de Backer
Gerard C. Madern
Cees P. van de Ven
Dick Tibboel
Frans W.J. Hazebroek

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ABSTRACT

Background
Cervical teratomas are extremely rare tumors with high perinatal mortality and morbidity rates.

Objective
To compare our experience and outcome in newborns with cervical teratoma with similar reports from the literature, in order to propose a structured approach.

Methods
A retrospective review of seven patients treated between 1986 and 2000 was performed. The results of these seven patients were compared with and added to a series of 44 well-documented patients retrieved from the literature.

Results
In four of the seven patients, the diagnosis was not suspected antenatally. Three of the patients survived, one died. In the other three, the diagnosis was made antenatally. Two were born using the ex-utero intrapartum treatment (EXIT) procedure, one by planned cesarean section. Only one of these three survived. Mortality in the total series of 51 patients was 33% overall, and 46% in the group in which the diagnosis had been made antenatally. Peri- and post-operative complications were reported in 27%. Although larger tumors caused polyhydramnios more frequently than smaller tumors, and were associated with more severe respiratory distress, the relationship between tumor volume at birth and final outcome could not be established. This makes difficult the identification of fetuses with a disastrous prognosis.

Conclusion
Although mostly benign, cervical teratomas are still associated with high mortality rates. Timely antenatal diagnosis is indispensable in reducing the morbidity and mortality caused by upper airway obstruction. A structured approach to the management of cervical teratoma is proposed.

INTRODUCTION

Teratomas in the cervical region are extremely rare tumors; their incidence is estimated at one in 40,000 – 80,000 live births, and they account for 2 - 6% of all teratomas and for 2% of all neonatal tumors.[21] Consequently, the literature comprises a few small series of patients and many single case reports,[11] describing a range of diagnostic measures and treatment modalities. Although most cervical teratomas in children are histologically benign, the final outcome remains rather poor with an overall mortality rate of 30 - 35%, and even up to 75% in some small series.[9,15,28] The outcome and prognosis are almost exclusively determined by the degree of airway compression at birth.[5]

The goal of our study was two-fold. First, to add seven well-documented cases from our institutions to the literature. Second, to analyze the factors that determine outcome in all the sufficiently documented cases published over the past 20 years. An emphasis is placed on analyzing pitfalls encountered in diagnosis and therapy, with the aim of establishing an optimal treatment scheme.

PATIENTS AND METHODS

We analyzed the records of seven cases of congenital cervical teratoma treated between 1986 and 2000 in the Erasmus MC-Sophia Children's Hospital in Rotterdam, The Netherlands (cases 1, 2, 3 and 5) and the Children's Hospital of the Free University of Brussels, Belgium (cases 4, 6 and 7). Each pregnancy was analyzed for possible complications, such as polyhydramnios and premature labor, duration, and possible antenatal diagnosis of a cervical tumor. Modes of delivery were analyzed, as well as the presence of respiratory distress in the newborn and the subsequent measures taken. Tumor volumes (measured at birth) were calculated by multiplying tumor three spatial dimensions in cm by 0.523 (a formula used by radiologists to calculate the volume of ovaloid masses starting from the three axes). Timing of operation, possible peri- and postoperative complications or findings were analyzed, as well as associated malformations and tumor histology.

These seven patients were compared with previous cases published between 1982 and 2002 that were described in sufficient detail. Details include: sex, gestational age, timing of diagnosis, complications of pregnancy (especially polyhydramnios), mode of delivery, presence of respiratory distress, necessity for intubation, tumor volume and histology, mortality and morbidity. The 44 patients thus retrieved[1,2,5,6,9,10,14-20,22,24-33] were added to the seven from our institutions, totalling 51 cases. In search of parameters that may influence outcome, relationships between the various parameters were analyzed. Data were statistically analyzed with Student's t-test, taking $P < 0.05$ as the level of significance.

RESULTS

Table 1 lists the clinical details of our seven patients.
In four patients (two male, two female), the diagnosis was not suspected antenatally and the patients were delivered vaginally. Cervical tumors with volumes ranging between 42 and 365 ml were clearly visible at birth. In one patient (no 5), the tumor was initially diagnosed as cystic hygroma and treatment was deferred. The other three were operated upon between the second and seventh day after birth, and perioperative complications were not encountered. In the postoperative course, however, two of the patients suffered from severe ventilatory problems. One of these, a very premature baby (no 2) died 48 hours after surgery. This 1500-g baby was born following forceps extraction for premature labor at gestational age of 31 weeks. The diagnosis of cervical tumor had been made at birth. Respiratory distress necessitated intubation and, during transportation to our center, ventilation was reported to be difficult. Upon arrival in our NICU, the baby was severely hypoxic; resuscitation measures resulted in pneumothorax. The tumor was removed on the second day of life. Postoperatively, serious ventilatory problems continued. Transfontanellar ultrasound (US) showed intra- and periventricular haemorrhage as a result of prematurity and perinatal asphyxia. Further treatment was withheld. The other three patients are alive and in good clinical condition 17, 14 and 9 years, respectively, after surgery.

In three patients (two female, one male), the diagnosis was made antenatally at gestational ages ranging between 19 and 29 weeks. Severe polyhydramnios, necessitating repeated amnioreduction, was present in two patients. Patients no. 4 and 7 had giant teratomas with tumor volumes of 884 and 2202 ml. Patient no. 4 was delivered by urgent cesarean section in the presence of a neonatologist and a pediatric surgeon. Severe respiratory distress was observed. Immediate nasopharyngeal intubation and subsequent ventilation resulted in insufflation of the cervical mass. The baby rapidly deteriorated and died 15 minutes after birth. At autopsy, tumoral insufflation appeared to have resulted from iatrogenic perforation of the trachea. Patients no. 6 and 7 were born by means of the ex-utero intrapartum treatment (EXIT) procedure. This procedure, introduced in the mid-1990s, involves cesarean section with the baby still on placental support, thus allowing time to secure an airway, either by intubation or tracheotomy. Patient no 6 (*Figure 1*) was intubated orotracheally before the umbilical cord was clamped. Hypothyroidism had already been diagnosed preoperatively, after which hormone replacement was started. The baby underwent a successful operation on the ninth day of his life, and recovered uneventfully from surgery and anaesthesia. Patient No 7 was also delivered using the EXIT procedure. Immediately prior to delivery, the largest cyst of the tumor was punctured, and 800 ml of fluid was evacuated. Cesarean section was performed and while on uteroplacental bypass the baby girl was intubated orotracheally with some difficulty. Clinical examination showed a monstrous anterior neck mass with multiple dilated vessels visible *(Figure 2)*
.

Table 1 Summary of clinical data in seven patients with cervical teratoma

Patient	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Year of treatment	1986	1989	1989	1992	1994	1999	2000
Pregnancy duration (wks)	40	31	43	31	40	32	35
Polyhydramnios	No	Yes	No	No	No	Yes (severe)	Yes (severe)
Antenatal diagnosis	No	No	No	Yes (29 wks)	No	Yes (21 wks)	Yes (19 wks)
Sex	M	F	M	F	F	M	F
Weight (g)	3100	1530	3990	1489	3000	2230	4450
Mode of delivery	Vaginal	Vaginal	Vaginal	Urgent c/section	Vaginal	EXIT	EXIT
Respiratory distress	Moderate	No	No	Severe	No	Irrelevant	Irrelevant
Tumor size (cm)	5 x 4 x 4	6,5 x 6 x 2,5	13,5 x 8 x 6,5	13 x 13 x 10	4 x 8 x 5	10 x 5,5 x 4,5	18 x 18 x 13
Tumor volume (ml)	42	51	367	884	84	129	2202
Timing of operation	Day 7	Day 2	Day 3	Not operated	7 months	Day 9	Not operated
Peroperative complications?	None	None	None		None	Tracheal tear, sutured	
Postoperative complications?	Lung atelectasis necessitating prolonged artificial ventilation	Severe ventilatory problems due to bilateral pneumothorax, intra- and periventricular cerebral bleeding	None		Severe gastro-esophageal reflux	Gastro-esophageal reflux; several weeks after discharge from hospital, resuscitation following massive aspiration	
Tumour histology	Mature teratoma	Immature teratoma	Immature teratoma	Mature teratoma	Mature teratoma	Immature teratoma	Mature teratoma
Associated Anomalies	None	None	Bifid sternum	None	Incomplete left cheiloschisis	Hypothyroidy necessitating substitution, already present before the operation	Situs inversus totalis
Outcome	Excellent	Died 48 h after operation	Excellent	Resuscitation immediately after birth resulted in insufflation of the tumor with demise of patient, died 15 min after birth	Excellent	Alive, but severely neurologically handicapped	Circulatory collapse due to steal phenomenon by this extremely vascularized tumor. emergency operation impossible, died 3 h after birth

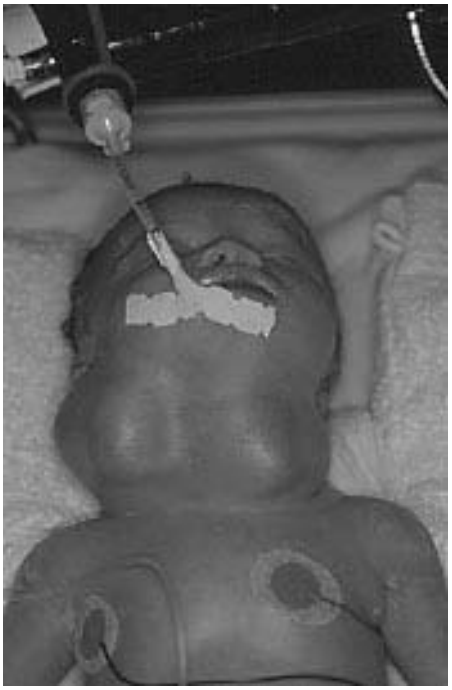

Figure 1 *Frontal view of cervical teratoma in case no. 6, immediately after the EXIT procedure.*

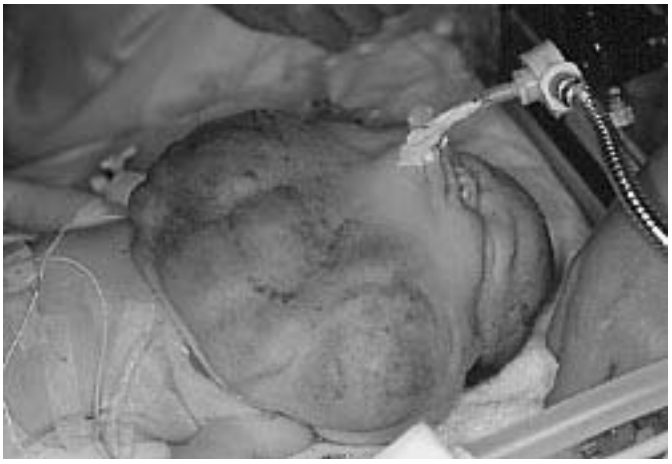

Figure 2 *Extremely huge and hyper-vascularized cervical teratoma in case no. 7, immediately after EXIT procedure. This baby was extremely hemodynamically unstable and died shortly after birth.*

The extreme vascularization of the tumor was responsible for steal phenomenon, resulting in circulatory collapse. Resuscitation was started immediately. Echocardiography demonstrated situs inversus totalis. Forceful compression of the tumor was necessary to maintain circulation. The baby's condition deteriorated progressively, resulting in death 3 hours after birth. The weight of the neck tumor was 2400 g, i.e. 54% of the total body weight. Tumor histology in this series showed mature teratoma in four patients and immature teratoma in three.

Table 2 lists the clinical data of 44 well-documented patients described in the literature, in addition to the seven patients reported for the first time in this paper. The total series of 51 patients shows a slight preponderance of females (57%) over males (43%). In 26 patients (51%) the diagnosis was made antenatally between 19 and 34 weeks of gestation (median: 27 weeks), in 24 patients (47%) at birth, and in one (2%) at a later age. In the group of patients with the larger tumors, prenatal diagnosis was made more frequently ($P < 0.05$) compared to those with smaller tumors. Polyhydramnios was present in 64% of all pregnancies; in the group diagnosed antenatally, it was present in 88% of pregnancies. However, no relationship could be found between the tumor volume and the presence/absence of polyhydramnios ($P = 0.164$, N.S.). In total, 12 of the 26 fetuses (46%) in whom the diagnosis was made antenatally were delivered by the EXIT-procedure. They were either intubated (n = 24) or underwent tracheostomy (n = 2) while on placental bypass. The other 14 babies were born by cesarean

section; 10 of them had severe respiratory distress at birth and were intubated. Respiratory distress was present in 68% of patients in whom the diagnosis was not made antenatally, reported as "severe" in 36%, and as "mild" in 32%. The patients with larger tumors had more severe respiratory distress than those with smaller tumors (P = 0.005). Gestational age at birth ranged between 21 and 40 weeks (median: 36 weeks). Overall, tumor volumes ranged between 19 and 2202 ml (mean, 410 ml; median, 242 ml). Tumor volume in the antenatal diagnosis group (mean, 556 ml; median, 368) was higher than in the at-birth diagnosis group (mean, 225 ml; median, 157 ml) (P < 0.05). Frank malignancy was not described in any of the patients. Overall, two-thirds of the patients had histologically mature teratomas. In the antenatal diagnosis group, however, immature teratoma (58%) was more frequent than the mature type (42%), whereas in those diagnosed at birth, immature teratoma (14%) was rather rare. The overall mortality rate in this series was 33%. Mortality in the antenatal diagnosis group (46%) was higher than that in the patients diagnosed at birth (20%). Surprisingly, tumor volumes at birth in the non-survivors (459 ± 159 ml) did not significantly differ from those in the survivors (351 ± 74 ml) (P = 0.487, NS) (*Figure 3*). A huge variety of peri- and postoperative complications were reported in 27% of the patients.

DISCUSSION

Though seemingly small, the series presented here is one of the larger series of patients with cervical teratoma in the literature (*Table 3*), thus confirming the extreme rarity of this lesion.

Most cervical teratomas in newborns and in children are histologically benign, and life-threatening associated anomalies are seldom present. Nevertheless, the mortality rate is high: 3/7 (42%) in our series, which compares to the 33% overall mortality reported in the literature. The observation of a higher mortality rate in the group diagnosed antenatally versus those diagnosed at birth might seem a contradiction. Several factors play a role, especially the hidden mortality in the group diagnosed at birth (spontaneous abortion, stillbirths, termination at request, death immediately following birth due to suffocation and inability to obtain an airway), which means that the group "diagnosed at birth" is a group of "selected" cases. Mortality seems mainly to result from airway compression by the tumor at birth. In the era of advanced technology [operation on placental support (OOPS), EXIT procedure, extra-corporeal membrane oxygenation (ECMO)], it would not seem an insurmountable problem to take care of a newborn expected to show severe airway compression at birth.[4,13,23,29-31]

Table 2 Summary of clinical data for 51 patients with cervical teratoma, collected from the literature, and including the 7 patients from the present publication

Ref	Sex	Diagnosis			Polyhydramnios	EXIT	Respiratory distress	Gestational age (weeks)	Tumour volume (ml)	Histology	Outcome	Late sequelae
		Antenatally weeks	At birth	Later								
26	F	29			Yes		Severe	30	268	Immature	Died	
16	M	25			Yes		Severe	36	368	Immature	Died	Hypothyroidy/parathyroidy
15	F	26			Yes		Severe	29	117	Mature	Died	
15	F	31			Yes		Stillbirth	31	316	Mature	Died	
33	F	-			Yes		Severe	34			Alive	Hypoplastic larynx & vocal cords
33	F	-			Yes	X		33	904	Mature	Alive	GOR, massive aspiration, Nissen
18		-			Yes		Severe	36	376	Immature	Alive	
27		34			Yes	X		38	904	Mature	Alive	
6	F	28			Yes		Severe	30		Mature	Died	Erosion of hypopharyngeal wall
25	F	34			Yes	X			220	Immature	Alive	
19	M	30			Yes				163	Immature	Died	Thyroid gland absent at autopsy
19	M	24			Yes		Severe	36	1142	Immature	Alive	GOR, feeding diff., Nissen
28	M	19						21	59		Died	
28	M	27			Yes		Severe	31			Died	
28	F	27			Yes	X		35			Alive	
28	F	27			Yes			28			Died	
2	F	23			Yes		Severe	34	577	Immature	Died	
17		25			Yes	X		37			Alive	Hoarseness, stridor (rec lar nerve weakness)
24	M	19			Yes	X		35	150		Alive	Tracheomalacia, hypothyroidy/parathyroidy
29		32			Yes	X		37	523	Immature	Alive	Tracheomalacia, subglottic stenosis
31		27			Yes	X		34	157	Immature	Alive	Hypothyroidy
30	F	24			No	X		36	828	Immature	Alive	Pharyngocut. Fist., tracheomalacia, vocal cord paralysis
22		20			Borderline	X		35	1414	Mature	Alive	
PS	F	29			No		Severe	31	884	Mature	Died	

PS	M	21			Yes	X		32	129	Immature	Alive	Hypothyroidy, GOR, tracheal tear
PS	F	19			Yes	X		35	2202	Mature	Died	
14	F		X		Yes		Mild	40	402	Mature	Alive	
15	F		X		No		No	40	31	Mature	Alive	
15	F		X		No		Positional	40	84	Mature	Alive	
15	F		X		Yes		Severe	38		Mature	Alive	
33	F		X		No		Mild	37	157	Mature	Alive	
5	M		X		No		Severe	31	523	Immature	Died	
20	M		X				No		42		Alive	Peroperative bleeding
1			X				Mild	29	179		Alive	
10	F		X		No		Severe	40		Mature	Alive	
9	M		X		No		No	40	73	Mature	Alive	
9	F		X		No		No	40	19	Mature	Alive	
9	F		X		Yes		Mild	36	242	Mature	Alive	
9	M		X		Yes		Severe	38	256	Mature	Died	
9	M		X				Mild	40	376	Mature	Alive	
9	M		X		Yes		Severe	38	1130	Mature	Alive	
9	M		X		No		Mild	38	38	Mature	Alive	
9	F		X		Yes		Severe	34	181	Mature	Died	
9	F		X		No		Severe	34			Died	
32	M		X		No		Severe			Mature	Alive	
32	M		X		No		No			Mature	Alive	
PS	M		X		No		Mild	40	42	Mature	Alive	
PS	F		X		Yes		Severe	31	51	Immature	Died	
PS	M		X		No		No	40	367	Immature	Alive	
PS	F		X		No		No	40	84	Mature	Alive	GOR; initially diagnosed as lymphangioma
32	M			X	No		No			Mature	Alive	

PS *present series*
GOR *Gastro-Oesophageal Reflux*

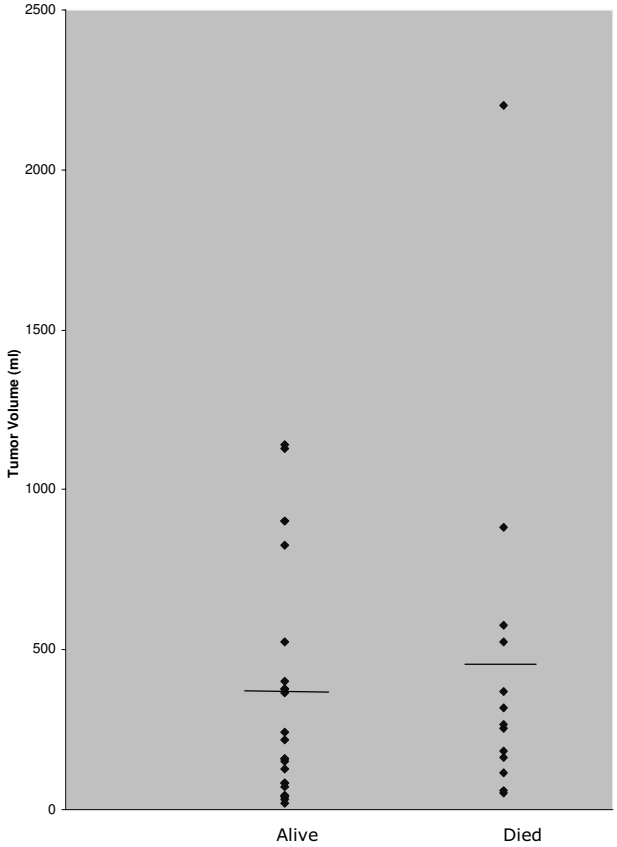

Figure 3 *Tumor volumes at birth by survival. Data are from well-documented cases reported in the literature between 1982 and 2002.*

Table 3 Summary of the largest series of patients with cervical teratoma (three or more patients).

Author (reference)	Year of publication	Number of patients reported	Number of institutes	Time span (years)
Azizkhan[3]	1995	14	9	23
Jordan[15]	1988	9	1	58
Elmasalme[9]	2000	9	2	13
Present Series	2004	7	2	15
Lack[21]	1985	6	1	54
Hany Hassab[12]	1996	5	1	10
Carr[6]	1997	5	2	10
April[1]	1998	4	1	-
Sbragia[28]	2001	4	1	7
Zerella[33]	1990	3	1	1
Wakhlu[32]	2000	3	1	5

Obviously, timely antenatal diagnosis is a prerequisite for optimum management of these difficult perinatal situations, as illustrated in our case no. 2. Antenatal diagnosis was not made in four of our seven patients (57%), which compares to the literature data. This may partially be attributed to different social security systems: Belgium provides for the reimbursement of two screening ultrasounds, whereas in The Netherlands antenatal ultrasounds are not routinely performed. Clinical suspicion of polyhydramnios is an absolute indication for (third level) obstetric sonography. Unfortunately, polyhydramnios is reported to be present in no more than two-thirds of all pregnancies with cervical teratoma. The remaining one-third could only be diagnosed by routine screening ultrasounds, as is the case in Belgium. The financial implications for such a policy are, of course, another point of debate.

After the sonographic diagnosis of a neck mass is made, an ideal treatment algorithm can be followed (*Figure 4*). Further imaging seems to be justified in order to distinguish between teratoma and cystic hygroma, and in order to determine to what degree the tumor compresses the trachea. Ultra-fast MRI[10,17,19,25] seems best to achieve this goal because of its multiplanar capacity, high contrast resolution and lack of radiation hazard. Repeated amniocentesis in case of severe polyhydramnios is, of course, mandatory in order to prevent premature labor.

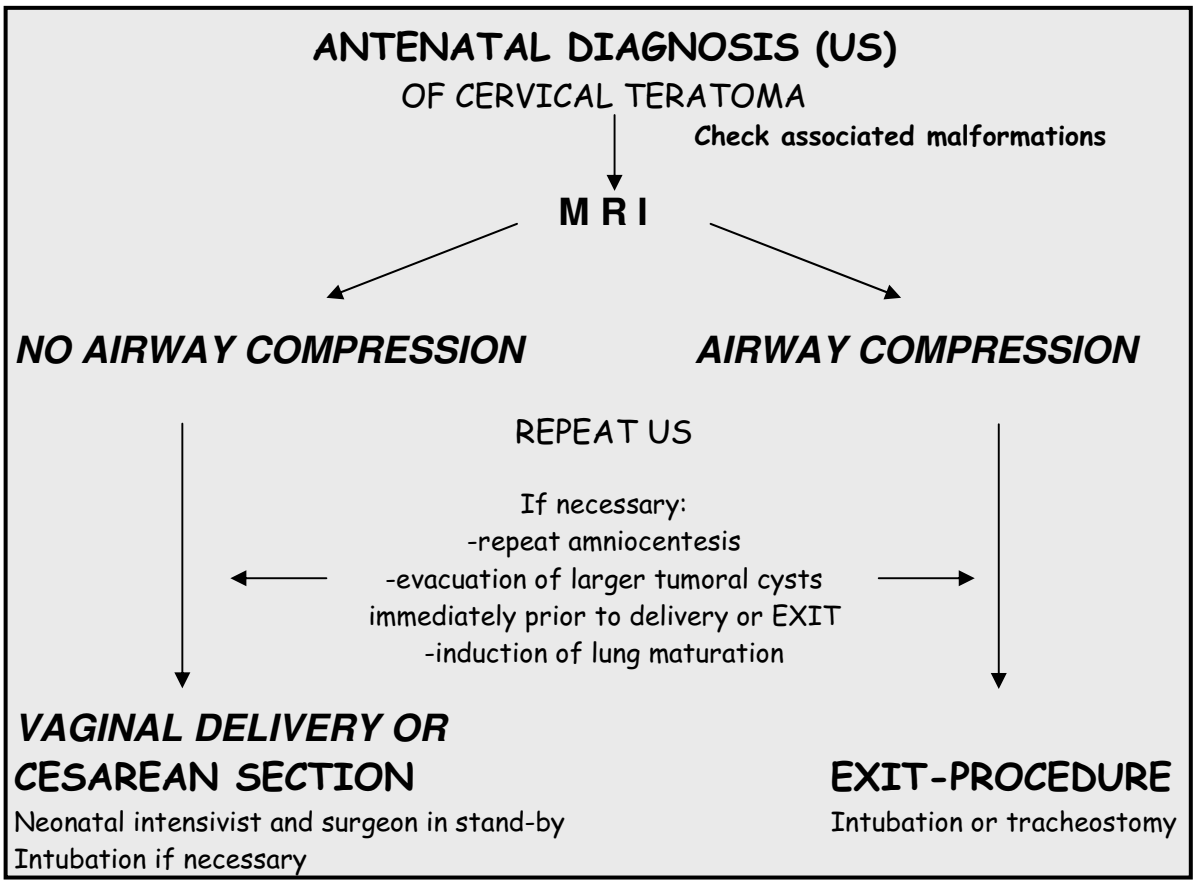

Figure 4 *Therapeutic algorithm for patients suspected of cervical teratoma.*

The optimal timing of delivery will be dictated by the degree of polyhydramnios, fetal development stage, and tumor characteristics with degree of tracheal obstruction. Lung maturation is certainly advisable, especially in the event of a larger tumor with higher likelihood of premature labor and, consequently, of less organized birth procedure. However, if possible, delivery should be postponed until a gestational age of 35 - 36 weeks. Although there are exceptions, a correlation between tumor volume, presence of polyhydramnios and severity of respiratory distress is usually present. A small tumor, which does not cause polyhydramnios, is unlikely to cause severe respiratory distress. In such cases, delivery may be vaginal, provided an experienced neonatal team is present. In all other cases the EXIT procedure should be used. From an anesthesiological point of view this is a complex event,[4] allowing a mean 30 ± 14 minutes of uteroplacental bypass to carry out tracheal intubation or tracheotomy. Intubation of a baby with a giant teratoma is difficult and hazardous; we prefer to use an armed endotracheal tube and to avoid a trocar wire. Under these extreme stressful circumstances, intubation and tracheotomy should be performed by a highly experienced neonatologist and a surgeon. Exceptionally, removal of the tumor while on uteroplacental bypass has been performed; this risky enterprise is certainly not routine.[23] Once an airway is established, the umbilical cord is clamped and the baby is transferred to the NICU. Patients with cervical teratoma are usually stable after a patent airway is achieved. Our seventh patient, however, was an exception to this rule. The extreme vascularization of the tumor led to a critical steal phenomenon with extreme hypotension, bradycardia and rapid demise. A garrot at the base of the tumor could perhaps have stabilized the baby's haemodynamic condition, but it is uncertain whether this would have allowed surgery to be carried out successfully.

