Progress in Pediatric Surgery

Volume 22

Pediatric Surgical Oncology

Volume Editors
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With 78 Figures and 44 Tables

Springer-Verlag
Berlin Heidelberg New York
London Paris Tokyo

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Volumes 1–17 of this series were published
by Urban & Schwarzenberg, Baltimore–Munich

ISBN-13: 978-3-642-72645-3 e-ISBN-13: 978-3-642-72643-9
DOI: 10.1007/978-3-642-72643-9

Library of Congress Cataloging-in-Publication Data
Pediatric surgical oncology / volume editors, L. Spitz, P. Wurnig, Th. A. Angerpointner.
p. cm. – (Progress in pediatric surgery; v. 22)
Includes bibliographies and index.

1. Cancer – Surgery. 2. Tumors in children – Surgery. I. Spitz, Lewis. II. Wurnig, Peter.
III. Angerpointner, Thomas. IV. Series.
[DNLM: 1. Neoplasms – in infancy & childhood. 2. Neoplasms – surgery. W1 PR677KA
v. 22 / QZ 268 P371] RD137.A1P7 vol. 22 [RD651] 617'.98 s – dc19 [618.92'994059]
DNLM/DLC 88-24765

Softcover reprint of the hardcover 1st edition 1989

Binding: Konrad Triltsch, Würzburg
2123/3145-543210 Printed on acid-free paper

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Congenital Soft Tissue Dysplasia: A New Malformation Entity and Concept

D. Pellerin, H. Martelli, X. Latouche, G. Couly, and F. Gasnier

Until recently, management of pathological conditions of soft tissue was scattered among subspecialities according to the clinical presentation: dermatologists, vascular surgeons, orthopaedists, plastic surgeons, neurologists, neurosurgeons, and, of course, paediatric surgeons all took their turn. The pathological conditions were termed giant hamartomas, segmentary gigantism, hypertrophic limbs, phacomatosis, angiodysplasia; or were grouped in syndromes such as Parkes-Weber or Klippel-Trenaunay. Hardly anything was known about their embryological or physiopathological development, and consequently complete cure was impossible.

In the light of some privileged observations, and because of a better understanding of the embryological mechanisms in the development of ectoderm and mesoderm, we propose to regroup these syndromes into a new entity, *congenital soft-tissue dysplasia* (CSTD). This entity is based on a histological characteristic common to all the above conditions, namely overgrowth of normal differentiated cells. All diseases included in the entity share the same type of natural history and have some important therapeutic aspects in common.

Before going into the historical review, we will show features in a 4-year-old boy (Fig. 1) that illustrate this entity, with its wide variety of clinical lesions linked by a common histological aspect. All his lesions are secondary to abnormal development of ectodermal and mesodermal tissues. There is an overgrowth of both thighs and the left leg, partial hypertrophy with gigantism of the feet, and a smaller area of overgrown soft tissue on the left side of the thorax. Such anomalies may be diffuse or localised. On the back, the hamartomatous hypertrophy may give rise to the typical bison-like appearance (Fig. 2). Dysplasia can be limited to a finger or a toe. Reflecting the ectodermal anomalies, the covering skin is often abnormal with superficial angiomatosis, pigmented naevus, or, occasionally, pilose naevi. Dermo-epidermal lymphangiectasis may result in chronic lymphorroea, with high risk of infection. In the case of bony hypertrophy, the bone's structure is radiologically normal. Whatever the clinical appearance, the pathology is always that of normal differentiated cells. Soft tissues are always constituted of normal mesodermal or ectodermal components. The abnormality lies in either the overgrowth or the abnormal localisation of these normal components. Here we can really talk of "polymorphic hamartoma", with combinations of lipomatous tissues, haemangiomas or lymphangiomas, often with large fibrous stromal components (Figs. 3–5).

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Progress in Pediatric Surgery, Vol. 22
Ed. by L. Spitz et al.