The surgical procedure is best carried out once the baby is stable. A neat cleavage plane is usually found between the tumor and the structures of the neck. Occasionally, dissection may be more difficult and tedious. Extreme thinning of the trachea could be the result of continuous pressure exerted by the tumor during pregnancy. Several papers report on the difficulty of separating the tumor from the thyroid gland. Frequently, it is reported that part of the thyroid (and parathyroid) glands had to be removed, or that the glands were absent.[15,16,24] The latter was the case in one of our patients (no. 6). In the postoperative course, therefore, thyroid hormone levels must be carefully monitored and hormone replacement must be started if necessary.

A substantial proportion of cervical teratoma patients are reported to suffer from severe gastroesophageal reflux during the postoperative course.[9,19,33] If present, this should be treated aggressively in order to prevent serious complications such as presented in our patient no 6.

Indications for termination of pregnancy, if any, are under debate.[7,8,19,22] Abortion at the parent's request has been reported several times. Even with very

sophisticated examinations it may be difficult or even impossible to distinguish between (predominantly cystic) teratoma and giant cystic hygroma, which usually has a less favorable outcome,[14] but in most cases differential diagnosis can be made with a good degree of certainty. We were unable to demonstrate a relationship between tumor size and the final outcome. So far, it has proven impossible to identify the fetuses with a disastrous prognosis, which renders termination of pregnancy an invalid option, except in the rare instances when serious associated anomalies are found.

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6 Chapter

MEDIASTINAL GERM CELL TUMORS: CLINICAL ASPECTS AND OUTCOMES IN 7 CHILDREN

A. De Backer
G.C. Madern
F.G.A.J. Hakvoort-Cammel
J.W. Oosterhuis
F.W.J. Hazebroek

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ABSTRACT

Background
Mediastinal germ cell tumors presenting during childhood are extremely rare. Publications on this entity are very scarce. This paper reports the clinical presentations, method(s) of treatment, complications, results and outcomes in a series of children with mediastinal germ cell tumors.

Methods
Retrospective chart review of 7 children treated between 1971 and 2001 for mediastinal germ cell tumor. Age at diagnosis and symptoms were recorded. Each patient's surgical treatment, intra- and postoperative complications, histological staging and final outcome were analyzed.

Results
The median age of the 4 boys and 3 girls was 3 years (range 21 months – 15 years). The most frequent symptoms were respiratory distress, persistent coughing, thoracic pain and anorexia/weight loss. Four patients had histologically benign tumors (mature teratoma). Their sole treatment consisted of complete surgical excision of the tumor and (part of) the thymus using either median sternotomy or left-sided thoracotomy. Recovery was uneventful. No recurrences have been observed. All four are alive with no evidence of disease, between 2.5 and 29 years after treatment. Malignant tumors were observed in three patients (1 yolk sac tumor, 1 choriocarcinoma and 1 malignant teratoma). Treatment consisted of either biopsy or debulking followed by chemotherapy (and radiotherapy in 1 case). Two of them died from uncontrollable metastatic disease. The patient with yolk sac tumor survived; he is now in remission, 4 years after diagnosis.

Conclusions
Both this study and the literature review performed testify to the extreme rarity of mediastinal germ cell tumors in childhood. Children with this type of tumor usually are severely symptomatic. Histologically benign tumors carry an excellent prognosis provided surgical excision is complete. Histologically malignant tumors, on the other hand, have worse prognosis. However, the use of platinum-based combination chemotherapy has considerably increased the survival rates.

INTRODUCTION

Germ cell tumors (GCT) are very rare tumors that are believed to arise from the totipotential primitive germ cells, and thus show a wide diversity of benign or malignant characteristics. They may occur in the gonads, but also, and even more frequently, in extragonadal locations along the central axis of the body (from the pineal region over the neck, mediastinum, retroperitoneal space till the sacrococcygeal region).[1] Most are found in the sacrococcygeal region and the ovary. GCTs in the mediastinum are extremely rare, and most are encountered in adulthood. Both clinical characteristics and treatment results differ between children and adults.[2] Few series with few patients have been published. Erasmus MC-Sophia Children's Hospital, Rotterdam, the Netherlands and the Children's Hospital of the Free University of Brussels, Belgium have treated 212 patients with GCT (all locations) over a 44-year span, seven of whom had mediastinal GCT. We report each patient's clinical presentation, pathologic findings, and details of treatment and outcome with the purpose of broadening the knowledge on mediastinal GCT in childhood.

PATIENTS AND METHODS

The patient population comprised 4 boys and 3 girls, treated for mediastinal GCT in the two institutions mentioned above between 1971 and 2001. Their age at diagnosis ranged from 21 months to 15 years (mean: 5.5 years, median: 3 years). The clinical staging system used defined stage I as a tumor that was completely excised; stage II as a tumor completely excised but with microscopic residual; stage III as biopsy only or gross residual tumor and stage IV as metastatic disease. The tumors were histologically classified according to the WHO classification.[3,4] Two of the 5 surviving patients are still followed at the pediatric oncology outpatient clinic. The three other patients, treated between 7.5 and 29 years ago are now aged between 13 and 37 years.

RESULTS

The clinical data of the seven patients are listed in *Table 1*.

All seven children were symptomatic. Symptoms at initial presentation were respiratory distress in 4, persistent coughing in 4, thoracic pain in 2, anorexia in 2, weight loss in 2, and fever, palpitations, pallor, nocturnal sweating and fatigue in 1 patient each. Precocious puberty was observed in none of the patients. As this small series covers three decades in which a phenomenal revolution in medical imaging has taken place, work-up of these patients differs. Various imaging techniques have been used over the years: standard chest X-ray, ultrasound, tomography, bronchiography, barium swallow, CT-scanning and MRI. Some patients also underwent bronchoscopy, upper digestive endoscopy and/or

angiography. All tumors originated within the anterior mediastinum, in or close to the thymus, and extended into the left hemithorax in 3 patients, into the right hemithorax in 2 patients, and into the neck in 1 patient. The tumors were composed of solid and cystic areas, fat densities and irregular calcifications. A pleural effusion was present in 3 patients (2 with mature teratoma and 1 with malignant GCT). Cytological analysis, however, showed no tumor cells in any of the fluid samples. Tumor markers were determined in all but the first case; alpha-fetoprotein was strongly elevated in the patient with yolk sac tumor and beta-HCG was strongly elevated in the patient with choriocarcinoma. Tumor markers were normal in the other patients.

Four patients had a benign, mature teratoma (cases 1 - 4). Treatment was by complete surgical excision of the teratoma and (all or part of) the thymus, using a median sternotomy in 3 and a left thoracotomy in 1. All four recovered uneventfully from surgery and showed no intra- or postoperative complications. Neither have recurrences been observed in these four patients, now aged 5, 13, 30 and 37 years, 2.5, 7.5, 27 and 29 years, respectively, after surgery. In general they are doing fine.

Three patients had malignant tumors. A 3-year-old girl with stage IV disease (supraclavicular metastasis) was treated in 1971. She underwent a debulking procedure via a 6^{th} intercostal thoracotomy. The tumor appeared to be adherent to the diaphragm with ingrowth into the (nonfunctioning) lung. The tumor was only partially resected including left pneumonectomy and resection of part of the diaphragm. Histological analysis of the resected specimen resulted in the diagnosis of malignant teratoma. Radiotherapy (2450 rads) and chemotherapy (initially consisting of actinomycin-D and prednisone, later vincristine, endoxan and prednisone) were administered without success. She died 8 months after the operation.

A 3-year-old boy with secreting yolk sac tumor initially underwent biopsy, which confirmed this diagnosis (*Fig. 1*). He received multiple courses of chemotherapy (cisplatin, etoposide, ifosfamide (= PEI) following the MAKEI-96 protocol), which normalized alpha-fetoprotein levels and shrank the tumor. The remaining tumor was removed via median sternotomy, and contained histologically only mature teratoma. This patient is now in remission, 4 years after diagnosis. The third, a 15-year-old boy presenting with a huge mediastinal tumor with metastases in both lungs and elevated beta-HCG levels, underwent initial biopsy confirming the diagnosis of choriocarcinoma. He was treated by multiple courses of chemotherapy according to the JEB-protocol (carboplatin, etoposide, bleomycin). After an initial good response, the tumor markers started to rise again; chemotherapy was switched to PEI regimen, without success. This boy died 8 months after the diagnosis.

Table 1 Summary of patients' clinical details, treatment, and outcome

Patient Number	Age	Sex	Year Treated	Symptoms	Stage	Location	Surgical Therapy	Histology	Adjuvant Therapy	Outcome
Patients with benign tumors										
1	8	M	1975	Thoracic pain	I	Ant. mediast. Ext to left	Sternotomy Complete excision including thymus	Mature Teratoma	No	NED (29 years)
2	1y9mo	F	1976	Respiratory Distress Cough	I	Ant. Mediast. Ext. to right	Sternotomy Complete excision	Well-differentiated Teratoma	No	NED (27 years)
3	5	M	1996	Persistent Coughing	I	Ant. Mediast. Ext to right	Sternotomy Complete excision incl. partial thymectomy	Mature Teratoma	No	NED (7.5 years)
4	2.5	F	2001	Coughing Fever Fatigue Weight loss	I	Ant. Mediast. Ext. to left	Left –sided thoracotomy complete excision incl. thymectomy	Mature Teratoma	No	NED (2.5 years)
Patients with malignant tumors										
5	3	F	1971	Respiratory Distress Palor Anorexia Weight Loss	IV	Ant. Mediast. Ext. to left	Left-sided thoracotomy Debulking	Malignant Teratoma	Chemotherapy Radiotherapy	Died, 8 months
6	3	M	1999	Respiratory Distress Weight loss Nocturnal sweating	III	Ant. Mediast. Ext. to neck	Biopsy first Sternotomy Debulking procedure	Yolk sac Tumor	Chemotherapy (PEI)	NED (4 years)
7	15	M	1999	Respiratory Distress Thoracic pain Nocturnal coughing	IV	Ant. Mediast.	Biopsy	Choriocarcinoma	Chemotherapy (JEB, PEI)	Died, 8 months

(M = male, F = female, NED = no evidence of disease)

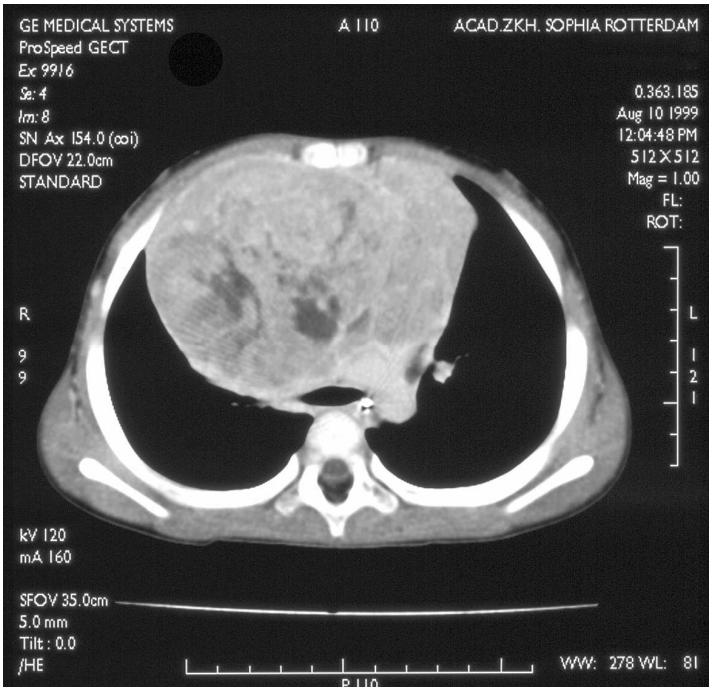

Figure 1 *CT scan of a 3-year-old with respiratory distress, weight loss and nocturnal sweating (patient no 6). This huge anterior mediastinal tumor reached into the neck. Alpha-feto-protein levels were very high. Biopsy confirmed the diagnosis yolk sac tumor. Multiple courses of cisplatin, etoposide and ifosfamide resulted in shrinkage of the tumor, which was removed via median sternotomy, and contained histologically only mature teratoma.*

DISCUSSION

The mere fact that we identified only 7 children with mediastinal germ cell tumors over a 44-year time span, would suggest that this tumor in this particular location is exceptionally rare. Its rareness is further brought out by the scarcity of published patient series, for we could retrieve no more than two series of pediatric patients in the English literature over the past 20 years.[5,6] Other publications were a report of 2 cases,[7] several single case reports and some cases included in series of germ cell tumors at other sites. Furthermore, a multicenter study report on 38 patients with malignant tumors was published in 2001.[8] Finally, several series of predominantly adult patients[9-13] include a few pediatric cases, but fail to single out the characteristics of the latter patient group. We trust, therefore, that the publication of the present series adds useful information and may be of help in improving our knowledge on this extremely rare tumor.

Some epidemiological data merit to be discussed. The vast majority of primary GCT in the mediastinum appears to become diagnosed and treated in adults (third till fifth decade of life),[5] and not in the pediatric age group. Only 22 of 129 mediastinal GCT patients treated over a 50-year-span were children (17%).[10] In another study from a pathology department, only 15 of 322 mediastinal GCT patients were children under 10 years of age (4.6%), and only 66 were 19 years

old or younger.[11] Furthermore, the adult patients reported in the literature outnumber the pediatric patients by a factor 4 or 5. Germ cell tumors are just one, and certainly not the most frequent of the many possible tumoral pathologies in the mediastinum, with neurogenic tumors (in the very young) or lymphoma (in older children) being more frequent.[2] In a series of 50 children with mediastinal masses, only 2 were germ cell tumors.[14] In our series of 212 GCT, those located in the mediastinum represented 3.5% of the total number, thus ranking at the seventh place only, after the sacrococcygeal region, the ovary, testis, brain, retroperitoneal space and neck. This finding is consistent with findings from others.[1]

Also in certain other aspects this series compares well with other series.[5,6] Sex distribution, however, is intriguing to some extent. While in children an overall slight preponderance of boys over girls is observed, malignant tumors are far more common in boys, with a 2:1 to 3:1 boy-girl ratio. Similar ratios are reported in some adult series,[10,12] whereas other adult series show an overwhelming predominance of males (300 males and only 2 females in Moran's series, males only in Economou's series).[11,13] It is not clear yet whether this discrepancy might be pure coincidence due to the rarity of this pathology.

Mediastinal GCT in children are being diagnosed at any age, from newborn till adolescence. Benign mature or immature teratomas are diagnosed at a younger age than are malignant GCT. Indeed, mean and median ages of those with benign tumors range between 1 and 4 years, whereas malignant GCT are usually diagnosed between 7 and 12 years (mean and median ages). Consequently, a mediastinal GCT in a newborn is very likely to be histologically benign; but the contrary is true for the adolescent. In other words, the probability for a mediastinal GCT to be malignant increases with age.

In contrast with certain publications reporting mediastinal GCT detected incidentally in otherwise healthy adult patients, most if not all reported children with mediastinal GCT were symptomatic. The symptoms reported by our patients were similar to those reported in other series, i.e. respiratory distress, thoracic pain and cough as the most frequent and important. At the time of diagnosis symptoms for those with malignant and those with benign disease did not differ. The same is true for pleural effusions, which were observed in 2 patients with benign disease, and in 1 with malignant disease. Cytological analysis did not show malignant cells in the latter case. Our small series again proves the efficacy and reliability of alpha-fetoprotein and beta-HCG as tumor markers for malignant GCT.

This series confirms the notion that children with benign mediastinal GCT (whether mature or immature) carry an excellent prognosis, provided complete surgical excision of the tumor is safely accomplished. In other series whose time span reaches back to the dawn of modern surgery, mortality has been reported in benign cases; nowadays, however, we may assume that in experienced hands

mortality is really exceptional. Recurrence does not appear to be a major issue in benign mediastinal GCT (in contrast to sacrococcygeal teratoma, for example). Indeed, in none of our patients we observed recurrence, in analogy to Lack.[5] Even gross residual tumors were reported not to be associated with recurrence.[12] Lakhoo, on the other hand, reported two recurrences in children with histologically immature teratoma.[6] Upadhyaya reported a similar case, also in immature teratoma.[15] In contrast to adults, immature teratomas in children seem to behave as mature ones.[12]

In contrast to benign cases, survival rates in children with malignant tumors are rather poor, both in our series and in others. Mortality rates range from 66% (this series) to 78% [5] and even 100%.[6] One reason might be the inclusion of patients treated long ago at a time when cancer therapy was nearly inexistent. Since the introduction of platinum compounds (cisplatin, carboplatin) in the late eighties, survival has improved dramatically. A recent American intergroup study of 38 children with malignant mediastinal GCT, treated between 1990 and 1996 [8] found a 4-year-survival rate of 71%. Similar results have been reported in adults.[16] In Europe, two treatment protocols are currently in use: the MAKEI-96 protocol of the German Society for Pediatric Oncology and Hematology and the UKCCSG-GCII protocol of the United Kingdom Children's Cancer Study Group. For limited tumors without visible metastases, complete tumor resection is the therapy of choice, if necessary followed by chemotherapy. For advanced tumors with bulky disease, either biopsy (if tumor does not express tumor markers) followed by chemotherapy or up-front chemotherapy followed by resection of residual tumor is recommended. The chemotherapeutic agents used in combination in the MAKEI-96 protocol are cisplatin (P), Etoposide (E) and Ifosfamide (I), called the PEI regimen. Two, 3 or 4 of such courses are administered at regular intervals depending upon the situation. The UKCCSG-GCII protocol uses multiple courses of JEB (Carboplatin (J), Etoposide (E), Bleomycin (B)) instead of PEI. The 2 non-survivors in our series were both stage IV (= metastatic disease) at diagnosis. It remains an open question whether case 5 would have survived if cisplatin had been available at that time.

CONCLUSION

This patient series and literature review confirm the improving clinical results achieved in children with germ cell tumors in the mediastinum. Especially those with benign tumors (mature and immature teratomas) show excellent outcome with (nearly) 100% survival rates and low recurrence risk provided complete surgical excision is achieved. The survival rates in those with malignant tumors have improved considerably, and are now around 70% thanks to cisplatin-based chemotherapy and aggressive attempts at tumor resection.

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7 Chapter

Retroperitoneal Germ Cell Tumors: A Clinical Study of 12 Patients

Antoine De Backer
Gerard C. Madern
Frans W.J. Hazebroek

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ABSTRACT

Purpose
The aim of the study was to examine the clinical presentation, method(s) of treatment, complications, and results in newborns and infants with retroperitoneal germ cell tumors (GCTs).

Methods
A retrospective chart review of all patients treated between 1974 and 2002 for GCT located in the retroperitoneum in 2 institutions identified 12 patients with histologically proven retroperitoneal GCT. Vital data concerning pregnancy and delivery were analyzed. Age at diagnosis and symptoms were recorded, as well as possibly associated anomalies. Data concerning surgical treatment, perioperative and postoperative complications, histological staging, and final outcome were all analyzed.

Results
In 3 patients, the diagnosis had been made antenatally between 31 and 35 weeks of gestation. In 1 patient, the diagnosis was made at birth, and in 8 later in life (ages 3, 5, 7, 8, 8, 11, 18, and 24 months). Symptoms in these 8 boys and 4 girls were abdominal distension and a palpable upper abdominal mass, right-sided in 5, left-sided in 5, and central in 2; the tumor was usually big. Associated anomalies were noted in 4 patients and were chromosomal in 3 (Down syndrome in 2 and Klinefelter syndrome in 1). One baby died of uncontrollable bleeding during an emergency operation immediately after traumatic birth. The other 11 infants survived. Four other patients showed serious perioperative complications (1 caval vein tear, 1 choledochal tear, 1 cyst rupture, and 1 esophagogastric tear) which were managed without further consequences. Histologically, 4 tumors were mature teratomas, 6 were immature teratomas (grade I in 4, grade II in 1, and grade II-III in 1), and 2 were malignant yolk sac tumors (YSTs). The patients with YSTs underwent surgical biopsy, followed by chemotherapy and excision of the remaining tumor and of the metastases. No adjuvant treatment was administered in the patients with benign disease. Nine survivors with benign tumor are disease-free between 1 and 30 years after surgery. Two patients with YST have now been in remission for 6 and 5 years, respectively.

Conclusions
Both this study and the literature review performed testify to the extreme rarity of GCTs in the retroperitoneum. Surgical removal of the tumors appeared to be hazardous because of the extent of the tumor, the displacement and elongation of adjacent structures and organs, and/or the adhesion of the tumor to surrounding tissues; this resulted in several perioperative complications. The long-term results are good, however, with 9 of 10 patients with benign tumors in good health after a mean follow-up of 12 years, and with the 2 patients with YST in remission for 6 and 5 years, respectively.

INTRODUCTION

Primary extragonadal germ cell tumors in the retroperitoneum are extremely rare. Histologically, more than 80% are teratomas (also called pararenal or perirenal teratomas in the older literature). They represent no more than 4% to 6% of all teratomas, which themselves already are very rare. The literature on this subject is quite scarce. Apart from some "historical" reviews (Palumbo,[1] Arnheim,[2] Engel et al,[3] Pantoja et al,[4] and Lack et al[5]) both in adults and children, most publications on this subject are individual case reports. Many of the cases reported are difficult to evaluate critically because of vague descriptions of pathological findings and incomplete clinical data and follow-up. Therefore, this study aims to report the clinical presentation, methods of treatment, complications, pathological features, and results of 12 babies and infants treated for primary extragonadal germ cell tumor (GCT) of the retroperitoneum, with the intention to broaden the knowledge on retroperitoneal GCT in childhood.

PATIENTS AND METHODS

We analyzed the records of 12 patients with retroperitoneal germ cell tumors treated between 1974 and 2002 in the Erasmus MC-Sophia Children's Hospital in Rotterdam, the Netherlands (cases 1 - 5 and 7 - 11) and the Children's Hospital of the Free University of Brussels, Belgium (cases 6 and 12). GCTs arising in the retroperitoneal pelvis were excluded because they have totally different characteristics. As the total number of children with GCT (all locations) during the same time span in our institutions was 186, the proportion of GCT in the retroperitoneum in our series amounted to 6.4%.

Each pregnancy was analyzed for duration, possible complications, and mode of delivery. Age at diagnosis, symptoms, and methods for diagnosis were recorded. Each operation chart was analyzed in detail, and the (reasons for) possible complications were critically assessed. The pathology reports were analyzed; the classification of Gonzalez-Crussi[6] served to assess pathological grade of immaturity. Finally, the hospital follow-up reports were summarized, including the dynamics of the tumor markers (α-fetoprotein [AFP] and β-human chorionic gonadotropin). At present, 5 patients are still followed up at the outpatient clinic, and tumor markers are checked at regular intervals.