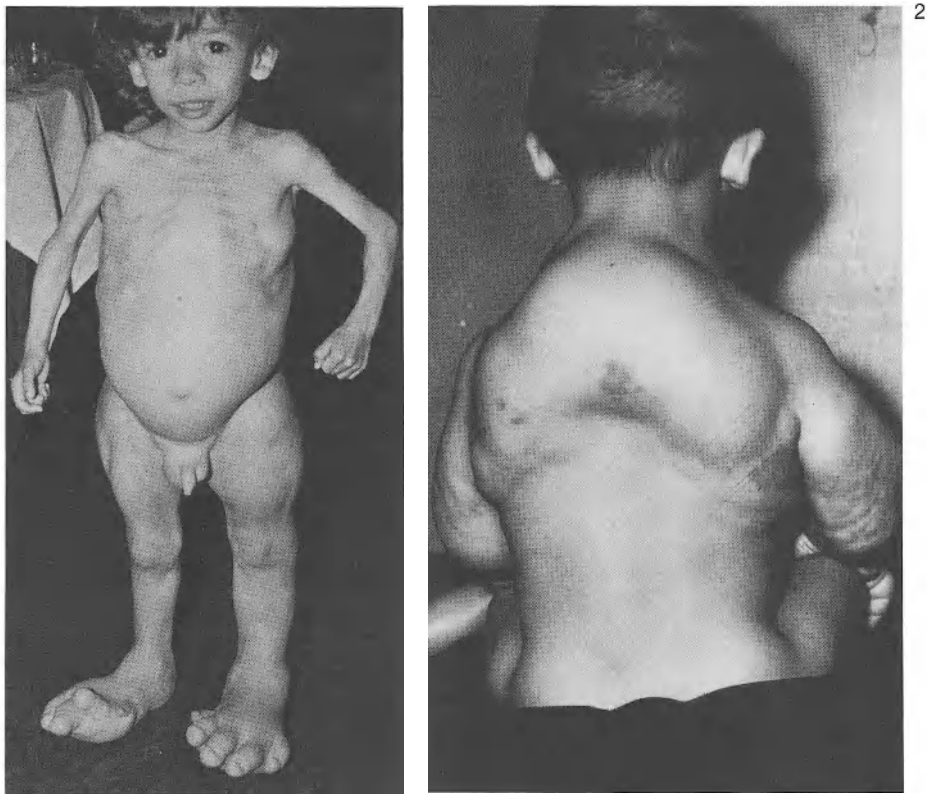


Fig. 1. Four-year-old boy with diffuse overgrowth of the thighs and the left leg, partial distal gigantism, and hamartoma of the left side of the trunk

Fig. 2. Bison-like hamartoma of the back with overgrown right upper limb

Historical Review

The clinical aspects of CSTD have been known for a long time. Early on, some cases were shown or published as curiosities or monstrosities. Two cases were described precisely by Chassaignac in 1858 to the Société des Chirurgiens de Paris, in these words: 'The limbs on the left side are those of a person of normal build; those on the right seem to belong to a giant' [7] (Fig. 6). Ten years later, Trelat and Monod [47] published in the *Archives Générales de Médecine* a clinical description of 'l'hypertrophie unilatérale partielle ou totale du corps' (partial or total unilateral hypertrophy of the body): 'Sometimes of limited extent, congenital hypertrophy may affect the whole system of an organ or a large portion of

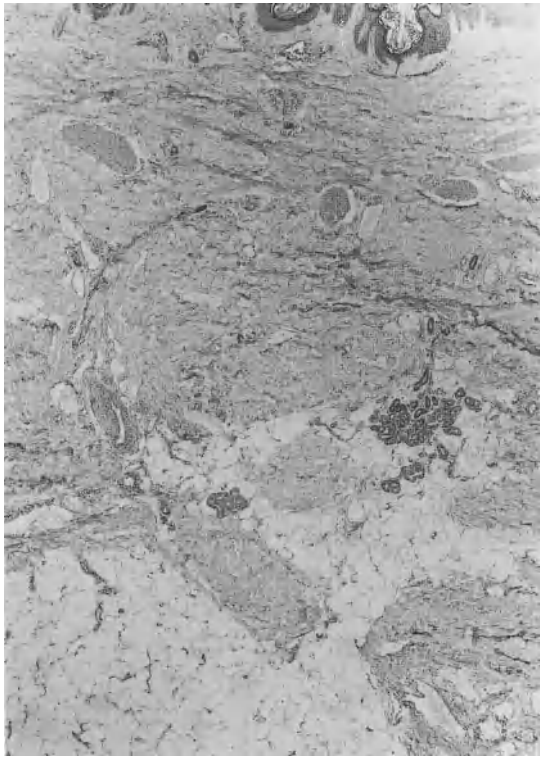


Fig. 3. Dermo-epidermal junction: specimen from patient in Fig. 9. Overgrowth of normal tissue. Thick connective tissue displacing the sweat glands. Overgrown lipomatous component. Some overgrown Schwann structures. H & E, × 2.5. (Courtesy of Professor Nezelof)

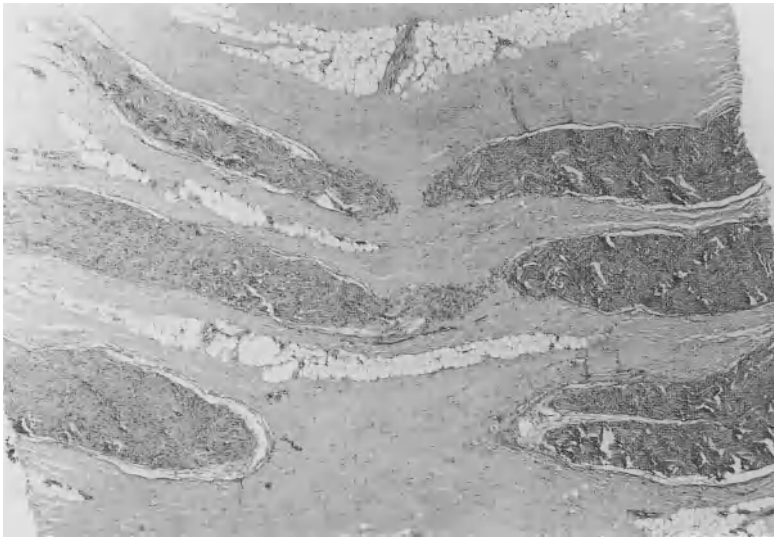


Fig. 4. The same as Fig. 3. Overgrowth of Schwann structures. H & E, × 25. (Courtesy of Professor Nezelof)

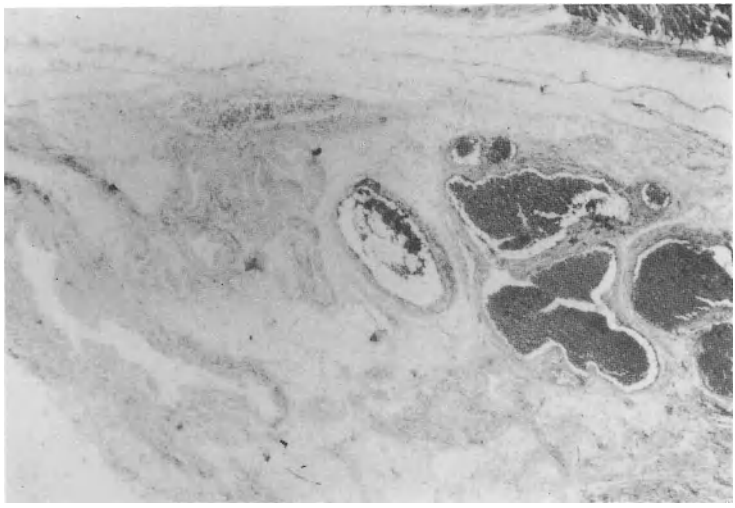


Fig. 5. Overgrowth of connective tissue with vascular component (from the patient in Fig. 13). (Courtesy of Professor Nezelof)

Séance du 28 avril 1858.

Présidence de M. Bouvier.

PRÉSENTATION DE MALADES.