RESULTS

A summary of the clinical data of the 12 patients is listed in *Table 1.*

Table 1 Summary of clinical data in 12 patients with retroperitoneal GCT

Patients	Year of treatment	Sex	Duration of pregnancy (wk)	Birth weight (g)	Age at diagnosis	Associated anomalies	Symptoms	Site/side	Age at operation
1	1974	M	?	?	7 mo	None	Palpable tumor/vomiting	Suprarenal/ left	7 mo
2	1986	M	38	?	3 mo	None	Palpable tumor	Bursa omentalis	3 mo
3	1987	F	40	?	8 mo	Down syndrome	Palpable tumor/vomiting	Perirenal/ left	8 mo
4	1987	F	39	3900	8 mo	None	Palpable tumor	Suprarenal/ right	11 mo
5	1989	M	35	5100	Antenatally (34 wk)	Down syndrome	Huge abdominal distension–hemodynamic instability after traumatic birth	Suprarenal/ right	0 d
6	1990	M	40	3790	5 mo	47 XXY genotype (Klinefelter syndrome)	Palpable tumor/fever/ postprandial discomfort	Suprarenal/ right	5 mo
7	1994	F	35	3730	Antenatally (31 wk)	Malrotation	Palpable tumor	Suprarenal/ left	1 d
8	1997	F	?	?	24 mo	None	Palpable tumor/ abdominal pain	Suprarenal/ left	30 mo
9	1998	M	?	?	18 mo	None	Palpable tumor/ constipation	Huge abdominal tumor extending into the right hemithorax	24 mo
10	1999	M	40	3400	At birth	None	Huge abdominal distension/ palpable tumor	Suprarenal/ right	4 mo
11	2000	M	39	3880	11 mo	None	Palpable tumor	Suprarenal/ right	11 mo
12	2002	M	39	3475	Antenatally (35 wk)	None	Palpable tumor	Suprarenal/ left	10 d

Surgical approach	Dimensions of tumor (cm)	Tumor volume (ml)	Perioperative complications	Tumor histology	Adjuvant therapy	Late complications	Actual status (years after treatment)
Transverse supraumbilical laparotomy	13 x 9 x 8	489	None	Mature teratoma	No	None	Disease-free since 30 y
Transverse supraumbilical laparotomy	11 x 7 x 7	282	None	Immature teratoma grade I	No	None	Disease-free since 18 y
Transverse supraumbilical laparotomy	12 x 12 x 12	900	Cyst rupture	Mature teratoma	No	Art. hypertension	Disease-free since 17 y
Transverse supraumbilical laparotomy	7 x 6 x 6	132	None	Mature teratoma	No	None	Disease-free since 15 y
Transverse supraumbilical laparotomy	15 x 15 x 15	1765	Uncontrollable diffuse bleeding leading to death	Immature teratoma grade II-III			Died a few hours after birth
Transverse supraumbilical laparotomy	11 x 9 x 8	414	Small caval vein tear, sutured	Immature teratoma grade I	No	None	Disease-free since 12 y
Transverse supraumbilical laparotomy	7 x 6 x 4	88	None	Immature teratoma grade I	No	None	Disease-free since 9 y
Biopsy → chemotherapy → excision of residual tumoral tissue + excision of liver metastasis	8 x 8 x 9	301	None	YST	Yes	Hearing loss	In remission since 6 y
Biopsy → chemotherapy → excision of residual tumoral tissue	10 x 9 x 6	300	None	YST	Yes	None	In remission since 5 y
Transverse supraumbilical laparotomy	14 x 10 x 9	659	Choledochal tear	Immature teratoma grade I	No	None	Disease-free since 3.5 y
Transverse supraumbilical Laparotomy	10 x 10 x 10	523	None	Mature teratoma	No	None	Disease-free since 2.5 y
Transverse supraumbilical Laparotomy	9 x 9 x 7	297	Esophagogastric tear	Immature teratoma grade II	No	None	Disease-free since 1 y

Clinical presentation in the patients diagnosed antenatally

In 3 patients (5, 7, and 12), the presence of a fetal intra-abdominal space-occupying lesion was suspected from ultrasound studies (USs) antenatally at 34, 31, and 35 weeks of gestation, respectively. In patients 5 and 7, differential diagnosis covered neuroblastoma, Wilms tumor, teratoma, and intestinal obstruction. In patient 12, the tumoral mass was interpreted as a convolute of intestines; the presence of calcifications led to a presumptive diagnosis of meconium peritonitis. These 3 cases were all transferred in utero to a tertiary care center. Cesarean section (C-section) was performed on patients 7 and 12; patient 7 appeared to be stable after birth and was operated upon on the second day of life. Patient 12, suspected of having meconium peritonitis, had severe abdominal distension. Moreover, palpation of the abdomen was painful, and the baby was moaning. Laparotomy revealed a tumor that seemed inoperable at first sight. A possible diagnosis was neuroblastoma; the tumor was biopsied, and the operation ended. After the histological diagnosis of teratoma became apparent, radiological investigation by US, serum tumor markers, computed tomography (CT) scan, and magnetic resonance imaging (MRI) (*Figs. 1 and 2*) were performed, and the baby was operated upon on the 10th day of life. The case of patient 5 was complex and complicated; his mother (gravida 8, para 5), age 37, had either von Willebrand coagulopathy or aspirinlike thrombocytopathy. At 33 weeks of amenorrhea, she was admitted for acute polyhydramnion. Fetal US revealed a "double-bubble" phenomenon, suggestive of high intestinal obstruction, which appeared to be caused by a space-occupying lesion in the upper part of the fetal abdomen. Amniocentesis resulted in removal of 4200 ml of amniotic fluid. Cordocentesis for determination of the patient's karyotype disclosed trisomy 21. Two days later, she suddenly got into partum. Delivery of the 5100-g baby was reported to be extremely difficult. Apgar scores were 1/5/9 minutes. The baby had an extremely distended abdomen, and a huge irregular tumor was palpable. The baby's condition deteriorated in the minutes after birth, necessitating intubation, artificial ventilation, and further resuscitation. The development of metabolic acidosis as well as a fall in hemoglobin concentration induced the decision to perform emergency laparotomy. Before the start of and during the operation, fresh frozen plasma, cryoprecipitate, and vitamin K were administered. A huge tumor in the right upper part of the retroperitoneal space was found; the tumoral capsule was ruptured, probably as a result of the traumatic delivery. Dissection of the tumor was attempted, but diffuse bleeding resulted in circulatory collapse and death of the patient.

Clinical presentation in the patients diagnosed at birth or at a later age

During these pregnancies, prenatal US had not been performed. Patient 10 was born at home after an uneventful pregnancy. Immediately after birth, the midwife noted an abdominal distension, but no attempt at further diagnosis was undertaken. At the age of 4 months, abdominal distension had significantly increased; at that time, an abdominal tumor was palpable. Further investigation

with US and CT disclosed the presence of the tumor, which was then removed at the age of 4 months.

Patients 1 to 4, 6, 8, 9, and 11 were all born after an uncomplicated pregnancy. Abdominal distension, the palpation of an abdominal tumor, and postprandial discomfort were the symptoms which led to the diagnosis in all 8 patients. These children were operated upon at ages between 3 and 30 months (mean, 12 months).

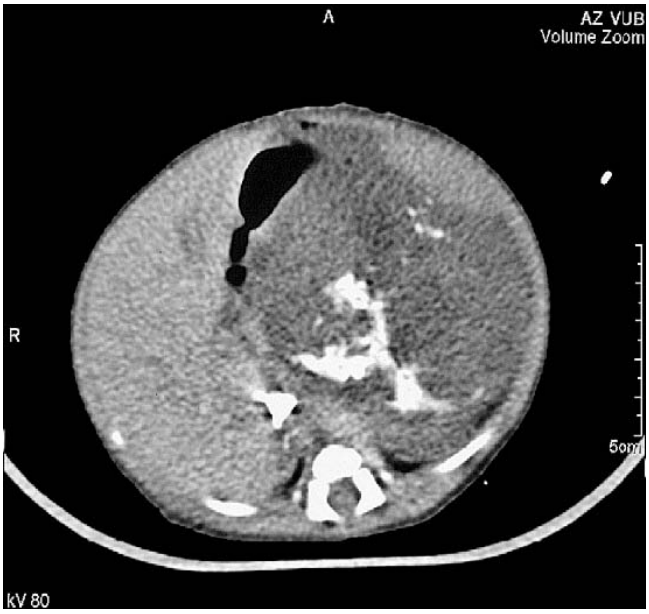

Figure 1 *Contrast-enhanced CT scan showing a huge retroperitoneal tumor with calcifications (congealed pattern) in a newborn with immature teratoma (case 12).*

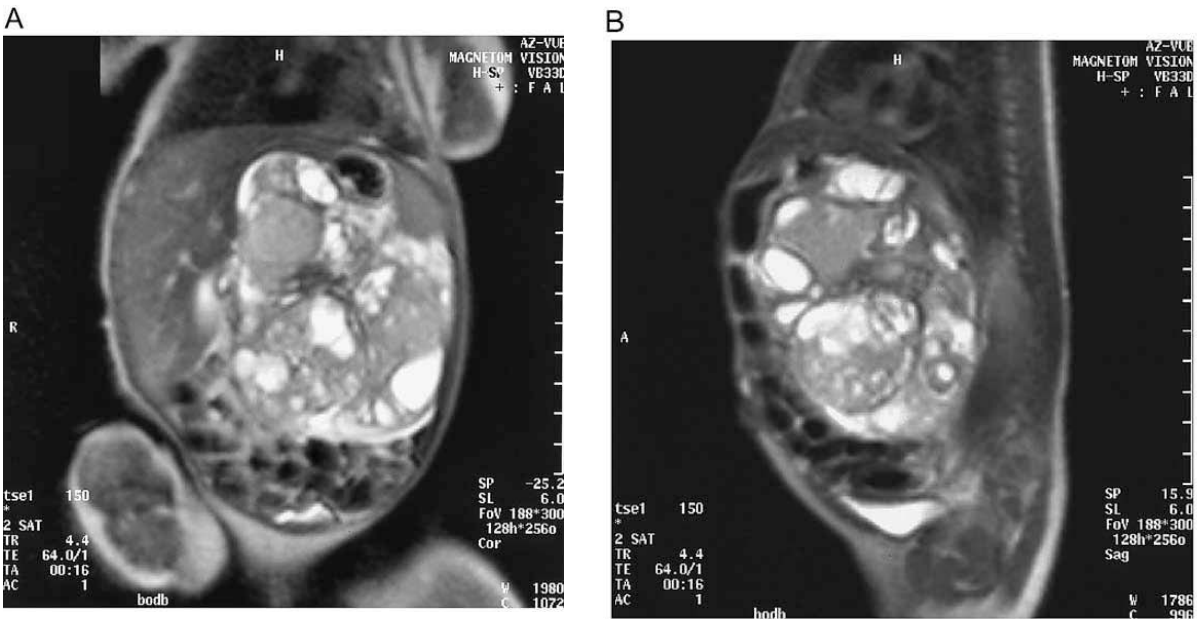

Figure 2 A, B *MRI study in the same newborn (case 12) with huge retroperitoneal immature teratoma (A, axial; B, sagittal view). The teratoma was encapsulated, partially (predominantly) cystic and partially solid with almost no fat content. The adjacent organs were displaced by the tumoral mass.*

Diagnosis, location, and size of tumors

As the patients reported herein were treated over a 30-year span, various radiological examinations were performed for diagnosis: plain abdominal film and intravenous pyelography in the oldest patients and US, CT scan, and MRI in the more recent cases. The latter investigations showed a usually big and complex upper retroperitoneal tumor with well-circumscribed fluid components, adipose tissue and/or sebum, and calcifications in the patients with teratoma (*Figs. 1 and 2*). Diagnosis in the first patient with yolk sac tumor (YST, patient 8) was made by US and CT. The latter showed an irregular retroperitoneal tumor with inhomogeneous contrast enhancement, ascites, pleural effusion, and liver metastases. In patient 9, MRI showed a huge retroperitoneal tumor with polycyclic contours, hypointense at T1-weighted images, hyperintense at T2-weighted images, and heterogeneous enhancement of gadolinium. The tumoral process reached into the thorax; mediastinal lymph node metastases were observed. The radiological diagnosis in both patients was neuroblastoma vs GCT.

In all but 2 patients, the AFP levels were considered normal when adjusted to age; the exceptions were the patients (8 and 9) with YST who had high levels of AFP.

The precise localizations of the tumor are given in *Table 1*; in patient 9, the tumor occupied the entire retroperitoneal space and extended into the right hemithorax. With the smallest tumor measuring 7 x 6 x 4 cm and the largest 15 x 15 x 15 cm, tumor volumes ranged between 88 and 1765 ml (mean, 531 ml; median, 414 ml), which are quite huge volumes for a neonate or an infant. The 2 patients with YST had advanced disease: liver and lung metastases were observed in patient 8; in patient 9, the tumor had extended into the right thoracic cavity.

Associated anomalies

Associated anomalies were observed in 4 patients: Down syndrome in two (in patients 3 and 5; the latter is the patient who did not survive), 47 XXY genotype (Klinefelter) in one, and malrotation intestinalis in the fourth patient.

Operative findings and complications

All children with benign tumors were operated upon by an experienced pediatric surgeon through a transverse supra-umbilical laparotomy. The extent of the tumor, the displacement and elongation of adjacent structures and organs, and/or the adhesion of the tumor to surrounding tissues rendered the operations difficult. This accounts for the perioperative complications reported in 5 patients. A small tear in the caval vein was sutured with a Prolene suture. In another patient, during the dissection of a localized intense adhesion, a gastric tear occurred between the tumor and the stomach close to the gastroesophageal junction; this tear was closed with interrupted sutures of Vicryl 4-0 and subsequently healed. In a third patient, a choledochal tear was recognized and sutured over a T tube. The patient recovered well from this complication. In the fourth patient, 1 of the cysts ruptured during removal. Otherwise, the tumors in the other patients were assumed to have

been removed completely without rupture or tumoral spill. The fifth complication encountered was diffuse uncontrollable perioperative bleeding in patient 5, but the circumstances (reported earlier in this paper) were particular.

Adjuvant therapy was not administered in any of the patients with mature or immature teratoma.

Surgery played a somewhat minor role in the patients with YST (8 and 9). Initially, a biopsy was taken from the tumors, which were both judged inoperable. Six courses of multiagent chemotherapy (cisplatin, etoposide, bleomycin) were administered in total; this resulted in nearly-complete disappearance of the tumors after 4 courses, leaving only a small residual tumor located in a paravertebral retrohepatic position (patient 9) and in a left paravertebral position (patient 8). These tumoral rests were excised; no viable tumor was found histologically. In patient 8, the liver metastasis was resected at the same time; no viable tumoral tissue was observed. In both patients, the lung and thoracic lesions were removed after the end of chemotherapy, but here too, no viable tumoral tissue could be observed.

Uneventful recovery from anesthesia and from surgery was reported in all 11 surviving patients.

Histology

Histological analysis using light microscopy showed mature teratoma in 4 patients, immature teratoma in 6 (grade I in 4, grade II in 1, and grade II-III in 1), and YST in 2. Microscopically, the benign tumors were removed completely in 7 cases. In 2 cases (10 and 11), it was reported to reach into the resection margins.

Late complications and results

No late complications nor recurrences were observed, except for patient 8 who had hearing loss, probably because of chemotherapy. The patients with benign tumors are now between 1 and 30 years after treatment (mean, 12 years; median, 12 years). Three are still on a follow-up scheme (10, 11, and 12); the 6 oldest have been dismissed from regular check ups. The patients with YST have been in remission for 6 and 5 years already.

DISCUSSION

The most frequent locations for teratomas and other germ cell tumors are the sacrococcygeal region, followed by the gonadal sites (ovary and testes). The other extragonadal sites such as the pineal region, neck, mediastinum, and retroperitoneum are far more rare. Indeed, previously published large series of patients with GCTs showed the tumor to be located in the retroperitoneal space in 3% to 6% of all cases.[7-11] In our series of patients, retroperitoneal GCT

represented 6.4% of all GCT, a percentage comparable to that reported in previous publications. The vast majority of these tumors are benign mature and immature teratomas; malignancy is reported to occur in approximately 15% of cases. In our study, a similar proportion was observed.

Diagnosis of retroperitoneal GCT has been reported at any age, from the prenatal period to senescence. In our series of pediatric patients, all children except two had been diagnosed and treated in the first year of life. In a series of patients reported between 1949 and 1968, diagnosis of such tumors was equally frequent in children and in adults.[3] More than 80% of a series of patients diagnosed between 1979 and 1988 were diagnosed during childhood, and half of these patients in the first 6 months of life.[12] Notwithstanding the extreme rarity of these tumors, we may expect improvements in imaging techniques to enable the diagnosis to be made at an earlier age.[13] In our limited series of patients, the antenatal diagnosis of retroperitoneal teratoma appeared not to be obvious. Actually, in 2 patients, the initial diagnosis appeared to be false: in one, the differential diagnosis between neuroblastoma, nephroblastoma, or some form of intestinal obstruction was forwarded; in the other patient, the presumed diagnosis was meconium peritonitis. This is not without consequences, given that in patient 12, the false diagnosis led to a semiurgent laparotomy without prior further imaging. Perhaps ultrafast MRI performed antenatally would allow a more precise diagnosis, but to our knowledge, such cases have not been published so far.

The method of delivery in our 3 patients diagnosed antenatally merits some attention. Two patients were delivered by C-section, whereas a third was delivered vaginally. In the latter patient, who ultimately died, vaginal delivery was reported to be extremely difficult (necessity for forceps extraction), lasting several hours. The baby was therefore born in very bad condition requiring intubation and resuscitation. Emergency operation showed the tumor to be ruptured; the baby died during the operation. So far, however, there are no other data to support the birth of babies with retroperitoneal teratoma by C-section; every case has to be considered individually. Yet, we feel that C-section should be performed for the larger tumors.

The clinical symptoms reported for the babies who were diagnosed at birth or later on were the usual ones: abdominal distension, palpation of an upper abdominal mass, aspecific feeding difficulties, and vague pain.

The radiological workup after birth also merits some attention. Several papers have reported the radiological characteristics of GCT.[12,14,15] Some papers report on the superiority of CT over US for the diagnosis of GCT.[12] To our knowledge, CT has not yet been compared with MRI. In our opinion, these 2 examinations are complementary; MRI has the definite advantage of images in the 3 planes, giving surgeons better opportunities to plan their operations and to foresee possible complications. Of course, if in some (very exceptional) cases, even histology is not

able to distinguish between, for instance, Wilms' tumor and retroperitoneal teratoma, how would CT or MRI do?[16]

The value (and also the limits) of tumor markers has already been established.[17,18] In our series, tumor markers were helpful in distinguishing benign from malignant cases; the AFP levels were normal in all 10 patients with benign tumors and were strongly elevated in the 2 malignant cases with YST. β-Human chorionic gonadotropin was never elevated; no cases with choriocarcinoma were present in this series.

Associated chromosomal anomalies in patients with (retroperitoneal) GCT have occasionally been reported.[18,19] Whether in our series the high incidence of chromosomal anomalies (27%) is coincidental remains to be determined.

The number of operative complications in this small series might seem high. These patients were all operated upon by experienced pediatric surgeons who reported the operations to be difficult and hazardous. The often large tumors were situated in the upper abdomen, which is a complex and narrow field to operate in. They therefore could not be manipulated easily, bled easily, and displaced and elongated the adjacent organs and structures. Moreover, intense adhesions between tumor and adjacent structures have been encountered; this finding has been reported previously.[4] Most complications could be managed without further consequences, although it remains an open question whether they could have been avoided. Previously published papers have not reported similar complications, but these papers did not focus on surgical technique and complications.

An interesting observation could be made in cases 10 and 11 with an immature teratoma grade I and a mature teratoma, respectively, whose tumors histologically reached into the resection margins. We have followed these patients for 3.5 and 4.5 years now but, so far, did not observe recurrence. Of course, in this particular operation field, it was impossible to resect the tumors with a margin of healthy tissue all around. Similar observations have not been reported in the literature. Nevertheless, and despite the fact that 6 tumors had immature components, the results obtained were perfect, with no recurrences. However, recurrences have been reported in the literature.[5,8,20,21] Close follow-up of benign GCTs remains therefore imperative. The successful outcome in our 2 patients with malignant retroperitoneal teratoma (YST) is not surprising, as a recent multicenter report[10] describes excellent results (80% - 90% 6-year survival) to be achieved with cisplatin-based combination chemotherapy together with resection, which need not be aggressive.

Both this study and the literature review performed confirm the excellent prognosis of newborns and infants with GCTs in the upper retroperitoneum. Surgical removal of the tumor, which is the cornerstone of treatment, should be performed with extreme caution, as the size of the tumor, the displacement and elongation of

adjacent structures and organs, and/or the adhesion of the tumor to surrounding tissues may lead to serious perioperative complications.

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8 Chapter

Study of the Factors Associated with Recurrence in Children with Sacrococcygeal Teratoma

Antoine De Backer
Gerard C. Madern
Friederike G.A.J. Hakvoort-Cammel
Patrick Haentjens
J.Wolter Oosterhuis
Frans W.J. Hazebroek

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ABSTRACT

Purpose
The aim of this study was to explore effects of (1) histological involvement of resection margins with microscopic residue, (2) incomplete removal of coccyx, and (3) tumor spillage on recurrence and on survival in children operated upon for sacrococcygeal teratoma (SCT).

Methods
Retrospective review of 70 patients treated between 1960 and 2003.

Results
Fifty-four girls and 16 boys presented with SCT diagnosed prenatally (12), at birth (37), or later (21). Thirty-six percent of tumors were Altman type I, 27% type II, 18% type III, and 18% type IV. Histologically, mature teratoma was observed in 48 patients, immature teratoma in 11, yolk sac tumor (YST) in 9, embryonal carcinoma in one, and mixed tumor in one. Eighty-four percent of patients solely underwent surgical extirpation. Six (8.5%) patients died. However, mortality for the group of 42 patients treated during the past 15 years was as low as 2.5%. Tumor recurrence was observed in 5 patients, 2 of whom died. Of 3 patients with initially mature teratoma, 1 showed local immature recurrence and 2 malignant recurrences. One of the latter died. Of 2 patients with initially immature teratoma grade I, one relapsed with a benign lesion and one with YST leading to death. Possible eliciting factors had been demonstrated in 3 patients. Histological analysis of resection margins showed tumoral involvement in 11 patients (and also in one patient after resection of a recurrent tumor). Only one of those with YST focus in the resection margin showed recurrence. Intraoperative tumor spillage presented in 2 patients, who both died of metastatic disease. Spillage of tumoral cyst fluid occurred in 6, none developed recurrence. One of 5 patients whose coccyx had not been removed died of metastatic disease. One with immature teratoma developed a benign recurrent tumor. The other 3 showed no recurrence.

Conclusions
Microscopic involvement of the resection margins of mature or immature SCT is rarely associated with recurrence, provided there are no YST foci in the resection margins. A conservative attitude then appears to be justified. Spillage of cyst fluid was never associated with recurrence, unlike spillage of tumor and absence of removal of coccyx.

INTRODUCTION

With an incidence of one in 35,000 to 40,000 live births, sacrococcygeal teratomas (SCTs), belonging to the type I germ cell tumors (GCTs), are extremely rare tumors.[1-5] Nevertheless, diagnosis and treatment of this condition have become fairly standardized, and as a rule, satisfying results are achieved.[5] Two major problems remain to be solved: the long-term functional sequelae (fecal + urological)[6-8] and recurrence.

Previously published series report recurrence in 2% to 35% of patients.[3-5,9-17] Possible causative factors for recurrence include incomplete resection with microscopic residue, nonresection of the entire coccyx, and tumor spillage.[18]

We reviewed the records of all patients with SCT treated either in the Erasmus MC-Sophia Children's Hospital, Rotterdam, The Netherlands, or in the Academic Hospital of the Free University of Brussels, Belgium, between 1960 and 2003, aiming at analyzing the intraoperative factors possibly associated with recurrence.

PATIENTS AND METHODS

During the 44-year period from 1960 to 2003, a total of 70 patients with SCT were treated, most in Rotterdam. Over time, numbers of patients had stepwise increased: 8 from 1960 to 1970, 7 from 1971 to 1981, 19 from 1982 to 1992, and 36 from 1993 to 2003. Thus, we have treated a mean of 3 patients per year in the past decade. Over the same 44-year period, a total of 212 patients with GCT (all locations) were treated in our institutions, which is consistent with 33% of all GCT being SCT, and the sacrococcygeal region being the most frequent site of all GCT. For each patient, we recorded data concerning pregnancy and delivery, timing of diagnosis, symptoms, radiological workup, tumor markers, methods of treatment, complications, histological analysis, and outcome. The Altman classification was used: type I were predominantly external tumors; in type II, the tumor was externally visible but had an intrapelvic component; in type III, the tumor reached into the abdomen; and type IV were those intrapelvic tumors with almost no externally visible component.[19] Recurrence was defined as development of a new tumor either in the same location of the primary tumor or at a distance. A new tumor in patients in whom no complete control of the primary tumor could be achieved was considered as progression of the disease rather than recurrence.

Relevant clinical data and patient characteristics were summarized descriptively. Overall survival (OS) and eventfree survival (EFS) were estimated according to the Kaplan-Meier method. Overall survival was defined as all-cause mortality and EFS as the time from diagnosis to the first relapse or death from any cause.[20] The surviving patients were censored at the time of the last reported examination. Overall survival and EFS were calculated for the whole patient population (n = 70),

as well as for the subgroup of patients treated from 1989 onward, that is, the cisplatin era (n = 42).

The univariate influence of each potential prognostic factor on OS and EFS was analyzed with the log-rank test. *P* values less than .05 were considered significant. Because of the limited number of patients, no multivariate (Cox) regression analyses were conducted.

All data analyses were performed using SPSS version 12.0 (SPSS, Inc, Chicago, Ill).

RESULTS

The study population consisted of 16 boys and 54 girls (male-to-female ratio 1:3.4). The diagnosis of SCT had been made antenatally in 12 (at gestational ages between 23 and 37 weeks), at birth in 37, and at a later age in 21 (mean, 14 months; range, 5 days to 3 years). Associated malformations were recorded in 7 patients: trisomy 21, clubfeet and hypospadias/congenital urethrovaginal fistula (1 patient each), obstructive uropathy (2 patients), and congenital dysplasia/luxation of hip (2 patients). By far, the most prominent clinical sign was a visible tumor in the sacrococcygeal region, except in the (usually somewhat older) patients with Altman IV tumors. According to Altman's classification, 25 (36%) tumors were type I, 19 (27%) were type II, 13 (18%) were type III, and 13 (18%) were type IV. Surgical extirpation of the SCT was the sole treatment in 59 (84%) patients. In 3, surgery was followed by chemotherapy. Three other patients underwent biopsy of the tumor, followed by chemotherapy and surgical extirpation of the remaining tumor. In 4 patients with apparently malignant tumors (very high levels of tumor markers), treatment started with up-front chemotherapy followed by delayed tumor resection. Treatment was intentionally withheld in a 29-gestational-week-old girl delivered after emergency cesarean section for fetal distress. The SCT appeared to be fixed at the placenta resulting in the delivery of a baby in very bad condition, necessitating resuscitation. Moreover, she showed several dysmorphic characteristics. It was decided, therefore, to refrain from further treatment.

Surgery was usually by well-known oncological principles, including en bloc resection of the tumor with the coccyx either perineally or abdominoperineally, except in 5 patients whose coccyx was left in situ. The reason for leaving the coccyx in situ was nonrecognition of the coccygeal or intrapelvic/low abdominal tumor as a GCT in all 5 cases; it was never an intentional decision. As this study covers a 44-year period, several chemotherapeutic agents were used over time: bleomycin (B), etoposide (E), cisplatin (P), carboplatin (J), vinblastine (V), actinomycin-D (A), cyclophosphamide (C), and ifosfamide (I), administered in combinations as VAC, PVB, PEB, JEB, and PEI and according to international protocols of SFOP, SIOP, and MAKEI.[18] Preoperative and intraoperative complications were reported in 13 (19%) patients. Tumor spillage (either rupture

of a solid tumor or rupture of a tumoral cyst) occurred in 8 patients, perforation of the rectum in 2, major bleeding in 3, and 1 needed resuscitation during the operation. Histological analysis of the resected specimens showed mature teratoma in 48, immature teratoma in 11 (grade I [2], grade II [1], grade III [0], grade not specified [8]), yolk sac tumor (YST) in 9, embryonal carcinoma in 1, and mixed YST + mature/immature teratoma in 1. In 11 patients, the tumor reached into the resection margins. In 1 patient, the resection margins of the recurrent tumor were histologically involved.

Overall mortality in this series was 8.5% (6 patients). Four patients died of metastatic disease irresponsive to therapy. One baby died on the fifth day of life from massive Gram-negative sepsis and meningitis. Treatment was withheld in a very premature baby with dysmorphic signs. The Kaplan-Meier estimates for OS and EFS of the 70 patients with SCT are shown in *Fig. 1A* and of the 42 patients treated during the past 15 years (1989-2003) in *Fig. 1B*.

Tumor recurrence was observed in 5 patients (7% of total) (*Table 1*), leading to death in 2 of them.We observed a statistically significant difference in OS between those patients who developed relapse and those who did not (*Fig. 2*, $P = .015$).

Histological involvement of the resection margins was observed in 12 patients, whose data are summarized in *Table 2A* and *B*. The Kaplan-Meier curves for the two main outcome measures (OS and EFS) were similar for patients with or without histological involvement of the tumor resection margins (*P* values of .424 and .996, respectively; curves not shown).

Intraoperative rupture of a tumoral cyst or of the tumor with spillage was reported in 8 patients (*Table 3*). The 2 patients in whom intraoperative tumor spillage was reported had a significantly lower OS ($P < .001$; curves not shown), a significantly lower EFS ($P < .001$; curves not shown), and a significantly higher number of relapses ($P < .001$). In 6 other patients, 5 with mature teratoma and 1 with YST, intraoperative rupture of a cystic structure resulted in spillage of cyst fluid only into the operative field. No recurrences have been observed in 5 of these patients after a mean of 12 years (median, 9; range, 7 - 22 years); the sixth died of sepsis 2 days after the operation.

The coccyx had not been removed during the initial operation in 5 patients (*Table 4*). The OS for these patients did not differ from that of the other patients ($P = .163$; curves not shown). Interestingly, the EFS for these patients was significantly lower ($P = .015$; curves not shown). This discrepancy is presumably related to the small sample size.

The influences of recurrence, margin involvement, tumor spillage, and nonresection of coccyx on OS and EFS in the subgroup of 42 patients treated from 1989 to 2003 did not differ from the total patient population (curves not shown).

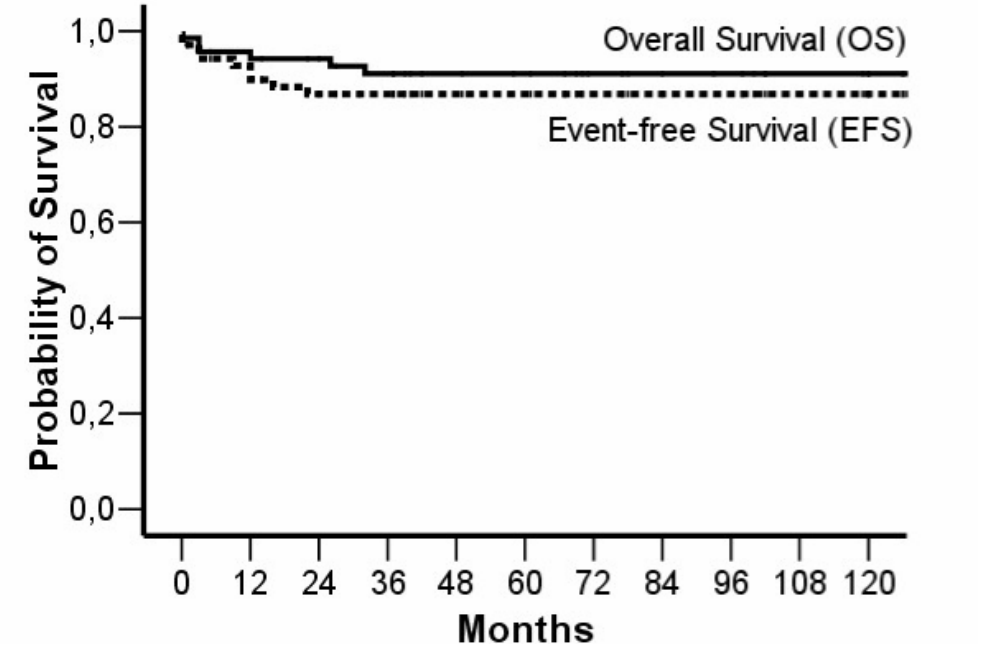

Figure 1A *Kaplan-Meier estimation of 10-year OS (0.91 ± 0.04 [64/70]) and EFS (0.87 ± 0.04 [61/70]) of 70 patients with SCT*

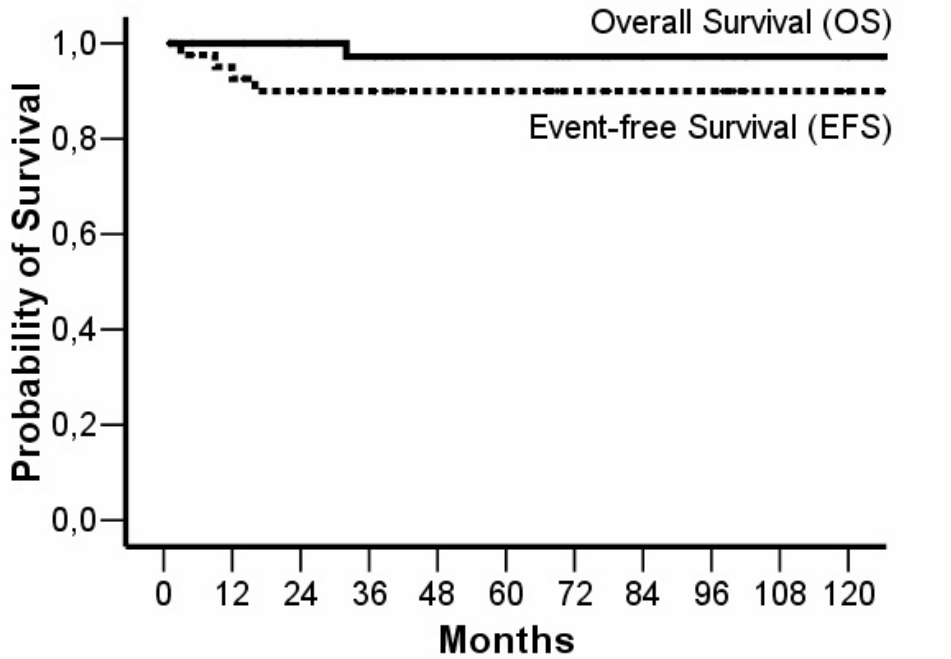

Figure 1B *Kaplan-Meier estimation of 10-year OS (0.97 ± 0.03 [41/42]) and EFS (0.89 ± 0.05 [38/42]) in the subgroup of 42 patients treated between 1989 and 2003 (cisplatin era)*

Table 1 Clinical data in 5 patients who developed recurrent disease

Patient	Year of treatment	Age at operation	Altman Grade	Initial Histology	Possible eliciting factors	Time till relapse	Site of recurrence	Treatment	Histology of recurrent tumor	Outcome
12	1997	8 d	I	MT	None	1 y	Local	Excision	IT; resection margins involved	NED, 5 y
24	1968	10 mo	III	MT	None	21 mo	Local + distant (vertebral)	Excision	Malignant teratoma	Died
6	2000	12 d	I	MT + 1 focus of YST	Tumor resection margins involved	6 mo	Local	Excision + Chemotherapy	YST	In remission for over 3 y
23	1997	4 d	III	IT	Coccyx not removed	18 mo	Local	Not treated	Not available	NED, 8 y after initial diagnosis
20	1996	1 d	II	IT	Tumor spill	9 mo	Local + distant (liver)	Multiple excisions; chemotherapy; adjuvant hyperthermia; autologous bone marrow transplantation	YST	Died

MT *mature teratoma*
IT *immature teratoma*
YST *yolk sac tumor*
NED *no evidence of disease*

Table 2a Clinical data in 11 patients whose resection margins of the primary tumor were involved

Patient	Year of treatment	Age at operation	Altman Grade	Initial Histology	Recurrence?	Outcome
1	2001	6 mo	IV	MT	No	NED, 2 y
2	2002	3 mo	II	MT	No	NED, 2 y
3	2002	6 d	II	MT	No	NED, 18 mo
4	1999	3 mo	II	MT	No	NED, 4 y
5	1977	1 d	II	MT	No	NED, 27 y
6	2000	12 d	I	MT + 1 focus of YST in resection margins	Yes (after 6 months)	In remission since 2 y
7	2001	6 wk	IV	IT grade I	No	NED, 3 y
8	2000	5 wk	I	IT grade I	No	NED, 2 y
9	1990	4 d	II	IT grade II	No	NED, 12 y
10	1996	6 mo	I	Mixed YST + IT	No	NED, 7 y
11	1999	13 mo	IV	YST/MT after chemotherapy	No	NED, 5 y

Table 2b Clinical data in the patient whose resection margins of the recurrent tumor were involved

Patient	Year of treatment	Age at operation	Altman grade	Initial histology	Time elapsed till recurrence	Histology of recurrent tumor	Second recurrence?	Outcome
12	1997	8 d	I	MT	1 y	IT	No	NED, 6.5 y

MT *mature teratoma*
IT *immature teratoma*
YST *yolk sac tumor*
NED *no evidence of disease*

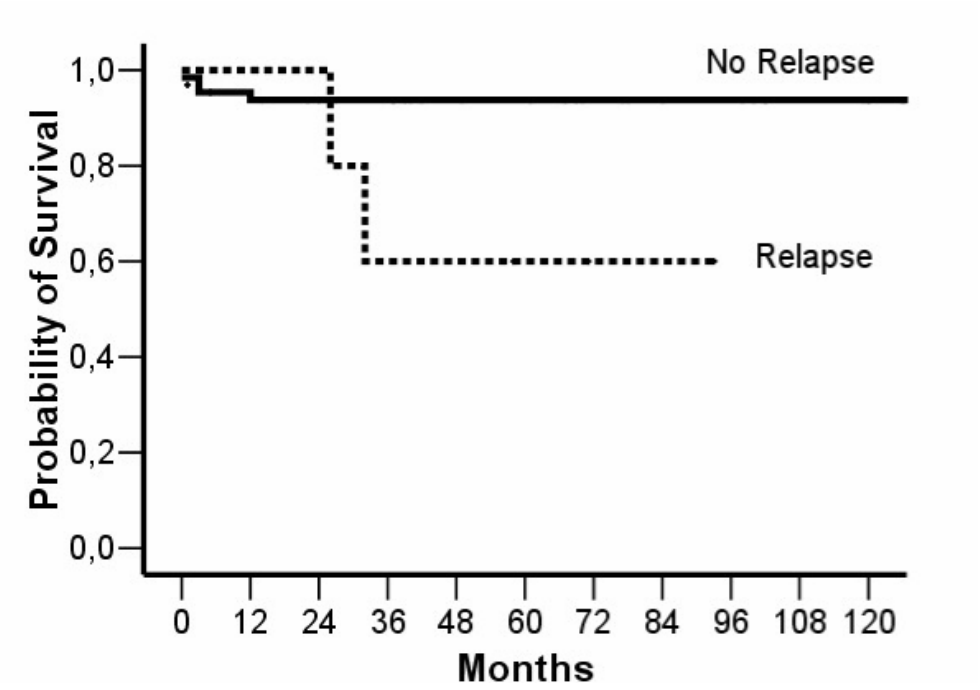

Figure 2 *Ten-year OS according to occurrence of relapse during the period from 1960 to 2003; OS in patients who experienced relapse (0.60 ± 0.22 [3/5]) was significantly lower than that in those without relapse (0.94 ± 0.03 [61/65]) (log-rank test, P = .015; hazard ratio [95% CI], 6.3 [1.2-34.2]).*

Table 3 Clinical data of 8 patients whose operations were complicated by spillage of cyst fluid (n = 6) or by rupture of the tumor (n = 2)

Patient	Year of treatment	Age at operation	Altman Grade	Initial Histology	Recurrence?	Outcome
Spill of cyst fluid						
13	1978	2 d	III	MT	No	Died of septicemia
14	1981	4 d	I	MT	No	NED, 22 y
15	1997	9 d	I	MT	No	NED, 16 y
16	1996	2 y	IV	YST	No	NED, 9 y
17	1995	2 d	III	MT	No	NED, 8 y
18	1996	2 d	II	MT	No	NED, 7 y
Tumor spill						
19	1982	8 mo	IV	YST	Yes	Died from metastatic disease
20	1996	1 d	II	IT grade I	Yes	Died from metastatic disease

MT *mature teratoma*
IT *immature teratoma*
YST *yolk sac tumor*
NED *no evidence of disease*

Table 4 Clinical data and course of 5 patients in whom the coccyx had been left in situ during the initial operation

Patient	Year of treatment	Age at operation	Altman Grade	Initial Histology	Recurrence?	Outcome
21	1960	8 mo	I	MT	No	NED, 43 y
22	1967	1 mo	III	MT	No	NED, 36 y
19	1996	8 mo	IV	YST		Died
23	1997	4 d	III	IT	Yes (developed a small presacral cystic lesion, not excised)	Stable for > 8 y
7	2001	6 wk	IV	IT grade I	No	NED, 2.5 y

MT *mature teratoma*
IT *immature teratoma*
YST *yolk sac tumor*
NED *no evidence of disease*

DISCUSSION

Table 5 summarizes the mortality and recurrence rates in the 13 most recently reported series of patients with SCT, including ours. Mortality rates range between 3% and 29% (mean, 14%). These figures, however, might to some extent underestimate the true rates, as the series reported by Ein et al,[10] Shanbhogue et al,[12] and Bilik et al[13] included patients with benign SCT only. Another series[17] reports only newborns younger than 4 weeks; the latter category usually shows lower mortality rates than older patients with Altman IV tumors and malignant cases. However, these are series of patients treated over several decades, in the course of which general knowledge and opportunities in (pediatric) medicine, but especially in oncology with the introduction of cisplatin in the mid-1980s, have considerably improved. Overall mortality in the present series was 8.5%, which is well below the mean and median values from the literature. Mortality in the subset of patients treated during the past 15 years (1989 - 2003), that is, when cisplatin had become available, was even as low as 2.5%. This would suggest that children born with SCT of all histological types nowadays have an excellent prognosis.

Table 5 also shows recurrence rates for SCT. Overall, recurrences have been observed in 2% to 35% of the patients (mean, 12.5%). For mature teratomas, recurrence rates range from 0% to 26% (mean, 10%). Higher rates have been observed in patients with immature teratoma, that is, from 12% to 55% (mean, 33%). Surprisingly, for frankly malignant tumors, the recurrence rate was lower again (0% - 36%; mean, 18%) thanks to chemotherapy, but in the event of malignant relapse, OS was lower.[21]

Recurrence has been attributed to several possible factors, that is, failure to achieve complete resection of the tumor, en bloc removal of the coccyx along with the tumor, tumor spillage, and failure to detect malignant components within the tumor.

Table 5 Survey of mortality and recurrence rates reported in 695 patients with SCT

Author (ref)	Year of publication	Period	No. of patients	Mortality (%)	Recurrence				Comment
					MT	IT	"Malignant" GCT	Total recurrences (%)	
Gonzalez-Crussi et al[9]	1978	1946 - 1976	40	22%	4/22 (18%)	10/18 (55%)	0	14/40 (35%)	Exclusively benign SCT
Ein et al[10]	1980	1951 - 1976	33	3%	1/33 (3%)	0	0	1/33 (3%)	Exclusively benign SCT
Engelskirchen et al[11]	1987	1960 - 1984	87	16%	9/76 (12%)	0	4/11 (36%)	13/87 (15%)	
Shanbogue et al[12]	1990	1954 - 1987	43	16%				1/43 (2%)	Exclusively benign SCT
Schropp et al[3]	1992	1950 - 1990	73	16%	5/57 (9%)		0%	5/73 (7%)	
Havranek et al[4]	1992	1980 - 1989	32	6%	4/23 (17%)	2/4 (50%)	1/5 (20%)	7/32 (22%)	
Bilik et al[13]	1993	1972 - 1990	28	?	6/28 (21%)	0	0	6/28 (21%)	Exclusively benign SCT
Rescorla et al[5]	1998	1972 - 1994	126	7%	9/80 (11%)	1/24 (4%)	2/13 (15%)	12/117 (10.2%)	Multicentric study (15 centers)
Schmidt et al[14]	1999	1976 - 1995	23	22%	5/19 (26%)		3/3 (100%)	8/22 (35%)	
Wakhlu et al[15]	2002	1983 - 2000	72	28%	0/47 (0%)	0	5/25 (20%)	5/72 (7%)	
Perelli et al[16]	2002	1985 - 1998	17	29%	2/11 (18%)	1/3 (33%)	0%	3/15 (20%)	
Huddart et al[17]	2003	1989 - 1997	51	4%	5/29 (17%)	2/16 (12.5%)	0%	7/51 (14%)	Exclusively newborns < 4 wk
Present series	2005	1960 - 2003	70	8.5%	3/43 (7%)	2/11 (18%)	0%	5/70 (7%)	
Total			695	14%				87/695 (12.5%)	

MT *mature teratoma*
IT *immature teratoma*

An entirely mature thus benign teratoma should not recur after surgical excision, unless the excision was incomplete or the coccyx was not removed or if histological underscoring has occurred because of the impossibility of examining every cubic inch of the usually large tumor. In our series, 3 patients with initially mature teratoma had a relapse after 6, 12, and 21 months, respectively; the relapsing tumors were histologically immature teratoma, malignant teratoma, and YST. In the latter case, one focus of YST was seen in the resection margins of the first operative specimen. On the other hand, our series included 4 other patients with mature teratoma whose resection margins were not free, but who did not relapse. In 2 patients with mature teratoma, the coccyx was left in situ; they have not relapsed and are now 36 and 43 years after surgery. From these findings, we might conclude that histological underscoring of the GCT probably underlies the high occurrence rate of relapse. Particular areas with abundant immature tissue or smaller foci of YST may be missed. In this particular operative area, surgery cannot be more radical, seeing that this would involve much more functional complications. The same is probably true for immature teratomas. In our series, 2 patients with immature teratoma grade I, one whose coccyx had been left in situ and one with intraoperative tumor spillage, relapsed with a benign local tumor and a malignant metastatic GCT, respectively. Our series, however, included 3 other patients with immature teratoma whose resection margins were histologically not free, but who did not relapse. Furthermore, in 2 patients, the coccyx was not removed; one is described above, the second did not show recurrence.

Patients with initially benign tumors may show either benign or malignant recurrence; patients with malignant tumors may as well show malignant, but also benign recurrence after chemotherapy. A considerable proportion of the mature or immature teratomas that relapse as malignant tumors are YST. Following Teilum's scheme, YST is not a further differentiation of an immature teratoma.[18] As a consequence, the development of these tumors can only be explained if the initial tumor contained (unidentified) foci of yolk sac elements and if the tumor was not excised completely. This was the case in patient 6, reported in *Tables 1* and *2*. Others have made similar observations.[22,23] A similar finding was made in patients with immature ovarian GCT: a central pathology review showed that the institutional pathologist had overlooked microscopic foci of YST in over 30% of the tumors.[24]

Recently, it was proposed that YST is the result of progression in a type I teratoma. This assertion is supported by chromosomal analyses showing that the teratoma component is diploid with chromosomal aberrations, while the YST has recurrent numeric abnormalities, that is, loss of part of 1p, 4, and 6q and gain of part of 1q, 12p (predominantly 12p13), 20q, and 22.[1,25,26] The late occurrence of YST in murine embryo–derived teratomas with chromosomal aberrations supports this view.[27]

In daily clinical practice, the following pressing question may arise: what to do when after gross complete excision of a SCT en bloc with the coccyx, histological analysis reveals that the tumor reached into the resection margins probably resulting in microscopic residual tumor? We have not found an answer in the literature. Eleven of the 12 patients with microscopic residue from the present series did not develop recurrence; those patients are now between 18 months and 27 years after surgery (*Table 2*). It would therefore seem justified to just follow such patients. Surgical reexploration is probably deemed to be unsuccessful, and chemotherapy is likely to be unnecessary. The 12th patient, who did develop (malignant) recurrence, was the baby in whom the resection line passed through a small focus of YST. In similar cases, adjuvant chemotherapy would be indicated. Of course, in the presence of grossly remaining tumor, reexcision seems mandatory whenever possible.

In conclusion, this study confirms the excellent prognosis of newborns and babies with SCT, even when malignant. Recurrence still remains a major problem. The basic principles of surgery, namely, complete en bloc resection of the tumor along with the coccyx and avoidance of intraoperative spillage of tumor content, certainly remain valid. Nevertheless, if definite histology shows microscopic involvement of the resection margins in mature or immature teratomas without the presence of foci with yolk sac elements, a conservative attitude involving close follow-up seems justified. If foci of YST are identified, then chemotherapy is warranted. The tumors should be thoroughly sampled for histology—at least one block per centimeter in the largest diameter is a rule of thumb—to detect small foci of YST. This should prevent histological underscoring of those benign tumors that recur as YST. Alternatively, YST may result from progression in residual teratoma after incomplete resection.

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Chapter 9

Factors Associated with Recurrence and Metastatic Disease in Sacrococcygeal Teratoma: Results in the Netherlands (1970-2003)

Joep Derikx
Antoine de Backer
Leon van de Schoot
Daniel C. Aronson
Zacharias de Langen
Thelma van den Hoonaard
Nicolaas Bax
Frans van der Staak
Ernest van Heurn

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ABSTRACT

Background
Sacrococcygeal teratoma (SCT) is a relatively uncommon tumour, with high risk for recurrence and metastasis. Factors associated with recurrence and metastatic disease were studied.

Patients and methods
A retrospective review was conducted of 173 patients with SCT treated from 1970 to 2003 at the paediatric surgical centres in the Netherlands. Risk factors were identified by univariate and multivariate analysis.

Results
Eight patients died shortly after birth or peri-operatively. Nine patients, all over 18 months, had metastases at presentation. Four metastasized teratomas showed mature histology of the primary tumour. Nineteen patients had recurrence of SCT after a median period of 10 months (range: 32 days - 35 months) after primary surgery. Risk factors for recurrence were pathologically confirmed incomplete resection: OR (CL) = 6.5 (2.1 - 20.3), immature: 5.7 (1.5 - 22.0) and malignant histology: 12.8 (3.3 - 50.4). Size, Altman-classification, age and decade at diagnosis were not risk factors. One-third of the recurrences showed a shift towards immaturity or malignancy, compared with the primary tumour. Seven patients died after recurrence, six with malignant disease.

Conclusion
This national study shows that SCT recurs in 12% of the patients within three years after operation. Risk factors are immature and malignant histology or incomplete resection. Mature teratoma possesses the biological behaviour to transform into malignancy and metastasize with advancing age.

INTRODUCTION

With a reported incidence of 1:40,000 live births, Sacrococcygeal Teratoma (SCT) is a rare tumour (*Fig.1*). However, it represents not only the most common site for a neonatal teratoma, it is also the most common neoplasm in newborns.[1] Soon after birth, complete resection usually provides an excellent prognosis. In a small number of patients teratoma recurs or presents with metastatic disease. This is accompanied by a relatively high morbidity and mortality.[2-5] It is unclear which factors are involved in recurrence and metastatic disease. Identification of the risk factors for recurrence and metastases may lead to better insight in the biologic behaviour of this tumour, its treatment and cure.

We performed an analysis of all Dutch patients with SCT in the period 1970 - 2003, and identified factors associated with recurrence and metastatic disease.