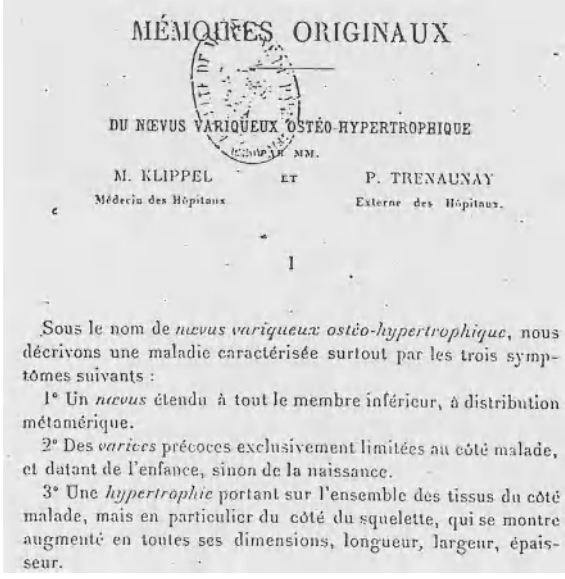
Hypertrophie congéniale des deux membres droits. — Taches sanguines multiples; varices, etc. — M. CHASSAIGNAC présente un jeune homme, âgé de dix-huit ans, nommé Charles Lemercier, entré dernièrement à l'hôpital Lariboisière pour y être traité d'un abcès ganglionnaire, de cause scrofuleuse, situé sur le côté droit du cou. Ce jeune homme est remarquable par l'extrême inégalité des membres du côté droit et du côté gauche. Les deux membres du côté gauche sont ceux d'un individu de taille ordinaire, ceux du côté droit paraissent appartenir à un géant. Mais les différentes parties de ces deux derniers membres sont loin d'être uniformément hypertrophiées. La main l'est beaucoup plus que le bras et l'avant-bras; sa moitié externe l'est plus que sa moitié interne. Le pouce, l'index et le médius sont relativement beaucoup plus longs et beaucoup plus volumineux que les deux derniers doigts. Au membre inférieur on trouve également que la jambe et la cuisse sont moins hypertrophiées que le pied. Celui-ci est vraiment colossal. Le gros orteil est énorme, mais il est relativement moins développé que les quatre derniers orteils.

Fig. 6. Chassaignac's description at the Société des Chirurgiens de Paris in 1858

the body. A tissue may develop in an unusual way.' In 1886, Duzea [13] started a controversy about the aetiology. He maintained that superficial angiomatosis was to blame, and spoke in favour of a vascular aetiology. After the publication of a paper entitled *Naevus variqueux ostéo-hypertrophique* by Klippel and Trenaunay in 1900 [18] (Fig. 7), almost all these conditions were attributed to vascular anomalies, especially peripheral congenital arteriovenous fistulae as seen in the Parkes-Weber syndrome [33] defined in 1907.

In 1965 Malan and Puglionisi [26] pointed out that dysplasia can affect arteries, veins and lymphatic vessels to a greater or lesser extent. They proposed use of the term 'vascular dysplasia', irrespective of the degree or the site of the vascular anomaly.

More recently, in 1979, O'Donnell [32], studying 19 cases of such abnormalities affecting the lower extremity, found a wide variety of vascular anomalies and proposed the term 'congenital mixed vascular deformities'. He proposed subdivision into three groups: Klippel or venous dysplasia, congenital arteriovenous fistulae, and diffuse angiomas. Seven patients with arteriovenous fistulae had hyperplastic lymph pathways; the other 12 patients had a normal lymphogram or hypoplasia or aplasia of the lymph pathways. He pointed out that the increase in tissue bulk is common to the three groups and suggested that this may result either from a failure of mesenchymal cell vacuolisation or lack of endothelial cell budding during fetal life. Congenital lymphoedema or trophoedema were for a long time considered to be the consequence of deep vein atresia or compression of lymphatic trunks [38, 39, 40, 41]. However, computed tomography shows that hamartomatous infiltration affects all the soft tissues and this was confirmed on routine histopathological examination.



MÉMOIRES ORIGINAUX

DU NŒVUS VARIQUEUX OSTÉO-HYPERTROPHIQUE

PAR MM.

M. KLIPPEL Médecin des Hôpitaux

ET

P. TRENAUNAY Externe des Hôpitaux.

I

Sous le nom de *nævus variqueux ostéo-hypertrophique*, nous décrivons une maladie caractérisée surtout par les trois symptômes suivants :

1° Un *nævus* étendu à tout le membre inférieur, à distribution métamérique.