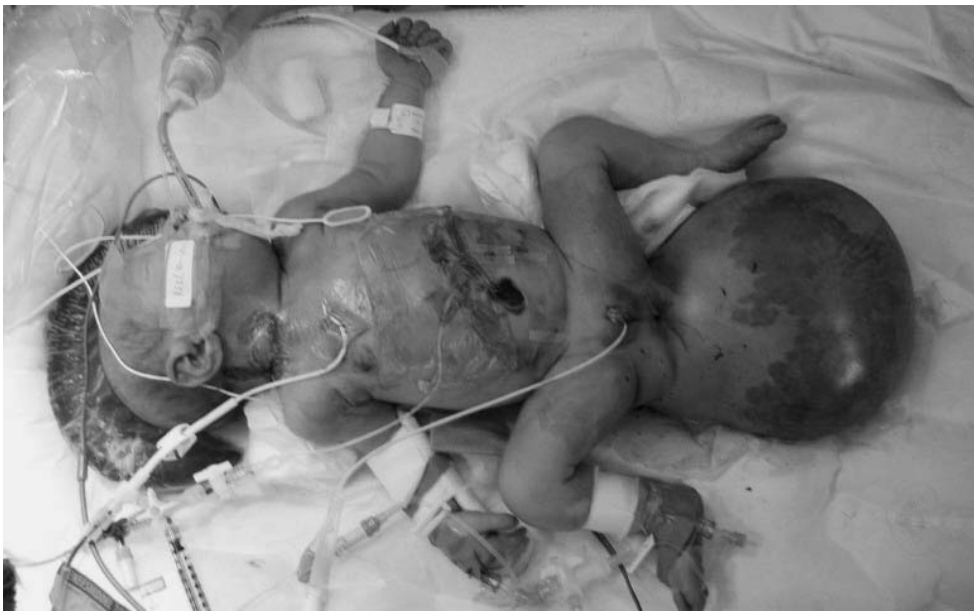


Figure 1 *Neonate with Sacrococcygeal Teratoma (SCT)*

PATIENTS AND METHODS

Patients

The medical records of all children with SCT treated from January 1970 to February 2003 at the six paediatric surgical centres in the Netherlands (Sophia Children's Hospital Rotterdam, University Medical Centre Nijmegen, Wilhelmina Children's Hospital Utrecht, University Medical Centre Groningen, Emma Children's Hospital AMC and Free University Medical Centre Amsterdam, University Hospital Maastricht) were studied retrospectively. Patients with a presacral teratoma as part of the Currarino triad were excluded. The following data were collected from the original medical records: method of delivery, sex, gestational age at birth, birth weight, age at diagnosis, associated defects, metastases, Altman

classification,[6] date of operation, operative technique, estimated size of the tumour, histopathological diagnosis, postoperative complications, recurrence, date of recurrence, treatment of recurrence, date of operation of tumour recurrence, histological diagnosis, and cause of death.

Postoperatively, patients were followed up at regular intervals. Patients lost to follow up were contacted and data were obtained by a questionnaire.

Statistical analysis

The incidence of SCT was calculated per decade by dividing the number of patients by the number of births in the Netherlands.

Univariate and multivariate relative risk analysis for recurrence and metastases at the moment of presentation were carried out for factors measurable before or at primary operation with the use of logistic regression. Risk factors investigated, with their respective categorizations, were as follows: Altman-classification (I, II, III, IV), complete resection (yes/no), histology (mature, immature, malignant), size of SCT (< 150 cm^3, 151 – 500 cm^3, > 500 cm^3), decade of diagnosis (1970 - 1979, 1980 - 1989, 1990 - 2003), age at diagnosis (< 8 days, 8 days - 1 year, > 1 year), and coccygectomy (yes/no). Tumours were classified histopathologically by a paediatric histopathologist into mature, immature, and malignant according to the most unfavourable component of the tissue. Histopathological data were obtained from the original reports.[1]

Overall and recurrence-free survival was calculated with the Kaplan-Meier method. Categorical variables were compared with the use of the chi-square test. Statistical analysis was performed on the Statistical Package for the Social Sciences™ (SPSS) for Windows version 12.0 software (SPSS, Chicago, Il). Unless stated otherwise, data are expressed as mean ± SD. Proportions are presented with 95% confidence intervals. Statistical significance was defined at $P < 0.05$.

RESULTS

One-hundred seventy-three patients were analyzed. There were 141 girls (81.5%) and 32 boys (18.5%). The calculated incidence in the 70s was 1:77,600 neonates, in the 80s: 1:31,606 neonates, and in the 90s: 1:28,567 neonates. 42 patients (24.3%) had 59 associated abnormalities, including musculoskeletal disorders (n = 12), uro-genitary abnormalities (n = 11), severe neuronal defects (n = 8), anorectal malformations (n = 4), ventricle septum defect (n = 3), persisting ductus arteriosus (n = 2), and other disorders (n = 12). The mean gestational age was 37.8 ± 2.8 weeks, with a mean birth weight of 3.2 ± 0.66 kg.

In the seventies 60% of the tumours were diagnosed within 24 hours after birth, and 40% thereafter. With the introduction of antenatal ultrasonography 14% was

diagnosed before birth, 54% within 24 hours after birth, and 32% thereafter in the period from 1980 to 1989. After this period 32% of the tumours were diagnosed prenatally, 34% at birth, and 34% more than 24 hours after delivery.

Sixty-seven children (38.7%) had a predominantly external tumour (Altman I), 45 children (26%) had an external tumour with a significant intrapelvic extension (Altman II), 21 children (12.1%) had an external tumour with a predominant pelvic mass (Altman III), and 36 children (20.8%) had an internal presacral tumour (Altman IV),[6] in 4 patients Altman-classification was unknown. The median age at the time of surgery was 8 days (range: 0 days - 17.5 years). Two patients died before operation, because of associated abnormalities and haemorrhage into the tumour, respectively. 171 patients entered further analysis. At operation, a sacral approach was used in all children. It was combined with a laparotomy in 28 patients. Other approaches (e.g. laparoscopic clipping of the sacral median artery followed by sacral approach) were chosen in 7 patients, and in 6 patients the approach was unknown. In 118 patients the resection margins were microscopically free of tumour, the resection was incomplete in 40 patients and in 12 patients it was unknown at histopathological examination. In 152 patients the os coccygis was removed, in 8 patients no coccygectomy was performed and in 10 patients it is unknown.

Six patients died intraoperatively or within 24 hours after surgery. All deaths were caused by circulatory failure and/or haemorrhage. Early postoperative complications were reported in 40 patients. These complications included wound infection or dehiscence of the wound (n = 23), urinary retention (n = 6), sepsis (n = 3), urinary tract infection (n = 3), circulatory failure (n = 2), coagulopathy, abscess, morphine-intoxication, and postoperative haemorrhage.

The histological diagnosis was a mature teratoma in 110 patients (64.3%), immature teratoma in 33 (19.3%), malignant germ cell tumour (GCT) in 22 (12.9%), and unknown in 8 patients. Nineteen of the 22 malignant tumours were Yolk sac tumours and three were embryonal carcinoma. With advancing age, the proportion of malignant teratoma increased (*Table 1, P* < 0.001).

Table 1 Age and histology at primary diagnosis of SCT

	Histology after resection of primary tumour (number of patients)			
Age at diagnosis	**Mature**	**Immature**	**Malignant**	**Unknown**
< 8 days	48	16	1	3
8 days - 1 year	31	10	9	3
> 1 year	13	3	11	1
Unknown	18	4	1	1

Mature SCT is usually detected soon after birth. Diagnosis at increasing age shows a significant higher proportion of malignancy of SCT

Metastases at presentation

At the time of diagnosis nine patients had metastases in spine (n = 4), liver (n = 3), lung (n = 3), lymph nodes (n = 1), unknown (n = 1). Metastatic disease at the time of presentation occurred only in children aged 1.5 years or older. Eight children underwent resection of the tumour, of whom four had delayed resection after treatment with chemotherapy. One child had chemotherapy as the only treatment. Histopathological evaluation of the SCT in these patients showed four mature, one immature, three malignant and one unclassified teratoma. Three of the four children with mature SCT received chemotherapy prior to resection of the tumour. Seven of the nine children survived between five and eighteen years after diagnosis. Two children died. One died because of a local recurrence and one because of recurrence with new metastases in the liver.

Recurrences

Nineteen patients had a recurrence of SCT after a median period of 10 months (range 32 days - 35 months) (*Fig. 2*). Nine recurrences were found by physical examination during routine follow-up, seven by raised serum alpha-Fetoprotein (aFP), one by the parents who noticed a recurrent tumour and in two patients the way of detection was unknown. In one of these children the os coccygis was not removed at the original operation. In ten patients the recurrence was confined to a local tumour, in seven it was combined with metastatic disease in liver (n = 2), spine (n = 2), spine and liver (n = 1), spine and lungs (n = 1), neck and mediastinum (n = 1), and two had suture line recurrences.

In seventeen of the nineteen patients the recurrent teratoma was resected. Resection was combined with cytostatic treatment in twelve patients and with radiotherapy in three patients. The histology of the primary tumour was compared with the recurrent tumour (*Table 2*). In ten patients the histological diagnosis after primary operation and after recurrence was the same. In five patients there was a shift towards immaturity or malignancy. In one patient, who had cytostatic treatment before resection of the recurrent tumour, an initial malignant process was mature at recurrence.

Table 2 Histology at primary resection and at resection of recurrence.

Histology after recurrence	**Histology before recurrence**		
	Mature	Immature	Malignant
Mature	4		1
Immature	1	1 (1†)	
Malignant	1	3 (3†)	5 (2†)
Unknown			2 (1†)

Most tumours show comparable histology after primary resection and after resection of the recurrent tumour. A shift towards a more undifferentiated tumour was detected in 5 of the 17 resected specimens after recurrence.
† *means death; 7 patients died after recurrence, most of them with malignancy*

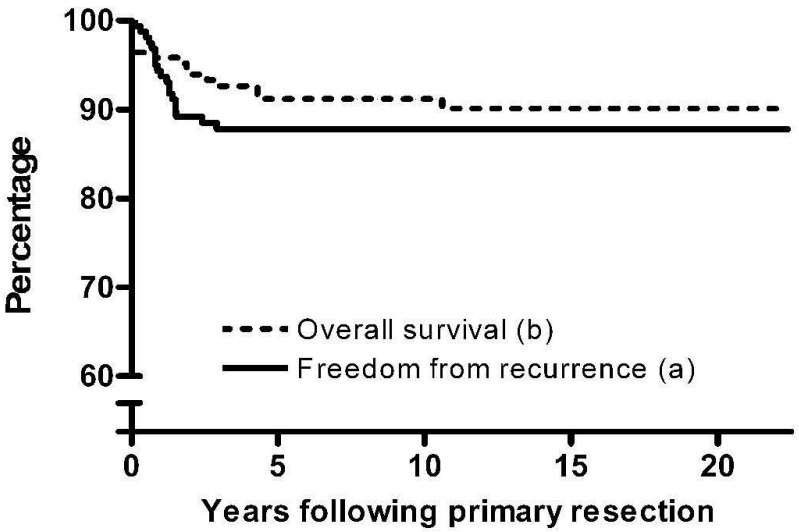
Twelve patients survived after treatment of the recurrent disease. Seven patients died after recurrence between 5 months and 5 years after detection of the first recurrence, most of them with malignancy. Four patients died with a second recurrence with metastases in liver (n = 2), lungs and spine (n = 1), neck and mediastinum (n = 1). One patient died because of second recurrence without known metastases. Two remaining patients died of other causes: sepsis and pulmonary fibrosis caused by chemotherapy.

Mortality

In the complete group of 173 patients, 17 patients (9.8%) died at age 1 day to 10.6 years (*Fig. 2*). Eight patients died shortly after birth or peri-operatively (age: 1 - 27 days), seven died after recurrence (age: 10 months - 10.6 years). Two children died without recurrence of the tumour. One died with sepsis after chemotherapy (age: 23 months), which was given because of tumour spill during resection. The other died because of metastatic disease (age: 22 months).

Risk factors for recurrence and metastases

One hundred and fifty patients with a follow-up period of more than three years were included into the analysis of risk factors for recurrence. They had a mean length of follow up of 14.1 years ± 7.7 years.



No. at risk

Freedom from recurrence	165	116	81	56	32
Overall survival	173	129	92	63	38

Figure 2 *Freedom from recurrence of 165 patients at risk (a) and overall survival of 173 patients (b) after SCT resection*

Table 3 shows that in a univariate analysis patients with pathologically proven incomplete resection during primary surgery at pathological examination were at an increased risk of recurrence (P = 0.001), even when the statistical analysis was adjusted for other factors. Immature histology (P = 0.011) and malignant histology (P < 0.001) were the other risk factors found for recurrence that were significant at the 5% level, with the 95% confidence intervals for the relative risk including 1. Immature and malignant histology remained significant after other factors were taken into account.

Size of the tumour (< 150 cm^3, 151 – 500 cm^3, > 500 cm^3), anatomical location and extension (Altman-classification), age at diagnosis (< 8 days, 8 days - 1 year, > 1 year), decade at diagnosis (70s, 80s, 90s), and coccygectomy were not risk factors for recurrence of SCT.

Recurrence rate for combinations of the factors complete resection with histopathological diagnosis changes from 2.6% in patients with mature histology and complete resection, towards a much higher incidence (50%) in patients with immature or malignant histology and incomplete resection.

Both Altman-classification (P < 0.001) and age at diagnosis (P < 0.001) are significant risk factors for metastases at diagnosis of SCT. Patients with metastatic disease at diagnosis had Altman type III (n = 2) or Altman type IV (n = 7), and all patients were over one year of age. Histopathology, size of the tumour, and decade of diagnosis were not associated with metastases.

DISCUSSION

The true incidence of SCT can only be assessed in the period after 1980 in which most patients with paediatric surgical disorders were treated in specialized centres in the Netherlands. After 1990 the risk of under-registration is further minimized by prospective and computerized registration. In this period the incidence of SCT was 1:28,500, which is higher than the generally accepted incidence of 1:40,000. In fact, the incidence may even be higher, because some patients with SCT may have died in utero or during delivery with high output cardiac failure. These patients were not even treated at the paediatric surgical units and have not been included in this study.

SCT is associated with other defects in nearly 25% of the patients. In most patients there is a direct relation with the mass of the tumour which may cause ureteric obstruction with hydronephrosis, or push aside structures with dislocation of the hips and neuronal disorders. In a small percentage of the patients associated defects are not directly related to the tumour mass such as associated heart defects. Postnatal cardiac ultrasonography may diagnose high cardiac output and associated cardiac defects.

Table 3 Risk factors for recurrence of SCT

			Odds ratios (95% CL)			
	Level	**Rate**	**univariate analysis**	**P Value***	**multivariate analysis**	**P Value***
Complete resection	yes	6/107	1		1	
	no	9/31	6.54 (2.11 - 20.31)	0.001	3.92 (1.13 - 13.64)	0.032
Histology	mature	4/97	1		1	
	immature	6/29	5.74 (1.49 - 22.05)	0.011	7.27 (1.57 - 33.61)	0.011
	malignant	7/19	12.83 (3.27 - 50.43)	< 0.001	14.06 (2.63 - 75.28)	0.002
Altman	I	8/60	1			
	II	1/40	0.16 (0.02 - 1.33)	0.089		
	III	3/18	1.18 (0.28 - 5.00)	0.82		
	IV	5/29	1.04 (0.70 - 1.56)	0.844		
Volume	< 150 cm^3	5/56	1			
	151 - 500 cm^3	4/27	1.94 (0.48 - 7.95)	0.356		
	> 500 cm^3	2/19	1.20 (0.22 - 6.76)	0.836		
Age at diagnosis	< 8 days	3/59	1			
	8 days - 1 year	6/42	3.03 (0.71 - 12.91)	0.13		
	> 1 year	5/27	4.21 (0.92 - 19.19)	0.06		
Decade	1970 - 1979	4/24	1			
	1980 - 1989	7/54	0.74 (0.19 - 2.82)	0.66		
	1990 - 2003	6/72	0.45 (0.12 - 1.77)	0.26		
Coccygectomy	yes	15/136	1			
	no	1/7	1.38 (0.16 - 12.32)	0.77		

*Relative risk estimation for recurrence after primary resection by logistic regression models; risk factors for recurrence are incompleteness of resection, immature and malignant histology of the primary resected tumour. * P was significant if < 0.05*

The mortality soon after birth and peri-operatively was relatively high with an incidence of 5%. All of these deaths were caused by high output cardiac failure, haemorrhage into the tumour or peri-operative bleeding. To minimize both the risk of operative cardiac failure and haemorrhage, laparoscopic ligation of the median sacral artery before resection of the SCT has been advocated.[7-9]

Nine patients presented with metastatic disease. All patients with metastatic SCT in our study were at time of diagnosis at least 1.5 years of age. The histopathological diagnosis of the tumour was mature teratoma in four patients. Three patients received chemotherapy before resection of the primary tumour which may have influenced the histopathological diagnosis as conversion of immature or malignant SCT into a benign tumour may be possible.[10] However, one patient with mature SCT and metastasis had no preoperative chemotherapy. In teratoma of the testis it has been proven that teratoma may metastasize even if diagnosed as mature.[11] This study confirms this finding for SCT. It suggests that mature SCT, diagnosed with classical histopathological examination, possesses the biological behaviour to metastasize.

The present study showed that 12% of the operated children had recurrent disease. In primary mature teratoma the recurrence rate was 5%, in immature teratoma 17% and in malignant GCT 37%. All recurrences occurred within 3 years after primary resection, emphasizing the need for at least 3 years follow-up in all patients. Other authors confirm this policy.[1,12,13] Very late recurrence of mature SCT over 20 years after surgery has been described.[14,15] Follow-up longer than three years after primary operation may be necessary to detect very late recurrent disease and to diagnose and treat long term functional deficits, which may be present in 30 - 65% of patients.[16-18] The prevalence of sequelae such as faecal and urinary incontinence, sexual disorders, and lower extremity weakness is relatively unknown.

There is an important difference between the histopathological diagnosis of the primary and the recurrent tumour (*Table 2*). In a large proportion of the recurrent tumours, the excision of the primary tumour had not been complete, but there were also recurrences after macroscopically and histologically radical excision of the tumour. These cases may reflect minute yolk sac tumour components missed in the original pathological examination with small remnants left in situ. This study also shows that despite incomplete resection, the teratoma does not always recur. Most cases show that histology after recurrence becomes more undifferentiated (malignant) compared to the histology after primary resection. The potential for malignant transformation of SCT is one explanation for this poorly understood biological behaviour.[2] The late development of a malignancy is suggested to originate from the retained capacity for continued embryonic growth. This point is further emphasized in our study by the finding that only 1.5% of the tumours were malignant when operated on in the first week of life; but thereafter the rate of malignancy rose to nearly 40% in children older than one year. This provides

evidence that mature SCT at classical histopathological examination possesses the ability to transform into a malignancy as the patient becomes older. Further studies with other markers for malignancy[19] may elucidate this phenomenon.

The most important risk factor for recurrence of SCT is pathologically confirmed incomplete resection during primary surgery. Furthermore, both immature and malignant histology of the primary tumour are other positive predictors of recurrence. Altman classification, age at diagnosis, decade at diagnosis, size of the teratoma and coccygectomy are not associated with recurrence. Bilik et al identified in 28 patients no factors that may influence the recurrence of SCT.[13] This national survey of SCTs extending more than three decades enabled us to describe a large group of patients with reliable identification of the risk factors for recurrence. A complete resection is essential in preventing recurrence. Whenever the histopathological examination of the resected specimen shows mature teratoma, a careful analysis to detect areas of malignancy in the specimen is mandatory.[13,20]

In conclusion, SCT is a tumour with a relatively high recurrence rate with high morbidity and mortality. We showed that mature SCT can metastasize and that every mature teratoma has the potential of malignant degeneration. The specimen should be carefully analyzed to detect small areas of malignant degeneration which is highly associated with recurrence.[13,20] Therefore, mature teratoma should be regarded as a premalignant condition.

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10 chapter

Sacrococcygeal Teratoma: Results of a Retrospective Multicentric Study in Belgium and Luxembourg

A. De Backer
P. Erpicum
P. Philippe
M. Demarche
J. B. Otte
K. Schwagten
M. Vandelanotte
M. Docx
T. Rose
A. Verhelst
D. De Caluwé
P. Deconinck

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ABSTRACT

Eighteen patients, operated upon for sacrococcygeal teratoma in 7 different centres in Belgium and Luxembourg between 1992 and 1996, were reviewed. From an epidemiological point of view, this series compares very well to others. Although excellent results were obtained, with all patients surviving, some imperfection in diagnosis, timing of delivery and of operation, and in operative technique was observed. Therefore, it is stated that for optimal treatment of sacrococcygeal teratoma to be achieved, these cases should be treated in just a very few centres of neonatal surgery.

Résumé
Entre 1992 et 1996, 18 patients ont été opérés pour tératome sacro-coccygien dans 7 centres Belgo-Luxembourgeois. Sur le plan épidémiologique, cette série est très comparable à d'autres. Bien que d'excellents résultats ont été obtenus, avec une survie de 100%, nous avons observé plusieurs imperfections dans le diagnostic, le moment et le mode d'accouchement, le moment de l'opération et la technique opératoire. C'est la raison pour laquelle nous pensons qu'un résultat optimal ne peut être achevé qu'à condition de centraliser cette pathologie dans quelques centres de chirurgie pédiatrique seulement

Resumen
Revisamos 18 pacientes operados entre 1992 y 1996 por teratoma sacrocoxígeo en 7 centros diferentes de Bélgica y Luxemburgo. Desde un punto de vista epidemiológico esta serie se compara con otras. Aunque se obtuvieron resultados excelentes con sobrevivencia de todos los pacientes, observamos algunas imperfecciones en el diagnóstico, momento del parto y operación así como en la técnica operatoria. Concluímos que para el tratamiento óptimo del teratoma sacrocoxígeo estos casos deberían ser tomados a cargo solamente por algunos centros de referencia en cirugía neonatal.

Zusammenfassung
Eine retrospektive multizentrische Studie von Belgien und Luxemburg wird vorgestellt. Sie umfasst 7 kinderchirurgische Kliniken, in denen im Zeitraum von 1992 - 1996 18 Patienten mit Steißbeinteratomen operiert wurden. Die epidemiologischen Daten entsprechen denen anderer großer Statistiken. Bei einem Patienten wurden ausgezeichnete postoperative Ergebnisse erreicht, alle überlebten, allerdings wird auf einige verbesserungswürdige Zusammenhänge hingewiesen wie mangelhafte pränatale Diagnostik, Probleme der Geburtsplanung, der Operationsplanung und der Operationstechnik. Es wird eine Zentralisierung dieser seltenen Tumoren empfohlen, um eine optimale Prognose auch hinsichtlich der Kontinenz zu erzielen.

INTRODUCTION

Sacrococcygeal teratoma (SCT) is a well-known condition of the newborn which carries an excellent prognosis provided adequate surgical treatment is prompt and excision complete. It is the most common tumour in the newborn period, with a reported incidence of approximately 1 in 35,000 - 40,000 live births. Extrapolation of these data to Belgium and Luxembourg would result in no more than 3 - 4 new cases each year. Some paediatric surgeons who had seen quite a few of these patients wanted to find out what the exact incidence is in both countries. Since no register of those anomalies is available, it was decided to set up a retrospective multicentric 5-year study in order to investigate the incidence of SCT. Similarly, the accuracy of diagnosis and the quality of treatment of SCT in both countries could be analysed.

PATIENTS

By means of a questionnaire, sent to all the members of the Belgian Association of Paediatric Surgery (Belaps) working in centres for paediatric surgery in Belgium and Luxembourg, we tried to gain insight into the treatment of SCT. Eighteen patients operated upon for SCT between 1992 and 1996 were thus reported (*Table 1*). The patients were treated in the following centres: CHR Citadelle Liège (6 patients), Academisch Ziekenhuis VUB Brussel and Centre Hospitalier du Luxembourg (4 patients each), UCL St Luc Bruxelles, AKA-Paola Kinderziekenhuis Antwerpen, St Vincentiusziekenhuis Antwerpen and AZ Sint Jan Brugge (1 patient each). Fourteen were female, four were male (ratio 4:1). They were born after a mean pregnancy duration of 38.4 weeks (extremes 35 - 41 weeks). Delivery was normal (vaginal) in 11 and seven (39%) were delivered by Caesarean section. The mean birth weight was 3304 g (extremes 2480 - 4190). Associated anomalies were present in 2 patients (11%): one cystic adenoid malformation of the lung and one sacral agenesis. The diagnosis was made antenatally in 6 patients only (33%) at gestational ages 23, 29, 30, 30, 32 and 34 weeks. In 10 patients, the diagnosis was made at birth whereas in 2 patients the diagnosis was made at a later age, namely at 19 and 24 months. Preoperative check-up included X-ray of the abdomen (11 pts) and spine (1 pt), ultrasound (16 pts), MRI (10 pts) or CT (4 pts). The tumours were classified preoperatively on clinical grounds as cystic (5), solid (1) or mixed (12) and as small (5) or large (13). They were classified Altman type I (13), type II (3), type III (1) or type IV (1). Four patients were operated upon on the day of birth, 2 of whom had rupture of the tumour. Six others were operated on during the first week of life, five at 1 - 4 weeks and 3 at a later age (10 months, 1 year 8 months, and 4 years). Operations were performed through a perineal (16) or abdominoperineal approach (2). The smallest tumour removed measured 2 x 2 cm, the largest 19 x 9 cm. *En bloc* coccygectomy was reported in 17 patients. No intraoperative complications were reported. Recovery from surgery and anaesthesia was uneventful in all patients. Two lesser wound infections were treated conservatively.

Table 1 Characteristics of 18 cases of sacrococcygeal teratoma

Pat.	Sex	Pregnancy duration (weeks)	Birth weight (g)	Partus	Diagnosis	Tumour morphology	Tumour dimensions	Altman type	Emergency operation	Surgical approach	Coccygectomy	Postop. complications	APD	Chemotherapy
1	M	39	3650	V	B	Cystic	2 x 3 cm	I	no	Perineal	en-bloc	none	Benign-mature	no
2	F	40	3870	V	B	Solid	2 x 2 cm	I	no	Perineal	en-bloc	none	Benign-mature	no
3	F	38	3200	CS	A (29 w)	Mixed	8 x 5 cm	I	yes (rupt)	Perineal	en-bloc	none	Benign-mature	no
4	F	39	3000	V	B	Mixed	4 x 2 cm	I	no	Perineal	en-bloc	none	Benign-mature	yes
5	M	40	3560	V	B	Cystic	4 x 2 cm	II	no	Perineal	en-bloc	none	Benign-mature	no
6	F	40	3590	CS	19 mo	Cystic	8 x 5 cm	I	no	Perineal	en-bloc + S5	none	Benign-mature	no
7	F	38	3350	CS	B	Mixed	8 x 4 cm	I	no	Perineal	partial	none	Benign-mature	no
8	F	40	?	V	B	Mixed	3 x 5 cm	I	no	Perineal	en-bloc	none	Benign-mature	no
9	F	35	2835	CS	A (32 w)	Mixed	19 x 9 cm	I	no	Perineal	en-bloc	Wound infection	Immature	no
10	M	40	3920	V	B	Mixed	12 x 8 cm	I	no	Perineal	en-bloc	none	Benign-mature	no
11	M	38	3050	V	B	Mixed	7 x 3 cm	I	no	Perineal	en-bloc	none	Benign-mature	no
12	F	38	4190	CS	A (34 w)	Mixed	8 x 8 cm	II	no	Perineal	en-bloc	none	Immature	no
13	F	36	2800	CS	A (30 w)	Cystic	12 x 6 cm	III	no	Abdom. + Perin.	en-bloc	Wound infection	Benign-mature	no
14	F	35	3045	V	A (30 w)	Mixed	16 x 7 cm	I	yes (rupt)	Perineal	en-bloc	none	Immature	no
15	F	37	2480	V	B	Cystic	2 x 0.5 cm	I	no	Perineal	en-bloc	none	Benign-mature	no
16	F	37	2750	CS	A (23 w)	Mixed	10 x 8 cm	I	no	Perineal	en-bloc	none	Malignant	no
17	F	41	3630	V	B	Mixed	13 x 9 cm	II	no	Abdom. + Perin	en-bloc	none	Malignant	no
18	F	41	3250	V	24 mo	Mixed	10 x 5 cm	IV	no	Perineal	en-bloc	none	Malignant	yes

Pat *Patient*
Sex: M = *male*, F = *female*
Partus: V = *vaginal delivery*, CS = *Caesarean section*
Diagnosis: B = *diagnosis made at birth*, A = *antenatal diagnosis (gestational age)*
rupt *emergency operation because of rupture of tumour*

Pathologic examination of the resected tumours revealed these to be benign in 15 pts (mature in 12, immature in 3) and malignant (yolk sac components) in 3. For the latter, surgery alone was curative in 2, while one patient needed chemotherapy. It was a girl with an Altman IV tumour, diagnosed at the age of 2 years. The tumour, which measured 5 x 5 x 10 cm, was partially removed together with the coccyx; there was infiltration into the posterior rectal wall. APD was immature teratoma, partially removed. Chemotherapy was started. The alpha-foetoprotein levels started to rise again after 6 months; at reexploration, the recurrence could not be removed completely. Intensive consolidation chemotherapy followed by stem cell transplantation was administered. This girl is now 4½ years old and in remission since 17 months. A second patient who needed chemotherapy was a 2-year-old who was born with an Altman I tumour, removed at the age of 8 days. APD showed a mature teratoma. At the age of 1½ years, her alpha-foetoprotein levels started to rise. Imaging, followed by reexploration, did not reveal any residual tumour. A short course of chemotherapy was given; this girl is now 4 years old and in remission since more than a year. At present, all 18 patients are alive and doing well.

DISCUSSION

From the epidemiologic point of view, this quite limited series compares remarkably well to larger series in the world literature.[1,4,16,17] More than three quarters of the patients are girls, most are full-term babies with a good birth weight, and only a few have associated anomalies. The tumours are present at birth in most patients, and predominantly mixed solid-cystic and benign. Most are Altman I or II, i.e. tumours with an important external component. Most patients were operated upon in the first month of life and their overall prognosis appeared to be excellent.

As far as we know, there is no registry of SCT in our countries. The methodology used in this study obviously does not permit the determination of the exact number of patients born with this condition in both countries. Theoretically, if the reported incidence of 1 per 30,000 – 40,000 live births is correct, there should be 15 to 20 new cases in five years (the number of live births per year being around 130,000 in both countries together). We have been able to collect 18 cases, but it is very likely that more cases were treated by paediatric surgeons in centres which did not collaborate, or by general surgeons or neurosurgeons in other hospitals. So we still believe (but cannot prove) that the incidence of SCT is higher indeed than the reported incidence in the literature. Obviously, close surveillance of congenital malformations is important. A survey may be a first step towards a national registry.

Some obstetrical data merit special attention (*Table 2*). At first sight, the low incidence of prenatally diagnosed teratomas in this series seems striking. One

would expect those tumours to be visualised easily during the third trimester ultrasound scan in nearly all patients (except perhaps in those with small intrapelvic tumours, Altman IV). However, this finding is not so unusual. First, presentation prior to 30 weeks gestation carries a high risk of fetal death.[3] Second, a certain number of tumours are so small that they could easily be missed with the ultrasound apparatuses for routine use. Third, some larger tumours have probably grown rapidly during the last few weeks of pregnancy. For tumours diagnosed after 30 weeks, it has been advocated to perform Caesarean section in order to avoid dystocia, tumour rupture or haemorrhage, as soon as foetal lung maturity is deemed adequate for neonatal survival.[6,9,11,15] This guideline has been followed strictly in our series, except in one case, where a large SCT was diagnosed at 30 weeks gestation, and where vaginal delivery took place at 35 weeks; the tumour measured 16 x 7 cm.

Despite this, despite the fact that in another patient the treatment was intentionally deferred until the age of four years, despite the fact that in two patients the coccyx had only partially been removed, the final results obtained are satisfactory so far. Of course, recurrence is still possible in some patients, as it is also possible that some will have to deal with faecal incontinence.[2,5,8,12-14] Moreover, when reviewing the pathology reports, and due to the rarity of this condition, there seems to be a great diversity in the quality of the pathology reports.[7,10] Therefore, we are convinced that for optimal treatment of SCT to be achieved, these cases should be treated in just a very few centres of neonatal surgery.

Table 2 Relationship between timing of diagnosis, mode of delivery and tumour size

	Timing of Diagnosis		
Mode of delivery	Antenatally (gestational age)	At birth	At later age
Caesarean section	**19 x 9 cm (32 w)** **12 x 6 cm (30 w)** **10 x 8 cm (23 w)** 8 x 8 cm (34 w) 8 x 5 (29 w)	8 x 4	(at 19 months) type I - 8 x 5 cm
Vaginal delivery	**16 x 7 cm (30 w)**	**13 x 19 cm** **12 x 8 cm** 7 x 3 cm 5 x 3 cm 4 x 2 cm 4 x 2 cm 3 x 2 cm 2 x 2 cm 2 x 0,5 cm	(at 24 months) **type IV – 10 x 5 cm**

The larger tumours (measuring more than 10 cm) are set in bold

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11 Chapter

Long-Term Functional Sequelae of Sacrococcygeal Teratoma: A National Study in the Netherlands

Joep PM Derikx
Antoine De Backer
Léon van de Schoot
Daniel C Aronson
Zacharias J de Langen
Thelma L van den Hoonaard
Nicolaas MA Bax
Frans van der Staak
LW Ernest van Heurn

Submitted

ABSTRACT

Background
Long-term functional sequelae after resection of sacrococcygeal teratoma (SCT) are relatively common. This study determines the incidence of these sequelae, associated clinical variables and its impact on quality of life (QoL).

Patients and methods
Patients with SCT treated from 1980 to 2003 at the pediatric surgical centers in the Netherlands aged older than 3 years received age-specific questionnaires, which assessed parameters reflecting bowel function (involuntary bowel movements, soiling, constipation), urinary incontinence, subjective aspect of the scar and QoL. These parameters were correlated with clinical variables, which were extracted from the medical records. Risk factors were identified by univariate analysis.

Results
Seventy-nine of the 99 (80%) posted questionnaires were completed. The median age of the patients was 9.7 years (range: 3.2 - 22.6 years). Forty-six percent reported impaired bowel function and/or urinary incontinence; 9% involuntary bowel movements, 13% soiling, 17% constipation, 31% urinary incontinence. In 40% the scar was cosmetically unacceptable. Age at completing the questionnaire, Altman-classification, sex, and histopathology were not risk factors for any long-term sequelae. Size of the tumor (> 500 cm^3) was a significant risk factor for cosmetically unacceptable scar (OR (CL): 4.73 (1.21 - 18.47), P = 0.026). Long-term sequelae were correlated with diminished QoL.

Conclusion
A large proportion of the patients with SCT suffer from problems with defecation, urinary incontinence or a cosmetically unacceptable scar which affects QoL. Patients who are at higher risk for the development of long-term sequelae cannot be clearly assessed by clinical variables.

INTRODUCTION

With an incidence of approximately 1:28.500 live births, Sacrococcygeal Teratoma (SCT) is a relatively uncommon congenital tumor.[1] Despite its rarity, diagnosis and treatment have become well standardized and good survival data are reported for the majority of patients.[1,2] However, sequelae, such as fecal incontinence, constipation, and urinary incontinence, frequently continue into adulthood.[3,4] The incidence and factors which contribute to these sequelae are relatively unknown and it is unclear how patients experience these sequelae.

This study has been performed to determine (a) the percentage of patients with functional sequelae in this large series of all Dutch patients with SCT treated in the period 1980 - 2003, (b) which factors could be associated with the development of functional sequelae and (c) how patients experience these sequelae.

PATIENTS AND METHODS

Patients

All children with SCT treated from January 1980 to February 2003 at the six pediatric surgical centers in the Netherlands (Sophia Children's Hospital Rotterdam, Radboud University Nijmegen Medical Centre, Wilhelmina Children's Hospital Utrecht, University Medical Centre Groningen, Emma Children's Hospital AMC and Vrije University Medical Centre Amsterdam, University Hospital Maastricht) received a questionnaire which was validated for patients with Hirschsprung's disease and anorectal malformation.[5] Self-report questionnaires were developed for the age groups 0 to 8 years, which the parents were asked to complete, 8 to 16 years, which the parents together with the children were asked to complete, and 17 years or older, which the patients were asked to complete. Questions were categorized into parameters reflecting 1. involuntary bowel movements, 2. soiling, 3. constipation, 4. urinary incontinence, according to the parameters used for evaluation of bowel function in patients with anorectal malformation introduced by Peňa.[6] Voluntary bowel movements are defined as the act of feeling the urge to use the toilet to have a bowel movement, the capacity to verbalize it, and to hold the bowel movement until the patient reaches the bathroom; this is considered the most valuable sign of fecal control. Soiling is defined as the involuntary leaking of small amounts of stool, which provokes smearing of the underwear. This may be present with or without voluntary bowel movements. Patients who suffer from involuntary bowel movements and soiling together are considered totally fecal incontinent. Constipation is defined as the incapacity to empty the rectum (without help) every day. Urinary incontinence is defined as minimally dribbling and wetness of the underwear day and night. Next to these four parameters, special attention was paid to a cosmetically acceptable scar. Quality of life was assessed by scoring the personal appreciation of patients' complaints. From medical records the following data were collected: sex, age at diagnosis, Altman classification,[7] estimated size of the tumor, and histopathological

diagnosis. Postoperatively, patients were followed up at regular intervals. Patients with a presacral teratoma as part of the Currarino triad were excluded. Analogous to the inclusion criteria of the parameters introduced by Peňa,[6] taking into account that some normal children younger than 3 years of age were still not toilet-trained, only patients aged 3 years and older were included.

Statistical analysis

Spearman's test for non-parametric correlations was used to test the significance of correlations.

Univariate relative risk analysis for voluntary bowel movements, soiling, constipation, urinary incontinence, and satisfaction with the scar were carried out for factors measurable before or at primary operation with the use of logistic regression. Risk factors investigated, with their respective categorizations, were as follows: Altman-classification (I, II, III, IV), complete resection (yes/no), histology (mature teratoma, immature teratoma, malignant germ cell tumor (GCT)), size of SCT (< 150 cm^3, 151 - 500 cm^3, > 500 cm^3), age at diagnosis (< 8 days, 8 days - 1 year, > 1 year), sex (female/male), and age at completing the questionnaire. Tumors were classified histopathologically into mature or immature teratoma, and malignant GCT according to the most unfavorable component of the tissue.[8]

Categorical variables were compared with the use of the chi-square test. Statistical analysis was performed on the Statistical Package for the Social Sciences (SPSS) for Windows version 12.0 software (SPSS, Chicago, Il). Unless stated otherwise, data are expressed as mean ± SD. Proportions are presented with 95% confidence intervals. Statistical significance was defined at $P < 0.05$.

RESULTS

Demographics

One-hundred and forty-eight patients with a diagnosis of SCT were treated at one of the six pediatric surgical centers in the Netherlands during the study period. Thirteen patients died (8.8%), of whom seven shortly after birth or perioperatively (age: 1 - 27 days), four after recurrence, most of them with malignancy (age: 10 months - 10.6 years), and two children because of other causes. At the time of the study, 11 patients were aged 3 years or younger. Twenty-five patients could not be contacted. A questionnaire was posted to the remaining 99 patients. Seventy-nine patients returned a completed questionnaire and entered further analysis (80% response). The median age of the analyzed patients was 9.7 years (range: 3.2 - 22.6 years); there were 64 girls and 15 boys (4.3:1). In all children the tumor was resected. In 58 patients the resection margins were microscopically free of tumor, the resection was incomplete in 17 patients and in 4 patients it was unknown. Fifty-five tumors were mature, 18 immature, and 6 malignant. Predominantly external (Altman type I) tumors were found in 31 patients, whereas

22 patients had external tumors with a significant intrapelvic extension (Altman type II). Predominantly pelvic tumors with abdominal extension (Altman type III) were found in 8 patients, and 17 patients had an internal presacral tumor (Altman type IV). The median estimated size of the tumors was 138 cm^3 (range: 4 - 6544 cm^3).

Table 1 provides a schematic overview of the results reported in 79 patients. Thirty-six of the 79 patients (45.6%) reported minimally one of the parameters reflecting bowel function (involuntary bowel movements, soiling, constipation, urinary incontinence) as positive. Adding cosmetically unacceptable scar as the fifth parameter for sequelae, 52 of the 79 patients (65.8%) indicated to suffer from at least one of the long-term sequelae.

Involuntary Bowel Movements
Three patients did not complete all items on the questionnaire belonging to the parameter involuntary bowel movements; 7 of the remaining 76 patients (9.2%) reported involuntary bowel movements. The clinical consequences were difficult to objectivate. The absence of voluntary bowel movements correlated very well with the reported loss of quality of life (Spearman's rho = 0.550, $P < 0.001$). Size of the tumor (< 150 cm^3, 151 – 500 cm^3, > 500 cm^3), anatomical location and extension (Altman-classification), histopathology (mature, immature, malignant), age at diagnosis (< 8 days, 8 days - 1 year, > 1 year), sex, and age at completing the questionnaire were not risk factors for involuntary bowel movements.

Soiling
Three patients did not complete all questions about this parameter. Of the remaining 76 patients 10 (13.2%) suffered from soiling. All 10 patients suffered from frequent soiling in their underwear during the day and sometimes during the night. Five patients with soiling also suffered from involuntary bowel movements; these patients were considered totally fecal incontinent. Loss of quality of life and soiling were correlated (Spearman's rho: 0.644, $P < 0.001$). In the patients with soiling histopathology, Altman-classification, age at diagnosis, sex, and age at time of completing the questionnaire could not be identified as risk factors.

Table 1 schematic overview of the functional sequelae reported in 79 patients

	Ratio (percentage)
Total fecal incontinence	5/76 (7%)
Urinary incontinence	23/75 (31%)
Involuntary bowel movements	7/76 (9%)
Soiling	10/76 (13%)
Constipation	13/78 (17%)
Unsatisfactory cosmetically scar	31/77 (40%)

Constipation
In 1 patient it was unknown whether constipation was diagnosed; in 13 of the 78 patients (16.7%) constipation was reported. Constipation was only present in 3 patients with soiling or involuntary bowel movements. Constipation bothered patients much (Spearman's rho: 0.534, $P < 0.001$). Histopathology, size of the tumor, Altman-classification, age at diagnosis, sex, and time at completing the questionnaire were not associated with constipation.

Urinary incontinence
Four patients did not complete all questions about urinary incontinence. Twenty-three of 75 patients (30.7%) had problems with urinary control. Two patients with urinary incontinence also had complaints of total fecal incontinence. In 6 patients with urinary incontinence, medical records showed neurogenic bladder with recurrent urinary tract infections. An excellent correlation was shown between diminished quality of life and urinary incontinence (Spearman's rho: 0.881, $P < 0.001$). Univariate analysis revealed that histopathology, Altman-classification, size of the tumor, age at diagnosis, sex, and age at completing the questionnaire were not risk factors for urinary incontinence. Comparing patients aged younger than 5 years (n = 19) with patients aged older than 5 years (n = 60), revealed no significant difference in the incidence of urinary incontinence between both age-groups (OR (CL): 1.84 (0.60 - 5.66), $P = 0.289$).

Scar
Two patients did not complete items related to the scar. Thirty-one of the 77 patients (40.3%) reported that the result of the scar was cosmetically unacceptable. No correlation could be demonstrated with involuntary bowel movements (rho: 0.022, $P = 0.853$), soiling (rho: 0.170, $P = 0.145$), constipation (rho: 0.087, $P = 0.453$), urinary incontinence (rho: -0.024, $P = 0.843$). Nine patients consulted a doctor because of scar. Size of the tumor (larger than 500 cm^3) is a significant risk factor for cosmetically unacceptable scar (OR (CL): 4.73 (1.21 - 18.47), $P = 0.026$). Diagnosis of SCT in patients younger than 8 days was also associated with unsatisfactory scar compared to age at diagnosis older than one year (OR (CL): 0.19 (0.04 - 0.98), $P = 0.048$). Histopathology, Altman-classification, sex, and time at completing the questionnaire were not risk factors for cosmetically unacceptable scar.

Discussion

The true incidence of SCT in the Netherlands can be assessed with these data. After 1980 treatment of almost each patient with SCT occurred in one of the 6 pediatric surgical centers and after 1990 prospective computerized registration was applied. With approximately 200,000 newborns each year in the Netherlands, the calculated incidence of SCT is 1:28,500 newborns. This is higher than the generally accepted 1:40,000 and our data are even an under-estimation, because only

patients treated at the pediatric surgical centers were included. Therefore, children who died in utero or at birth or before they were seen by a pediatric surgeon did not enter this study.

The questionnaire sent to the study group is a validated quality of life instrument for patients after treatment for Hirschsprung's disease and anorectal malformation (ARM).[5] Evaluation of the bowel function by our questionnaire was performed using the parameters defined by Peňa[6] and recorded in the Krickenbeck conference (2005)[9] to score bowel function after anorectal malformation. Although different questionnaires were used to assess long-term sequelae of SCT, no specific questionnaire to study bowel function and quality of life in patients treated for SCT exists.[10] We adapted the questionnaire and scoring system from patients treated for ARM, a disease with a much higher incidence (1:3,500 newborns) than SCT, because these tests were validated, and many problems of patients after treatment for ARM were identical to the problems of our patient group.

The percentage of patients who developed functional sequelae following removal of SCT is comparable to previous studies. Ninety-two percent of the patients treated for SCT reported voluntary bowel movements, a valuable sign of fecal control. Thirteen percent of the patients suffered from soiling. Half of the patients with soiling also had involuntary bowel movements, indicating total fecal incontinence. In other smaller studies about soiling after resection of SCT, assessed by review of the medical records or by sending a questionnaire to patients, soiling was reported in 24 - 27% of the patients in all age-groups.[3,4,10] Constipation was present in 16.7% of patients in this study. Others found a wide range of 8 - 35% of patients with constipation.[3,4,10] Malone found an association between the incidence of functional sequelae (including urinary incontinence) and tumors with large intrapelvic extensions (Altman type IV) requiring an abdomino-sacral approach for resection.[3] Nor Havranek,[4] nor Rintala[10] supported this finding. The relatively large number of patients in our study permitted us to use univariate relative risk analysis for fecal incontinence and constipation using logistic regression. Age at the time of completing the questionnaire (median: 9.7 years, range: 3.2 - 22.6 years), Altman classification, sex, histopathology, pathologically confirmed incompleteness of resection and age at diagnosis were not risk factors. Also after this study, the cause for the relatively high incidence of dysfunctional bowel habits in patients surgically treated for SCT remains unclear: this may be related to the compression effect of the large tumor on the pelvic organs or to surgical injury.

More than 30% of the patients suffered from urinary incontinence after excision of SCT. This involuntary loss of urine is subjectively demonstrated by our questionnaire and is a large social problem according to the reported loss of quality of life. Our data showed that the majority of patients suffer from urinary incontinence alone. Previous smaller studies, using questionnaires or retrospective analysis of medical records, reported a slightly lower incidence of urinary complications of 16 - 28% than this study.[3,4,10,11] Studies, which prospectively

objectivated urological sequelae after resection of SCT with electromanometry, ultrasound, uroflowmetry, video urodynamic studies, and voiding cystourethrogram, showed an incidence of 29 - 81%.[12-14] The origin of vesical dysfunction is still debated. Urologic problems may be myogenic or neurogenic and a result of tumor compression or surgical injury. Evidence and cases are provided for all combinations of the possible origin of vesical dysfunction,[11-13,15-17] and it is not likely to find a unifying pathogenesis for the origin of these sequelae. Our results show that tumor characteristics as size, localization and extension in the pelvis (Altman classification) and histology are not associated with the risk for urinary incontinence. Further pre- and postoperative urological studies are needed to clarify the origin of urological sequelae.[13]

Studies about the cosmetic results after excision of SCT are scanty.[18] Fishman developed a closure technique to minimize deformity and cosmetically unacceptable scars. Our data show that this is important for many patients, because more than 40% of the patients reported the scar as cosmetically unacceptable. This opinion is subjective and therefore it is justified to score cosmetic sequelae by a questionnaire. Especially large SCTs and children with young age at diagnosis were found to be at greater risk for developing subjectively unacceptable cosmetic results. Large external tumors are discovered at younger, and have more cosmetic consequences than small internal tumors. Surgical technique should not end after timing of surgical intervention, vascular control, completeness of resection, and preservation of function, but continue into successful reconstruction with a normal-appearing buttock contour with hidden, cosmetically acceptable, scars.[18]

In conclusion, this large evaluation of sequelae after resection of SCT showed that fecal incontinence, constipation, urinary incontinence and especially cosmetically unacceptable scar are frequently reported, which also have shown to diminish quality of life. From the present analysis, children who are at higher risk for development of such sequelae cannot be defined. Early assessment of bladder and anorectal function should therefore be integrated into pre- and postoperative follow-up of patients with SCT and resection of SCT without question implicates care for cosmetic result.

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12 chapter

General Discussion

A first goal of this thesis was to study all patients treated for germ cell tumor in our institutions over a long time period in order to analyze symptoms, diagnosis, operative issues and outcomes. In Chapters 3 - 8, we have systematically presented and discussed the epidemiological and clinical data from our patient population for the respective sites of occurrence. This large series also allowed us to comparatively analyze epidemiological, clinical and histological features. Publication of these data served the purpose of adding valuable information to the knowledge of these tumors.

One of the words most employed in these papers is '*rare*'. Overall, 193 patients is a satisfactory number, but some locations (cervical and mediastinal, for instance) concerned only a few patients. Therefore, adding information from our patients to others' may render conclusions more valid. Retrospective studies have been labeled as being of little value anymore, especially when compared to randomized prospective clinical trials. However, when dealing with very rare tumors, as in the case of pediatric germ cell tumors, those studies remain very valuable. More than 97% of clinical research in pediatric surgery consists of retrospective data.[1] Clinical practice in surgery relies heavily on observational data. This is especially true for pediatric surgery where many rare and exceptional cases are seen regularly. Of course, retrospective studies indeed have significant limitations, but they fundamentally shape clinical practice within the field.