2° Des *varices* précoces exclusivement limitées au côté malade, et datant de l'enfance, sinon de la naissance.

3° Une *hypertrophie* portant sur l'ensemble des tissus du côté malade, mais en particulier du côté du squelette, qui se montre augmenté en toutes ses dimensions, longueur, largeur, épaisseur.

Fig. 7. Original publication by Klippel and Trenaunay, Paris, 1900

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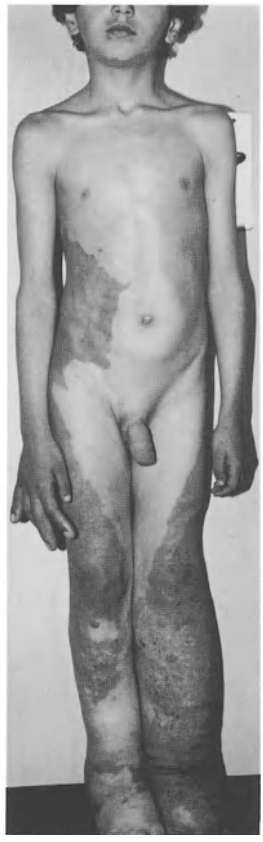

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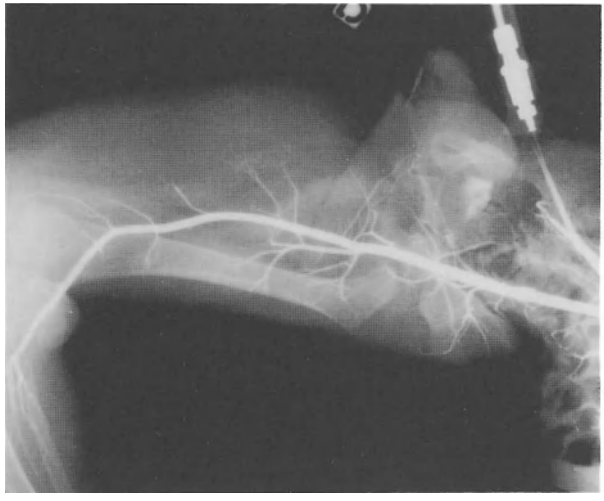

Fig. 8. Twelve-year-old boy. Klippel-Trenaunay-Weber syndrome. Overgrown right hand with megadactyly. At this side, no angiodysplasia

Fig. 9. Eighteen-month-old boy: monstrously overgrown right lower limb, fourth and fifth toes preserved

Fig. 10. The same patient as in Fig. 9. The angiogram shows normal main vessels and skeleton

Today, angiography and ultrasound are able to demonstrate that main vessels are normal in many cases of what is now called Klippel-Trenaunay-Weber syndrome. This was the case in the diffuse dysplasia of soft tissues of the trunk and both lower limbs shown on Fig. 8, and also in an enormous congenital hypertrophy of lower limb, of which the angiogram was normal (Fig. 9, 10). We there-

fore believe that the purely vascular conception of these anomalies is old-fashioned and a new aetiopathogenetic concept should be developed, based on the common histopathological feature of overgrown cells of well-differentiated tissues.

We believe that all these conditions should be comprehended by a single term, congenital soft-tissue dysplasia. This concept is supported by recent discoveries in fundamental embryology, especially regarding the unity of the mesectoderm [24].

Material

Over the last 30 years at the Hôpital des Enfants Malades of Paris we have accumulated experience of 185 patients with CSTD. Retrospectively, they can be classified into four groups (Table 1):

Localised CSTD

This corresponds to soft-tissue hamartomas. The common small hamartomas were excluded and we limited inclusion in this category to the large hamartomas which presented as extensive soft-tissue tumours (19 cases). In addition to the well-known sites (limbs), we wish to draw attention to the frequency with which they are seen in the trunk, especially the back (Fig. 11; Table 2).

Segmental CSTD Without Gigantism

Soft-tissue dysplasia extends here to a whole segment of the trunk affecting either or both limbs, but never crossing the midline. We have treated 98 cases. In 20, the dysplasia was a pure, homogeneous, polytissue, soft tissue hypertrophy without any vascular component (Fig. 12; Table 3). In the remaining 78, there was a clini-

Table 1. Classification of 185 cases of congenital soft-tissue dysplasia

Localised CSTD	19
Segmental CSTD without gigantism	
without angiodysplasia	20
with angiodysplasia	78
CSTD with gigantism	43
Ectodermal CSTD	14
CSTD in Recklinghausen's disease	11

Table 2. Distribution of localised CSTD (hamartomas) in 19 patients

Head		1
cheek	1	
Upper limb		6
shoulder	2	
arm	1	
elbow	2	
hand and fingers	1	
Lower limb		7
root	2	
thigh	1	
leg	2	
foot	2	
Back		5

Table 3. Distribution of pure, homogeneous, bulky soft-tissue hypertrophy in 20 patients

Upper limb and trunk		1
Upper limb		2
Hand		2
Lower limb		13
whole	7	
leg	1	
leg and foot	5	
Perineum		2

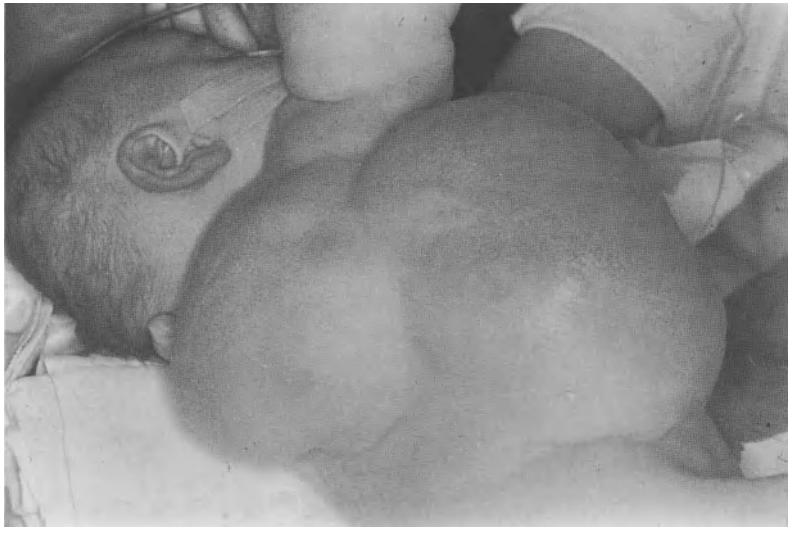

Fig. 11. Infant with a segmentary CSTD of the trunk. Pure soft tissue hypertrophy without angiodysplasia

cal and/or histopathological vascular component, either as an angiomatosis superficial to the main mass of dysplasia (on the trunk, a limb, or head and neck) or as a deeper vascular component (Table 4) – varicosities or subcutaneous angiodysplasia (such as in classical Klippel-Trenaunay-Weber syndrome) in the upper (Fig. 13) or lower limb.

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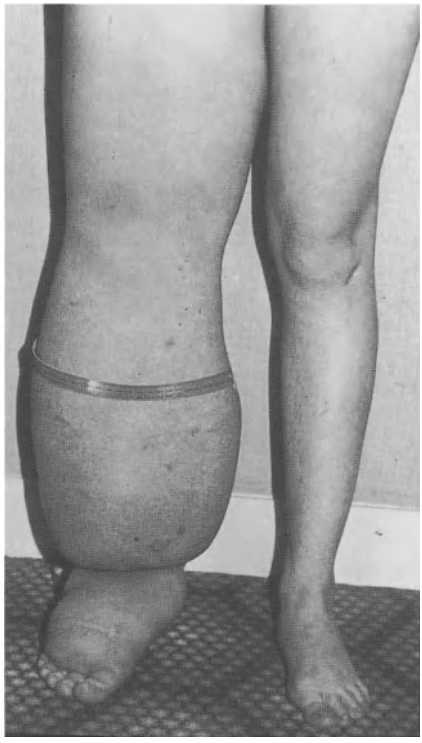