Another issue resulting from the extreme rarity of these tumors is the absolute *need for centralization*. As stated in the introductory chapter, the exact incidence of childhood germ cell tumors in Belgium and in the Netherlands is not know. The only solid fact is the number of patients with malignant types reported to the Cancer Registration Networks: per annum 15 in the Netherlands and 10 in Belgium (corresponding to an approximate incidence of 0.52 - 0.54 in 100,000 children under the age of 15 years). Number of children with benign germ cell tumors operated upon in these countries are not known; we may assume that some of these patients are treated in peripheral hospitals, by general surgeons, urologists or gynecologists, without being referred to a pediatric surgical center. Proportions of benign v. malignant types are also unclear (see below). Nevertheless, a total of 30 - 40 new cases of germ cell tumors (all types) per year in the Netherlands and 20 - 25 cases per year in Belgium seem realistic figures. For the Netherlands this would be consistent with 9 - 12 ovarian, 6 - 8 sacrococcygeal, 6 - 8 CNS and 5 - 7 testicular germ cell tumors, as well as 1 mediastinal, 1 retroperitoneal and 1 cervical case per annum. The studies presented in chapters 9 and 11 show a yearly mean of 7 patients with sacrococcygeal teratoma in the six pediatric surgical centers, reaching 10 in some years, indicating that the assumed total numbers might well be correct. Treatment of children with germ cell tumors is necessarily of a multidisciplinary nature. Every discipline involved (radiologist, pathologist, surgeon, oncologist, …) should see a sufficient number of patients in order to acquire the necessary knowledge, skills, experience and routine. For tumoral pathology in the pediatric age in the Netherlands, centralization in academic

'centers' has been pursued, but in view of the low numbers of patients with GCT, 'super-centralization' between centers would perhaps be the logical next step. The Belgian situation, when compared with the Netherlands, is far less ideal: too many 'centers' treat even fewer patients.

We have attempted to compare the *epidemiological profiles* of our patient series to other series. This was an almost impossible task, because

1. only very few series have published details on epidemiology;
2. some series include patients with intracranial tumors;
3. some series concern malignant tumors only, or teratomas only
4. some series are on extragonadal types, others on non-seminomatous types;
5. some series include patients up to age 19 years; etc.

The only meaningful comparison could be made with a an older study by Billmire[2] and with a well-documented series of 1442 patients from the German Childhood Cancer Registry, published by Schneider in 2004.[3] The latter series includes 303 patients with intracranial germ cell tumor, which we excluded for the partitioning into tumor sites. However, as we did not know the histologies of these intracranial tumors, the bottom part of the right column in the table below lists percentages for all tumors, including intracranial ones (*Table 1*).

Table 1 Comparison of the relative proportions of tumor sites and histologies (expressed as %), and of male-to-female ratios, in the series of 193 patients reported in this thesis and in 2 other studies from the literature

	Present series	**Billmire**	**German Childhood Cancer Registry**
Number of patients	193	142	1442/1139*
Ovary	34%	10.6%	37%
Sacrococcygeal	36%	59%	25%
Testis	10%	10.6%	22%
Mediastinal	3.6%	9.9%	5%
Retroperitoneal	6.2%	4.9%	4.4%
Other	9.3%	4.9%	6.3%
Male:female ratio	1:2.6	1:4.4	1:1.3
Teratoma	78%	72%	37.5%
Yolk sac tumor	14%	28%	27.3%
Germinoma	1%		18.3%
Mixed GCT	4%		12.7%
Choriocarcinoma	0.5%		2.2%
Embryonic carcinoma	0.5%		2.2%

* *cerebral GCT excluded*

These 3 series show several striking differences. For one, proportions of sacrococcygeal teratomas range from 25 to 59%, those of ovarian teratomas from 10.6 to 34%, etc. Seventy-eight percent of the patients in our series (and 72% in Billmire's series) had teratomas, which more than doubles that in Schneider's

series. In the latter series, 62.5% of the tumors are malignant (45% if CNS tumors are omitted) compared to 20% in our series and 28% in the series reported by Billmire. None of the series is population based, demonstrating the importance of referral patterns.

Then, the difference in male:female ratio is striking as well: the 1:2.6 ratio encountered in our series is in between the 1:1.3 reported by Schneider and the 1:4.4 reported by Billmire. Of course, differences in partitioning of tumor sites result in different sex ratios, as sacrococcygeal teratomas predominantly occur in girls.

The median age of our patients was 1 year, with the age distribution showing the classically reported bimodal distribution with an initial peak in the first year of life (caused by the high number of sacrococcygeal teratomas), and a second (weaker) peak between ages 7 - 8 to 14 years (caused by the high number of ovarian GCT) (*Figure 1*).

One paper, by Van Winter et al., presented data discordant to ours for ovarian GCT;[4] we found more malignant tumors in the older patients (age 11 - 15 years) when compared to younger patients (0 - 10 years), whereas Van Winter found malignant tumors more frequently among the youngest patients.[4] Of course, the small numbers of patients as well as referral patterns may explain this discrepancy, as has been shown above.

Table 2 summarizes general epidemiological and clinical data per site of occurrence (for the sake of completeness, we also added data on intracranial tumors). Although this is a rough oversimplification, it presents a good overview of our patients reported in Chapters 3 – 8.

In pediatric oncology, *recurrence* is an important issue. In our global series, we have encountered an overall recurrence rate of 6.7%. Recurrence was rare in patients with mature teratoma (3.5%), higher in patients with immature teratoma (10.8%) and in patients with yolk sac tumor (11.1%), and was particularly high in patients with choriocarcinoma and embryonic carcinoma. The latter finding should be considered invalid, however, as these two diagnoses concerned only a few patients. Striking though the high recurrence rate (10.8%) in the patients with immature teratoma may seem, this finding is in concordance with other reports.[5] As to site, recurrence was rather rare in ovarian (4.5%) and testicular germ cell tumor (5%), more frequent in sacrococcygeal teratoma (8.6%), and high in mediastinal germ cell tumor (28.6%). No recurrences at all were observed in retroperitoneal and cervical tumors. Others have reported similar observations.[5,6] Age plays an important role in mediastinal immature teratoma: in the young infant, immature teratomas show rather benign behavior, which is not the case in older children.[7]
Except in the newborn period, the tumors markers *α-FP and β-HCG* were proven to be extremely reliable parameters of malignancy and of recurrence in our series of patients.

Table 2 Summary of general epidemiological and clinical data per site of occurrence

	(Peak) Age	Sex	Symptoms	Histology	% Malignancy	Recurrence	Mortality
Gonadal (40% of all)							
Ovary	all ages -median: 9 years	F	pain and visible abdominal mass	predominantly mature + immature teratuma, and mixed malignant tumors	20-25%	rather rare (5%)	low (3%)
Testis	almost exclusively in the first five years of life -median: 1,5 years	M	hard, hemiscrotal swelling, mostly painless	mature + immature teratoma (50%), yolk sac tumor (50%)	50%	low (5 - 10%)	low (5%)
Extragonadal (60% of all)							
Central nervous system	all ages, but mostly later on in childhood -median: 10 years	M > F	headache, vomiting, diplopy	germinoma, yolk sac tumor, mixed tumors	70-80%	high (37%)	high (37%)
Neck	newborn	F>M	neck mass, upper airway obstruction	mature + immature teratomas	0%	none	high (37%)
Mediastinum	all ages, median: 3 years	M>F	respiratory distress, persistent coughing, thoracic pain, anorexia/weight loss	mature teratoma (50%) - malignant tumors (50%)	50%	14%	high (28%)
Retroperitoneum	in first two years of life	M>>F	abdominal distension and palpable mass	mature + immature teratoma; yolk sac tumors to a lesser extent	15%	none	moderate (8%)
Sacrococcygeal	newborn and first year of life	F>>>M	sacrococcygeal tumor	predominantly mature + immature teratomas, yolk sac tumor	15%	8 – 10%	moderate (8%)

With an overall *mortality rate* of 8.3% over a 44-year span and an overall survival probability of 0.91 ± 0.2, this series compares favorably to other larger series, which reported mortality rates between 9 and 36%.[8-10] We expected (from series with malignant tumors only[11]) mortality rates to diminish gradually over time, but to our surprise, found this not to be the case. Mortality rates in the first three 11-year periods virtually remained unchanged (15%, 12.5% and 13%); only during the last decade a significant reduction in mortality rate (2.5%) could be observed, indicating that not only chemotherapy can be held responsible for better outcome. We have indeed witnessed tremendous improvements in medical imaging, in surgical skills and technical possibilities, in postoperative intensive care, and especially in chemotherapy with the introduction of cisplatin-based chemotherapy in the eighties. As prenatal diagnosis has improved also, sophisticated procedures such as the EXIT-procedure (ex-utero intra-partum treatment)[12-14] have saved the lives of some children who otherwise might have died in utero or during transportation to a tertiary center. Finally, ethical considerations and concerns for expected quality of life have been responsible for some deaths. Nevertheless, with an overall mortality rate of 2.5% in the recent decade, we cannot but conclude that germ cell tumors overall carry a very good prognosis.

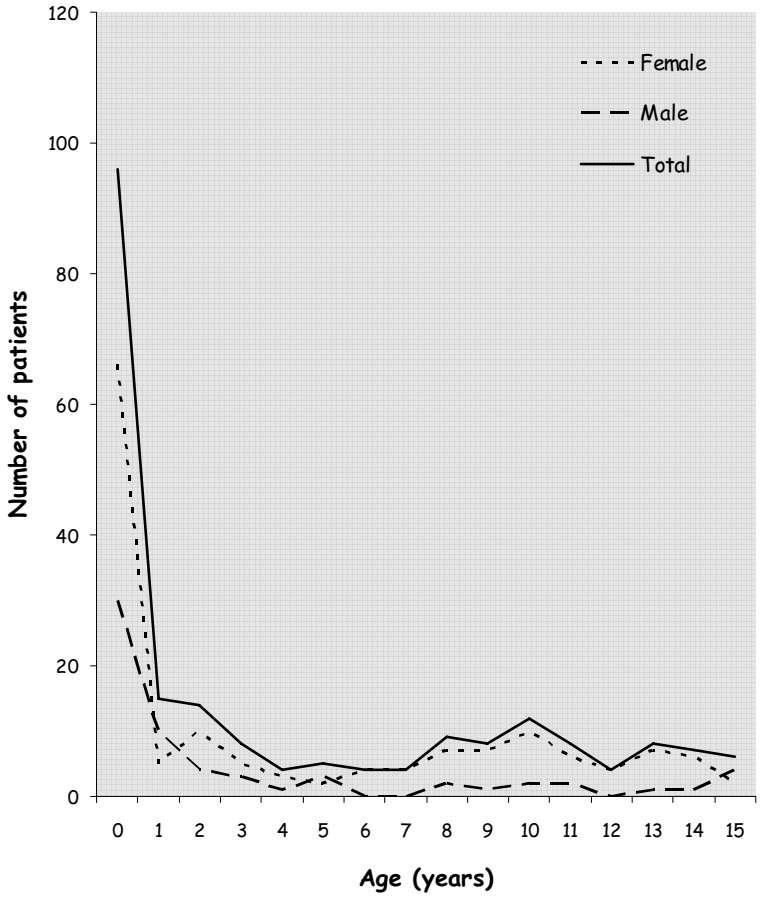

Figure 1 *Sex distribution correlated with age*

A second goal for this thesis was to define risk factors that influence overall prognosis. As has been demonstrated in Chapters 3 - 8, the prognosis of the patients varies considerably depending on tumor site, histology, and perhaps also on other factors. We therefore performed survival studies for the whole patient group. We have demonstrated statistically significant differences between the various tumor sites and the various histologies. Patients with gonadal germ cell tumors (ovary and testis) appeared to have a statistically higher probability of survival than those with extragonadal types. Patients with tumors in the neck and mediastinum had statistically significant lower probability of survival than those with gonadal, retroperitoneal or sacrococcygeal tumors. Patients with choriocarcinoma, embryonic carcinoma, immature teratoma, yolk sac tumor and mixed types had lower probability of survival than patients with mature teratoma or gonadoblastoma.

More in particular for sacrococcygeal teratomas, we could identify intra-operative tumor spill and non-resection of the coccyx as factors responsible for recurrence and hence for impaired survival (see below).

Since the nineties, the search for prognostic factors (in other words: identifying precisely those patients with a lower probability of survival) has indeed progressed towards improving survival whilst keeping toxicity to a minimum.[15-17] A Pediatric Intergroup Study, conducted from 1990 to 1996 and published in 2004,[18] nicely illustrated that dose-intensification is not always advantageous. One hundred thirty-four patients with high-risk malignant stage II - IV gonadal or extragonadal (all stages) germ cell tumors were randomly enrolled into this study comparing high-dose PEB (HDPEB, cisplatin 40 mg/m^2) and normal-dose PEB (PEB, cisplatin 20 mg/m^2). HDPEB resulted in significantly improved EFS rate (HDPEB 89.6% ±/- 3.6% v. 80.5% ±/- 4.8% for PEB), without showing a significant difference in OS rate (HDPEB 91.7% +/- 3.3% v. PEB 86.0% +/- 4.1%). Tumor-related deaths, however, were more common after PEB (14 v. 2 deaths), but toxic deaths were more common after HDPEB (six deaths v. 1 death), and other treatment-related toxicities were more common with HDPEB. This is why we need to identify those patients who are at higher risk of treatment failure, so as to limit high-dose therapy to these patients only. Several possible prognostic factors have been analyzed: primary site, histology, age, tumor markers, stage, localized v. generalized (i.e. metastases at diagnosis), metastatic sites, tumor size, etc. Unfortunately, some studies contradict each other. For example, Baranzelli in 1999 found that initial α-FP > 10,000, Stage III-IV and a sacrococcygeal or mediastinal site were the most important prognostic factors in malignant nonseminomatous germ cell tumors.[15] Calaminus on the other hand found that stage, extent of metastases and extension into bone, tumor size and α-FP had no prognostic significance.[17] Our findings do not conflict with others' findings: histology and tumor site were found to be important determinants of ultimate prognosis, whereas age at diagnosis, sex and time period of treatment were not. The ultimate

solution will probably be 'tailored' (individual) treatment, whereby patients would receive exactly what they need and nothing more.

The third and fourth goals of this thesis concerned the subgroup of patients with sacrococcygeal teratoma. First, we intended to study the factors that traditionally are held responsible for recurrence, and, as a consequence, for impaired prognosis. In the national study presented in chapter 9, tumor recurrence was found in 19 (11%) patients. Incomplete resection of the tumor, either macroscopically or microscopically, was observed in 40 of the 165 patients (8 died peri-operatively) of whom 9 patients developed a recurrent tumor (P = 0.001). Ten other patients, who apparently had undergone complete tumor excision, showed as well recurrence. A significant relationship with immature and malignant histology could be demonstrated. Absence of coccyx removal, reported in 8 patients, lead to recurrence in only 1 patient (P = 0.77, N.S.). In the series of 70 patients, treated in Rotterdam and Brussels, recurrence was observed in 5 patients (7%). Microscopic tumoral involvement of the resection margins in patients with predominantly teratoma (observed in 11 patients) did not appear to be a risk factor for recurrence (1 recurrence), whereas intraoperative spillage of tumor and absence of complete removal of coccyx was. Regarding coccyx resection findings from both studies are contradictory; of course, numbers of patients being so small, findings should be interpreted with extreme caution. More studies in large patient series are needed to elucidate this uncertainty, as this is a crucial practical issue. Pathologists not infrequently report microscopic involvement of resection margins in mature sacrococcygeal teratoma, possibly leaving microscopic residue; it is not clear what the attitude of the attending pediatric surgeons should be. In such situations, reoperation is very likely to be unsatisfactory. If we could show that recurrence is unlikely, then a wait-and-see attitude would be justified. The development of recurrent malignant sacrococcygeal teratoma (either locally, distant or both) is associated with impaired prognosis: indeed, a recent series demonstrated that remission could be achieved in half of the patients only. The complete resection of the local recurrence is the cornerstone of salvage therapy, preceded and followed by chemotherapy combined with regional hyperthermia.[19]

A fourth goal of our thesis was to examine functional sequelae in patients that had been treated for sacrococcygeal teratoma, and the impact of these sequelae on patients' quality of life. Previous reports from the literature on rather small series of patients indicated that a significant number of patients with sacrococcygeal teratoma suffered from urinary incontinence, or from some form of fecal incontinence.[20-24] By means of a questionnaire, we indeed were able to document that a large proportion of patients suffered from fecal and/or urinary problems. Thirty-six of 79 patients (45%) reported at least one of the parameters on bowel function (soiling, involuntary bowel movements, frank fecal incontinence) or on urinary incontinence as positive. If, in addition, unsatisfactory scarring is regarded as a functional sequel, then 65% of all patients had sequelae, which is a

considerable proportion. Our attempts to identify those patients at risk for the development of sequelae were futile, for we could not find any risk factors. The only risk factor for unacceptable scar was tumor size larger than 500 cm^3. What could be found, as expected, was that long-term functional sequelae were correlated with diminished quality of life. As we have not been able to identify those patients that are at a higher risk for developing functional sequelae, all patients need to be followed regularly intervals at the outpatient clinic.

Conclusions and future perspectives

By now, excellent results can be achieved for the vast majority of patients with germ cell tumors, provided a diagnosis is obtained without delay. For a subset of patients (e.g. those with sacrococcygeal, cervical and retroperitoneal teratoma), this means a correct antenatal diagnosis which may allow for the choice of the best timing (at term, before term) and method of delivery (vaginal, cesarean section, EXIT-procedure, OOPS-procedure) and even for some (still experimental) fetal procedures such as stapling of the exophytic part of sacrococcygeal teratoma in children with an hyperdynamic state that poses a threat of hydrops. For tumors at other sites also, a diagnosis must be made as early as possible. The tremendous improvements in radiology and medical imaging should allow for making an early diagnosis of tumors in the remaining locations.

Thanks to the multicenter grouping of patients into protocols, it has been possible to establish excellent treatment protocols that continue to be refined and updated in order to achieve better and better survival rates, but also to diminish the complications of therapy. Indeed, prevention of the side effects of chemotherapy – infertility, hearing loss, alveolitis caused by bleomycin, etc. – is one of the major challenges for the near future. Risk-adapted strategies should take into account all these concerns.

Avoiding the functional sequelae in children with sacrococcygeal teratoma (neurogenic bladder and fecal incontinence) that are the result of tissue compression by the tumor or of the surgical procedure itself (traction, damage to nerves and plexuses) presents another major challenge for pediatric surgeons. However, as the most skillful surgical treatment will not always be able to prevent those sequelae, the organization of a follow-up clinic is therefore obvious.

Another step forward, finally, is expected to come from fundamental research into the pathogenesis of germ cell tumors. Molecular biology and genetic studies have indeed advanced a long way already, but there is an even longer way ahead. To date, no correlation has been established between findings from these studies and histology, site and outcome. Whether these findings will some day have possible diagnostic and/or prognostic and, as a consequence, therapeutic implications, remains an open question thus far.[25]

Although this thesis proved that the role of the many other specialists involved in the care for children with germ cell tumors is vital, we learned that the

contribution of the pediatric surgeon too, certainly is a substantial one. Knowledge, experience, meticulous surgical skills, patience and perseverance are all prerequisites for the pediatric surgeon to achieve optimal results.

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summary

The Introduction to this thesis describes the history, incidence, theories of origin, histopathological classification and histological description of the various germ cell tumors in children. It furthermore emphasizes the importance of tumor markers and summarizes the treatment modalities. The aims of the study and the contents of the different chapters are also presented.

Chapter 2 first presents our series of 193 patients with extracranial germ cell tumors treated between 1960-2003 as one group. The aim was to study long-term survival stratified for tumor site and tumor histology. The tumors arose in the following anatomical sites: sacrococcygeal region (n = 70), ovary (n = 66), testis (n = 20), retroperitoneal space (n = 12), neck (n = 8), mediastinum (n = 7), female genital tract (n = 3), face (n = 2), urinary bladder (n = 2), spinal cord in association with myelomeningocele (n = 2) and nasopharynx (n = 1). Histological analysis revealed 152 teratomas (mature: 115, immature 37), 27 yolk sac tumors, 8 mixed tumors, 2 dysgerminomas, 2 gonadoblastomas, 1 choriocarcinoma and 1 embryonal carcinoma. Overall survival probability (OS) was 0.91 ± 0.02 and event-free survival probability (EFS) was 0.88 ± 0.02 at ten years (Kaplan-Meier estimates ± standard error). We observed statistically significant differences in OS/EFS between tumor sites and between histologies. The prognosis for gonadal GCT (regardless of histology) is better than that for tumors at extragonadal sites. GCTs in the neck or mediastinum (regardless of histology) or a histologic diagnosis of choriocarcinoma, embryonal carcinoma or immature teratoma (regardless of site), are associated with less favorable outcome than GCTs at other sites or with other histologies. Mortality is not only dictated by malignant histology, but also, as in the case of mature teratoma, by occurrence at certain sites.

Our patients with gonadal GCTs were extensively studied in Chapters 3 and 4. Both series confirm the excellent prognosis of gonadal GCT.
In Chapter 3, we evaluated the records of 66 girls with ovarian germ cell tumor. Their most frequent symptoms were pain and an abdominal mass. Sixteen patients had an emergency operation for tumor torsion. Histologically, teratomas were most frequent (mature: 45, immature: 9), followed by mixed tumors (n = 7), yolk sac tumors (n = 3), dysgerminoma (n = 2), gonadoblastoma (n = 2), and embryonal carcinoma (n = 1). Surgical removal of the tumor with or without the ovary and/or adnex was the sole treatment in 55 patients, chemotherapy was administered in 10. Intra-operative spillage of tumoral fluid occurred in 6; this did not influence outcome in 5. Recurrence was observed in 3 patients. Two patients, with malignant disease, died. This series, with a recurrence rate of 4.5% and a mortality rate of 3%, confirms the excellent prognosis for girls with ovarian GCT.

Chapter 4 reports a series of 20 boys with testicular GCT (mature teratoma: 7, immature teratoma: 4, yolk sac tumor: 9). Of the 11 teratomas, 10 were treated by orchiectomy and 1 by testis-sparing tumor excision only. All boys have survived and show no evidence of disease between 10 and 28 years after surgery. The 9 patients with yolk sac tumor were managed by orchiectomy, in 2 plus

retroperitoneal lymphadenectomy, and in 7 plus chemotherapy. One patient is in remission for 10 months, 7 are alive with no evidence of disease for 5.5 - 23 years, and one patient died from T-cell acute lymphoblastic leukemia, two years after tumor treatment. This study confirms the excellent cure rates obtained in children with testicular germ cell tumor.

The next chapters describe the studies on various extra-gonadal germ cell tumors. In Chapter 5 we report on seven newborns with cervical teratoma. Findings were compared with and added to a series of 44 well-documented patients retrieved from the literature. In four of our seven patients, cervical teratoma had not been suspected antenatally. Three of them survived, one died. In the other three, the diagnosis had been made antenatally. Two were born using the EXIT procedure, one by planned cesarean section. Only one of these three survived. Mortality in the total series of 51 patients was 33% overall. Peri- and post-operative complications were reported in 27%. Although larger tumors caused polyhydramnion more frequently than smaller ones did, and were associated with more severe respiratory distress, relationship between tumor volume at birth and final outcome could not be established. This makes it difficult to identify fetuses with a disastrous prognosis. Although mostly benign, cervical teratomas are still associated with high mortality rates. Timely antenatal diagnosis is indispensable in reducing the morbidity and mortality caused by upper airway obstruction. A structured approach to the management of cervical teratoma is proposed.

Chapter 6 reports findings for another tumor site that does not have a very good prognosis either, namely the mediastinum. The most frequent symptoms in our 7 patients (median age: 3 years) were respiratory distress, persistent coughing, thoracic pain and anorexia/weight loss. Four patients had histologically benign tumors (mature teratoma). Their sole treatment consisted of complete surgical excision of the tumor and (part of) the thymus using either median sternotomy or left-sided thoracotomy. No recurrences have been observed. All four are alive with no evidence of disease, between 2.5 and 29 years after treatment. Malignant tumors were observed in three patients (1 yolk sac tumor, 1 choriocarcinoma and 1 malignant teratoma). Treatment consisted of either biopsy or debulking followed by chemotherapy (and radiotherapy in 1 case). Two of them died from uncontrollable metastatic disease. The patient with yolk sac tumor survived; he is now in remission, 4 years after diagnosis. Histologically benign mediastinal germ cell tumors carry an excellent prognosis. Histologically malignant tumors, on the other hand, have worse prognosis.

The purpose of the study reported in Chapter 7 was to examine the files of 12 newborns and infants with retroperitoneal GCT whose symptoms were abdominal distension and a palpable upper abdominal mass. Associated anomalies were noted in 4 patients, 3 of whom with chromosomal anomalies. One baby died from uncontrollable bleeding during an emergency operation immmediately after traumatic birth. The other eleven infants survived. Surgical removal of the tumors

in infants with retroperitoneal GCTs appeared to be hazardous due to the extent of the tumor, the displacement and elongation of adjacent structures and organs and/or the adhesion of the tumor to surrounding tissues. This resulted in a serious intraoperative complication in 4 patients (one caval vein tear, one choledochal tear, one cyst rupture and one esophagogastric tear) that was managed without further consequences. Histologically, four tumors were mature teratomas, six were immature teratomas and two were malignant yolk sac tumors (YST). The long-term results are good, with 9 of 10 patients with benign tumors alive and in good health after a mean follow-up of 12 years, and with the 2 patients with yolk sac tumor in remission since 6 and 5 years.