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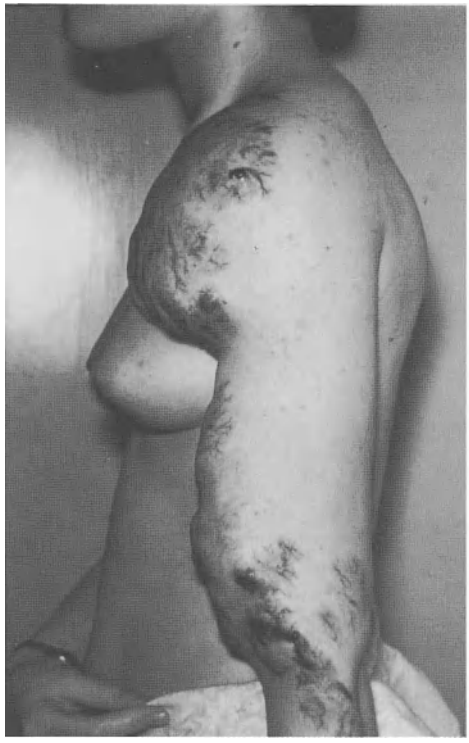

Fig. 12. Twelve-year-old girl. Congenital soft tissue hypertrophy without angiodysplasia, in spite of the resemblance to trophoedema

Fig. 13. Segmental CSTD with angiodysplasia of upper limb and root: Klippel-Trenaunay-Weber syndrome

Table 4. Distribution of CSTD with angiodysplasia but without gigantism in 78 patients

Head		18	Lower limb		17
face and skull	2		whole	6	
face and mouth	5		root	2	
face and neck	11		thigh	4	
Neck and trunk		2	leg	4	
Trunk		6	foot	1	
Upper limb and trunk		11	Genitalia		4
Upper limb		19	Multiples		2
shoulder	6				
arm	3				
hand	3				
arm and forearm	7				

Among these 78 cases, there were only four with arteriovenous fistulae. Like pure soft-tissue hypertrophy, this segmental CSTD has a selective regional localisation [face and neck (Fig. 14, 15), neck and thorax, limbs and roots]. This suggests a selective and localised disturbance of the normal embryonic mechanism of tissue growth regulation.

Dysplasia with Gigantism

This anomaly (43 cases) combines a soft-tissue dysplasia, with or without vascular component, and overgrown skeletal tissue (Table 5). Gigantism was observed on the upper or the lower part of the limb, or both. It was occasionally localised independently of the main soft tissue dysplasia or on another limb (see Fig. 8). Distal gigantism, especially on fingers (16 cases) and toes (38 cases), was common and sited either medially or laterally (Figs. 16, 17). Gigantism observed at birth was usually remarkably stable later and followed the child's normal growth rate. Five

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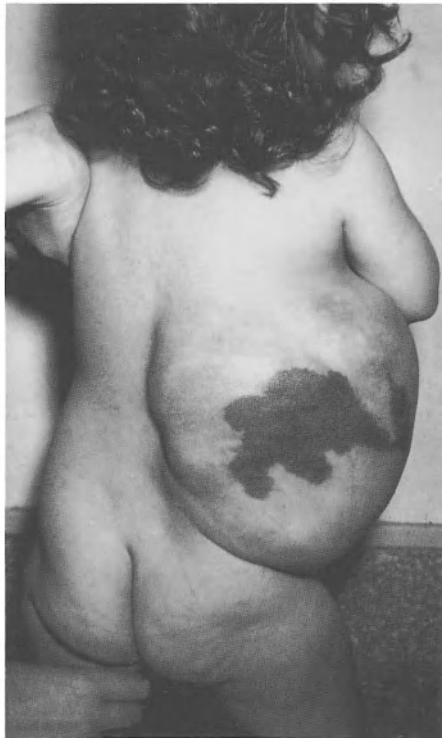