Chapters 8, 9, 10 and 11 deal with sacrococcygeal teratoma (SCT). One of the problems with this tumor (site) is the relatively high tendency to recur and the impaired prognosis whenever recurrence happens. We therefore searched, in Chapter 8, for factors that could be associated with recurrence in our series of 70 patients. Histologically, mature teratoma was observed in 48 patients, immature teratoma in 11, YST in 9, embryonal carcinoma in 1, and mixed tumor in 1. Eighty-four per cent of patients solely underwent surgical extirpation. Six patients died (8.5%). Mortality for the group of 42 patients treated during the past 15 years was as low as 2.5%, however. Tumor recurrence was observed in 5 patients, two of whom died. Of 3 patients with initially mature type, one showed local immature recurrence and 2 malignant recurrences. One of the latter died. Of 2 patients with initially immature type grade I, one relapsed with a benign lesion and one with YST leading to death. Possible eliciting factors had been demonstrated in 3 patients. Histological analysis of resection margins showed tumoral involvement in 11 patients (and also in 1 patient after resection of a recurrent tumor). Only one of those, with YST focus in the resection margin, showed recurrence. Intraoperative tumor spillage presented in 2 patients, who both died from metastatic disease. Spillage of tumoral cyst fluid occurred in 6, none developed recurrence. Of five patients whose coccyx had not been removed, one died from metastatic disease, one with IT developed a benign recurrent tumor and the other 3 showed no recurrence. We conclude that microscopic involvement of the resection margins of mature or immature SCT is rarely associated with recurrence, provided there are no YST foci in the resection margins. A conservative attitude then appears to be justified. Spillage of cyst fluid was never associated with recurrence, unlike spillage of tumor and absence of removal of coccyx.

The aims of the study reported in Chapter 9 were identical to those in chapter 8, but now we studied 173 patients with SCT treated from 1970 to 2003 at the 6 pediatric surgical centers in the Netherlands. Eight patients died shortly after birth or peri-operatively. Nine patients, all over 18 months, had metastases at presentation. Four metastasized teratomas showed mature histology of the primary tumor. Nineteen patients (12%) had recurrence of SCT after a mean period of 10 months (range: 32 days - 35 months) after primary surgery. Risk factors for recurrence were pathologically confirmed incomplete resection,

immature histology, and malignant histology. Size, Altman-classification, age and decade at diagnosis were not risk factors. One-third of recurrences showed a shift towards immaturity or malignancy, compared with the primary tumor. Seven patients died after recurrence, six with malignant disease.

Chapter 10 is a plea for centralization of specialized pediatric surgery cases in Belgium. Eighteen patients with SCT were treated in seven centers in Belgium and Luxembourg from 1992 to 1996. Although excellent results were obtained, with all patients surviving, several imperfections in diagnosis, timing of delivery and of operation, and in operative technique were observed. Therefore, we recommend that patients with SCT should be treated in just a very few centers of neonatal surgery.

Chapter 11 examines another major problem encountered in patients operated upon for SCT, namely the functional and esthetic sequelae. The study determines the incidence of these sequelae, associated clinical variables and its impact on quality of life (QoL). Patients with SCT treated from 1980 to 2003 at the pediatric surgical centers in the Netherlands older than 3 years of age were administered age-specific questionnaires on bowel function, urinary incontinence, subjective aspect of the scar and QoL. These parameters were correlated with clinical variables extracted from the medical records. Risk factors were identified by univariate analysis. Seventy-nine of the 99 posted questionnaires (80%) were completed. The median age of respondents was 9.7 years. Forty-six percent reported impaired bowel function and/or urinary incontinence; 9% involuntary bowel movements, 13% soiling, 17% constipation, 31% urinary incontinence. Forty percent labelled the scar as cosmetically unacceptable. Age at completing the questionnaire, Altman-classification, sex, and histo-pathology were not risk factors for any long-term sequelae. Size of the tumor (> 500 cm^3) was a significant risk factor for cosmetically unacceptable scar. Long-term sequelae were correlated with diminished QoL. We conclude that a large proportion of the patients with SCT suffer from problems with defecation, urinary incontinence or a cosmetically unacceptable scar which affects QoL. Patients who are at higher risk for the development of long-term sequelae cannot be clearly identified by clinical variables.

Chapter 12 is the general discussion of this thesis and reviews the results and conclusions drawn from the different studies.

samenvatting

Dit proefschrift gaat over diverse chirurgische aspecten van de behandeling van kinderen met een kiemceltumor, alsook over de uitkomsten op de lange termijn.

In de inleiding komen achtereenvolgens aan de orde de geschiedenis, incidentie, theorieën over het ontstaan, histopathologische classificatie en histologische beschrijving van de verschillende kiemceltumoren. Het belang van tumormerkers wordt onderstreept en de verschillende behandelingsmodaliteiten worden samengevat. De inleiding besluit met het doel van de studie en de inhoud van de verdere hoofdstukken.

Hoofdstuk 2 beschrijft de evaluatie van de volledige groep van 193 kinderen met extracraniale kiemceltumoren die tussen 1960 en 2003 werden behandeld in onze twee instellingen. De studie beoogde de overleving op lange termijn te bepalen in relatie tot de lokalisatie en de histologische classificatie van de tumor. Naar aflopende frequentie was de plaats waar de tumor zich bevond als volgt: sacrococcygeale gebied (n = 70), ovarium (n = 66), testis (n = 20), retroperitoneale gebied (n = 12), hals (n = 8), mediastinum (n = 7), vrouwelijke genitaliën (n = 3), aangezicht (n = 2), urineblaas (n = 2), ruggenmerg, in associatie met myelomeningokèle (n = 2) en nasopharynx (n = 1). Het histologisch onderzoek bracht de volgende diagnoses: 152 teratomen (waarvan 115 matuur en 37 immatuur), 27 dooierzaktumoren, 8 gemengde maligne tumoren, 2 dysgerminomen, 2 gonadoblastomen, 1 choriocarcinoom en 1 embryonaal carcinoom. De 10-jaarsoverleving voor de gehele groep bedroeg 0.91 ± 0.02 en de recidiefvrije overleving bedroeg 0.88 ± 0.02 (Kaplan-Meier schatter ± standaardafwijking); hiermede bevestigt deze studie de uitstekende prognose voor kinderen met een kiemceltumor. Er bleken statistisch significante verschillen in overleving te zijn tussen de diverse tumorlokalisaties en histologieën. De prognose voor patiënten met een gonadale kiemceltumor (ongeacht de histologie) is beter dan voor hen met een extragonadale tumor. Lokalisatie in hals of mediastinum (ongeacht de histologie), of een histologische diagnose van choriocarcinoom, embryonaal carcinoom of immatuur teratoom (ongeacht de site) is geassocieerd met een minder goede levensverwachting dan andere lokalisaties of andere histologieën. Niet alléén de histologische maligniteit bepaalt dus de prognose, maar ook, zoals voor mature teratomen, de lokalisatie van de tumor.

De patiënten met gonadale kiemceltumoren worden uitvoerig besproken in hoofdstuk 3 en hoofdstuk 4. Hierin wordt bevestigd dat zowel jongens als meisjes met een kiemceltumor ter hoogte van de geslachtsorganen een uitstekende prognose hebben.

In hoofdstuk 3 werden 66 meisjes met een kiemceltumor van het ovarium bestudeerd. Hun belangrijkste symptomen waren pijn en een zwelling van de buik. Bij 16 patiënten was een spoedoperatie noodzakelijk geweest vanwege torsie van het ovarium met tumor. Histologisch gezien ging het om 45 mature en 9 immature teratomen, 7 gemengde tumoren, 3 dooierzaktumoren, 2 dysgerminomen, 2

gonadoblastomen en 1 embryonaal carcinoom. Bij vijfenvijftig patiënten was de tumor chirurgisch verwijderd, met of zonder ovarium en/of adnexa; bij tien andere was bijkomende chemotherapie nodig. Tijdens de operatie kwam cystevocht vrij bij 6 patiënten; in 5 gevallen had dit geen invloed op het uiteindelijk resultaat. Recidief trad op bij 3 patiënten. Twee patiënten met een kwaadaardige tumor overleden. Het recidiefpercentage van 4,5% en het sterftepercentage van 3% uit deze patiëntenreeks bevestigen de uitstekende prognose bij meisjes met ovariële kiemceltumor.

In hoofdstuk 4 wordt een reeks van 20 jongens met kiemceltumor van de testis gepresenteerd. Bij 7 van hen was sprake van een matuur teratoom, bij 4 van een immatuur teratoom en bij 9 van een dooierzaktumor. Tien van de 11 kinderen met een teratoom hadden orchiëctomie ondergaan, de elfde een testissparende tumorectomie. Alle elf overleefden en toonden, 10 - 28 jaar na de operatie, geen tekenen van ziekte. Alle 9 patiënten met dooierzaktumor hadden eveneens orchiëctomie ondergaan. Bij 2 was ook een retroperitoneale lymphadenectomie uitgevoerd en 7 hadden chemotherapie gekregen. Eén patiënt is in remissie sinds 10 maanden, 7 zijn in leven zonder tekenen van ziekte 5,5 - 23 jaar na behandeling, en één patiënt is 2 jaar na zijn behandeling gestorven aan acute lymfoblastische T-cel-leukemie. Ook deze bevindingen bevestigen de uitstekende genezingskansen bij kinderen met een kiemceltumor van de testis.

De overige hoofdstukken beschrijven de studies bij de patiënten met extragonadale kiemceltumoren.

In hoofdstuk 5 beschrijven wij zeven pasgeborenen met een teratoom aan de hals. Hun gegevens werden vergeleken en samengevoegd met die van 44 patiënten uit de literatuur. Bij 4 van onze 7 patiënten was de diagnose antenataal niet gesteld. Drie van deze patiënten leefden nog, één was overleden. Bij de andere drie was de diagnose antenataal gesteld. Twee waren geboren via de EXIT-procedure, de derde via een geplande keizersnede. Slechts één van deze patiënten was nog in leven. Het sterftepercentage in de reeks van 51 patiënten was 33%. Bij 27% traden peri- en postoperatieve complicaties op. Grote tumoren waren vaker verantwoordelijk voor polyhydramnion dan kleinere en waren vaker geassocieerd met ernstige ademnood. Er kon echter geen statistisch verband gelegd worden tussen tumorvolume bij de geboorte en uiteindelijke prognose, en derhalve is het moeilijk om die foetussen te identificeren welke een slechte prognose hebben. Hoewel ze meestal histologisch goedaardig zijn, blijken teratomen van de hals toch een hoge sterftekans te geven. Het antenataal stellen van de diagnose is essentieel om de morbiditeit en mortaliteit ten gevolge van obstructie van de bovenste luchtwegen tot een minimum te beperken. Het hoofdstuk besluit met een gestructureerde benadering van de behandeling van pasgeborenen met cervicaal teratoom.

In hoofdstuk 6 worden de gegevens beschreven voor een andere tumorlokalisatie die ook niet zo'n goede prognose heeft, namelijk het mediastinum. De

belangrijkste symptomen bij onze 7 patiënten (met een gemiddelde leeftijd van 3 jaar) waren ademnood, aanhoudend hoesten, thoraxpijn en anorexia/gewichtsverlies. Vier patiënten hadden een histologisch goedaardige tumor (matuur teratoom). Hun behandeling had bestaan uit volledige excisie van de tumor met (een deel van) de thymus, door middel van mediane sternotomie of linkszijdige thoracotomie. Recidief trad niet op. Alle 4 patiënten zijn, 2,5 - 29 jaar na behandeling, in leven zonder ziekte. Drie patiënten echter hadden een maligne tumor (1 dooierzaktumor, 1 choriocarcinoom, 1 maligne teratoom). Bij hen bestond de behandeling uit ofwel biopsie of debulking gevolgd door chemotherapie (en radiotherapie bij 1 patiënt). Twee patiënten overleden als gevolg van veralgemeende metastasering. De patiënt met de dooierzaktumor is nog in leven en nu, 4 jaar na de diagnose, nog steeds in remissie. Onze bevindingen wijzen er op dat histologisch goedaardige mediastinale kiemceltumoren een uitstekende prognose hebben. Histologisch kwaadaardige vormen daarentegen hebben een slechtere prognose.

De opzet van de studie die in hoofdstuk 7 wordt beschreven was het onderzoeken van statusgegevens van 12 pasgeborenen en kinderen, met een retroperitoneale kiemceltumor, waarvan de belangrijkste symptomen een bolle buik en een palpabele massa in de bovenbuik waren. Bij 4 van hen werden bijkomende afwijkingen gevonden, waaronder in drie gevallen chromosoomafwijkingen. Eén baby overleed ten gevolge van een bloeding tijdens een spoedoperatie direct na een traumatische geboorte. De 11 andere kinderen bleven in leven. De uitgevoerde operaties bleken echter zeer risicovol door de grote omvang van de tumor, de verdringing en uitrekking van omringende structuren en organen en/of door adhesie tussen tumor en omringende weefsels. In vier gevallen was derhalve sprake van ernstige intra-operatieve complicaties: scheur in de vena cava, scheur in ductus choledocus, ruptuur van tumorcyste, scheur ter hoogte van de esophago-gastrische overgang. Alle complicaties werden zonder nadelige gevolgen behandeld. Histologisch gezien was er sprake van 4 mature teratomen, 6 immature teratomen en 2 maligne dooierzaktumoren. De resultaten op lange termijn bij deze patiënten waren goed, want 9 van de 10 met een benigne tumor zijn in leven en in goede gezondheid na gemiddeld 12 jaar, en beide patiënten met dooierzaktumor zijn in remissie sinds respectievelijk 6 en 5 jaar.

De hoofdstukken 8, 9, 10 en 11 gaan over kinderen met een sacrococcygeaal teratoom. Eén van de problemen met deze tumoren is het relatief hoog recidiefpercentage alsook de slechtere prognose die hiermee gepaard gaat. Daarom zochten wij in hoofdstuk 8 naar factoren die mogelijk geassocieerd zijn met recidief, in onze reeks van 70 patiënten. Histologisch gezien ging het om 48 patiënten met een matuur teratoom, 11 met een immatuur teratoom, 9 met een dooierzaktumor, 1 met een embryonaal carcinoom en 1 met een mengvorm. Bij 84% van de patiënten bestond de behandeling alleen uit chirurgische verwijdering van het gezwel. Zes patiënten overleden (8,5%). Het sterftepercentage in de subgroep van 42 patiënten die in de afgelopen 15 jaar waren behandeld, was

echter nog maar 2,5%. Tumorrecidief trad op bij 5 patiënten, waarvan er 2 zijn gestorven. Bij 3 patiënten met oorspronkelijk een matuur teratoom zagen wij één lokaal immatuur recidief en 2 maligne recidieven. Eén van de laatste twee overleed. Van de 2 patiënten die oorspronkelijk een immatuur teratoom graad I hadden, kreeg één een recidief in de vorm van een goedaardig letsel, en één een dooierzaktumor; de laatste patiënt overleed later. Bij drie patiënten konden wij mogelijk uitlokkende factoren aantonen. Het histologisch onderzoek van de snijranden van de tumor toonde dat deze niet tumorvrij waren bij 11 patiënten (en ook bij één patiënt na resectie van tumorrecidief). Slechts één van deze 12 patiënten, bij wie een haardje van dooierzaktumor in de snijrand gezien werd, recidiveerde. Intra-operatief trad bij 2 patiënten een tumorruptuur op met vrijkomen van de inhoud; beiden overleden ten gevolge van veralgemeende carcinomatosis. Ruptuur van de cyste met vrijkomen van cystevocht trad op bij 6 patiënten, maar leidde niet tot een recidief. Van de 5 patiënten bij wie de coccyx niet werd weggenomen, overleed er één ten gevolge van veralgemeende carcinomatosis, een andere met een immatuur teratoom ontwikkelde een goedaardig tumorrecidief, en de andere drie vertoonden geen recidief. Uit deze studie kunnen we concluderen dat, wanneer de snijrand van een matuur of immatuur sacrococcygeaal teratoom niet geheel schoon is – en er dus wellicht alleen microscopisch aantoonbaar tumormateriaal achterblijft – dit slechts in uitzonderlijke gevallen resulteert in recidief. Daarom menen wij dat in dergelijke situaties een conservatieve houding gerechtvaardigd kan zijn. De enige uitzondering is als er haarden van dooierzaktumor in de snijrand zichtbaar zijn; in die gevallen is adjuvante behandeling geïndiceerd. Het vrijkomen van cystevocht was in geen van de gevallen geassocieerd met recidief. Het vrijkomen van tumorinhoud en het niet verwijderen van de coccyx daarentegen wel.

In hoofdstuk 9 wordt dezelfde vraagstelling geformuleerd, maar nu voor een groep van 173 patiënten met een sacrococcygeaal teratoom die tussen 1970 en 2003 behandeld werden in de zes kinderchirurgische centra van Nederland. Acht patiënten waren overleden tijdens of kort na de operatie. Bij 9 patiënten, allen 18 maanden of ouder, waren al metastasen aanwezig toen de diagnose werd gesteld. In vier van deze gevallen was er sprake van een mature primaire tumor. Recidief werd gezien bij 19 patiënten (12%), gemiddeld 10 maanden (uitersten 32 dagen – 35 maanden) na de eerste behandeling. Als risicofactoren voor recidief werden gevonden: onvolledige tumorresectie, immature histologie en maligne histologie. De afmetingen van de tumor, Altman-classificatie, leeftijd en de tijdsperiode van behandeling waren geen risicofactoren. Eén op drie recidieven vertoonde een verschuiving naar immaturiteit of naar maligniteit, in vergelijking met de primaire tumor. Zeven patiënten overleden na het optreden van het recidief (bij zes was de histologie maligne).

In hoofdstuk 10 wordt een pleidooi gehouden voor centralisatie van gespecialiseerde kinderchirurgie in België. Tussen 1992 en 1996 werden 18 patiënten met een sacrococcygeaal teratoom behandeld in zeven verschillende

centra in België en Luxemburg. Hoewel eigenlijk goede resultaten werden bereikt, gezien het feit dat alle patiënten in leven bleven, werden toch diverse onvolmaaktheden gezien met betrekking tot diagnosestelling, tijdstip van bevalling, tijdstip van operatie en operatietechniek. Daarom bevelen wij aan de behandeling van patiëntjes met een sacrococcygeaal teratoom te centraliseren in slechts enkele centra voor neonatale kinderchirurgie.

Hoofdstuk 11 behandelt een ander groot probleem bij kinderen met sacrococcygeaal teratoom, namelijk de functionele en esthetische gevolgen. We hebben naar de omvang van deze gevolgen gekeken, naar de eventuele geassocieerde klinische variabelen en naar de invloed op de kwaliteit van leven. Voor dit doel verspreidden wij leeftijdspecifieke vragenlijsten onder alle patiënten van 3 jaar en ouder, met een sacrococcygeaal teratoom welke tussen 1980 en 2003 behandeld waren in een van de zes Nederlandse kinderchirurgiche centra. De vragenlijsten peilden naar constipatie of fecale incontinentie, urine-incontinentie en naar het litteken. Deze parameters werden gecorreleerd aan diverse klinische variabelen, welke uit de status van de patiënten gehaald werden. De risicofactoren werden berekend door middel van variantieanalyse. Negenenzeventig van de 99 verstuurde vragenlijsten werden ingevuld geretourneerd (80%). De mediane leeftijd van de respondenten was 9,7 jaar. Zesenveertig procent vermeldde problemen met de ontlasting en/of urine-incontinentie: 9% fecale incontinentie, 13% lekken van vloeibare feces ("soiling"), 17% constipatie, 31% urine-incontinentie. Veertig procent noemde het litteken cosmetisch onaanvaardbaar. Leeftijd op het ogenblik van invullen van de vragenlijst, Altman-classificatie, geslacht en histopathologie bleken geen risicofactoren voor latere nadelige gevolgen. De omvang van de tumor (> 500 cm^3) was een significante risicofactor voor een onaanvaardbaar geacht litteken. Er bestond een duidelijk verband tussen de latere gevolgen en verminderde levenskwaliteit. Wij concluderen dat een zeer groot deel van de patiënten met een sacrococcygeaal teratoom later last heeft van defecatieproblemen, urine-incontinentie of het litteken cosmetisch onaanvaardbaar beschouwt – en dat dit hun kwaliteit van leven in negatieve zin beïnvloedt. Het blijkt niet mogelijk om aan de hand van de onderzochte klinische variabelen patiënten te identificeren die een hogere kans hebben op het optreden van deze sekwellen op de lange termijn.

Ter afsluiting brengt hoofdstuk 12 de resultaten en bevindingen van de vorige hoofdstukken met elkaar in verband.

abbreviations

A	Actinomycin-D
AFP	Alpha-Fetoprotein
α-FP	Alpha-Fetoprotein
ALL	Acute Lymphoblastic Leukemia
APD	Anatomo-Pathological Diagnosis
ARM	Ano Rectal Malformation
B	Bleomycin
β-HCG	Beta-Human Chorionic Gonadotropin
BTTP	British Testicular Tumour Panel
C	Cyclophosphamide
CCG	Children's Cancer Group
CI	Confidence Interval
CL	Confidence Limits
CNS	Central Nervous System
COG	Children's Oncology Group
C-section	Cesarean Section
CT	Computerized Tomography
E	Etoposide
ECMO	Extra-Corporeal Membrane Oxygenation
EFS	Event-Free Survival
EST	Endodermal Sinus Tumor (Syn. = Yolk Sac Tumor)
EXIT	Ex-Utero Intrapartum Treatment
F	Female
FIGO	Fédération Internationale de Gynécologie Oncologique International Federation of Gynecologic Oncology
GCT(s)	Germ Cell Tumor(s)
HDPEB	High-dose PEB (cisplatin 200 mg/m^2/cycle)
I	Ifosfamide
IT	Immature Teratoma
J	Carboplatin
JEB	Carboplatin – Etoposide – Bleomycin
JVB	Carboplatin – Vinblastine – Bleomycin
M	Male
MAKEI	Maligne Keimzelltumoren

MAHO	Maligne Hodentumoren
MGCT(s)	Malignant Germ Cell Tumors
MRI	Magnetic Resonance Imaging
MT	Mature Teratoma
n	number (of patients)
NED	No evidence of disease
NICU	Neonatal Intensive Care Unit
NS	Not Significant
OOPS	Operation on Placental Support
OR	Odds ratio
OS	Overall Survival
P	Cisplatin
PEI	Cisplatin – Etoposide – Ifosfamide
PEB	Cisplatin – Etoposide – Bleomycin
POG	Pediatric Oncology Group
PVB	Cisplatin – Vinblastine – Bleomycine
QoL	Quality of Life
SCT	Sacrococcygeal Teratoma
SIOP	Société Internationale d'Oncologie Pédiatrique
SPSS	Statistical Package for the Social Sciences
SFOP	Société Française d' Oncologie Pédiatrique
TIP	Taxol – Ifosfamide – Cisplatin
TNM	Tumor- Node- Metastasis Staging system
UKCCSG	United Kingdom Children's Cancer Study Group
US	Ultrasound
	United States (of America)
V	Vinblastine
VAC	Vinblastine – Actinomycin-D – Cyclophosphamide
VcrAC	Vincristine – Actinomycin-D - Cyclophosphamide
VAPB	Vinblastine – Actinomycin-D – Cisplatin - Bleomycin
WHO	World Health Organization
YST	Yolk Sac Tumor

dankwoord

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curriculum vitae

Antoine (Toon) De Backer werd geboren op 26 Mei 1956 te Aalst, een kleine stad in hartje Vlaanderen. In 1974 behaalde hij het middelbareschooldiploma, en begon in datzelfde najaar geneeskundestudies aan de Vrije Universiteit te Brussel. Op 30 Juni 1981 behaalde hij met grote onderscheiding het diploma "Doctor in Genees-, Heel- en Verloskunde".
In de zomer van 1981 begon hij de opleiding Chirurgie in het Academisch Ziekenhuis van de Vrije Universiteit Brussel o.l.v. Prof. René Kiekens en, na diens overlijden, van Prof. G. Willems. In 1984 liep hij stage op de afdeling kinderchirurgie van het Hôpital des Enfants-Malades te Parijs o.l.v. Prof. Denys Pellerin, Nihoul-Fékété en Yann Révillon. Hier kreeg de kinderchirurgische microbe hem te pakken. Van 1 oktober 1985 tot 30 September 1986 werkte hij in de dienst kinderchirurgie van het Sophia Kinderziekenhuis (toen nog aan de Gordelweg) o.l.v. Prof. Jan Molenaar en Prof. Frans Hazebroek. Nadat hij de erkenning als chirurg had bekomen (zomer 1986), trad hij in dienst van het Academisch Ziekenhuis van de Vrije Universiteit Brussel als kinderchirurg. Hij werkte er de eerste jaren samen met Prof. Peter Deconinck en, na diens oprusttelling, nu met Dr. Kristel Devogelaere. Hij is auteur van een 60-tal wetenschappelijke publicaties en heeft een honderdtal voordrachten op nationale en internationale congressen gehouden. Hij vervulde zowat alle bestuurlijke functies van de Belgische Vereniging voor Kinderchirurgie (BELAPS) waarvan hij de voorzitter was in 2000-2001. Van 2001 tot 2002 was hij vice-voorzitter van de EUPSA (European Union of Paediatric Surgical Associations), nadat hij van 1994 tot 2000 de rol van secretaris van deze vereniging had vervuld. Hij is associate editor van het European Journal of Paediatric Surgery en zetelt in de review board van Acta Chirurgica Belgica. Daarnaast doet hij reviews voor tal van medische tijdschriften. In de tweede helft van de tachtiger jaren deed hij experimentele research naar de gevolgen van gastro-oesofageale reflux en van andere endogene en exogene factoren op de celproliferatie van het slokdarmepitheel. Het onderzoek dat hier wordt voorgesteld begon in het najaar van 2001; hij beschouwt dit proefschrift zeker niet als een eindpunt, maar eerder als een begin en hoopt deze research verder te kunnen zetten aan het Erasmus MC-Sophia.
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