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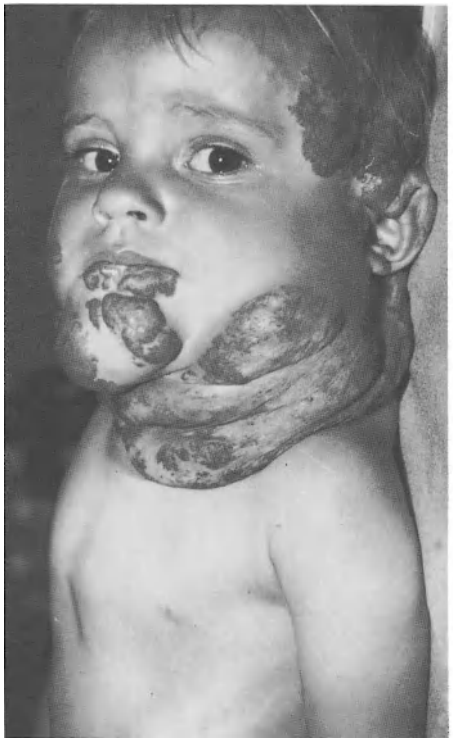


Fig. 14. Two-year-old girl. Segmental CSTD of the trunk with vascular component

Fig. 15. Fourteen-month-old girl. Large CSTD of the face: haemangioma

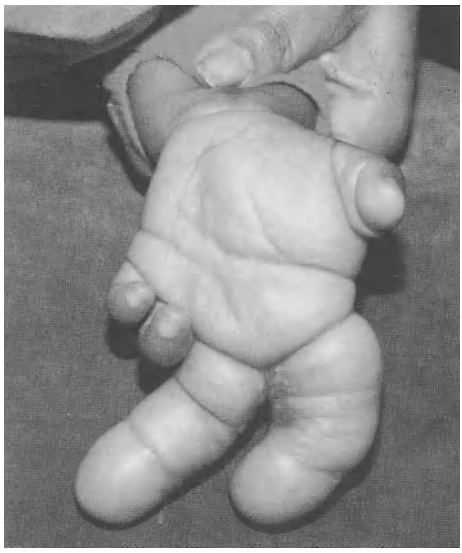


Fig. 16. Pure macrodactyly of two fingers

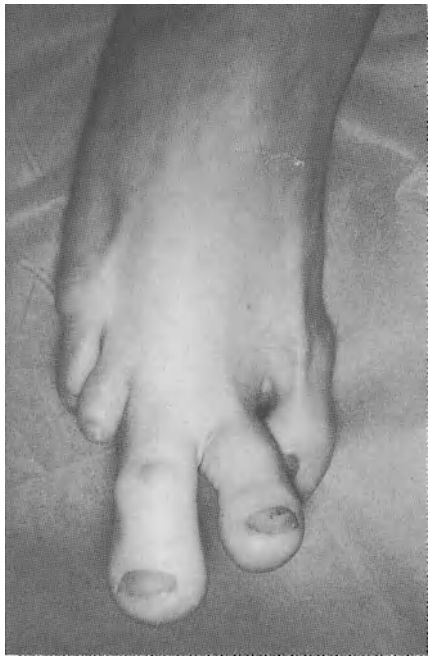


Fig. 17. Pure macrodactyly of two toes

patients were followed up from 1 to 15 years and all remained strictly within 2 cm overgrowth on millimetric X-ray measurement. There was only one case of macrodactyly, diagnosed at birth, which had rapid overgrowth during the 1st week of life, but it later stabilised.

Table 5. Distribution of CSTD with gigantism with or without angiodysplasia in 43 patients

Lower limb		25
left	10	
right	9	
with macrodactyly	6	
Lower and upper limb		1
Multiple		1
Isolated macrodactyly		16
fingers	8	
toes	8	

Table 6. Distribution of pure ectodermal dysplasia (giant naevi) in 14 patients

Skull	1
Nape	1
Nape + scattered naevi (dalmatian)	1
Back and shoulder	2
Back	4
Back + dalmatian	2
Trunk	2
Trunk + dalmatian	1
Buttock	1

Pure Ectodermal Dysplasia

Pigmented or pilose giant naevi, pure or associated with other types of soft-tissue dysplasia (14 cases), have strictly the same topography as other kinds of CSTD (Fig. 18; Table 6). Today we recognise that pigmentary cells originate from the pioneer neural crest cells, and consequently ectodermal cell overgrowth must occur in a similar manner to other types of CSTD.

Soft-Tissue Dysplasia and Recklinghausen's Disease

Because of its genetic transmission, a special mention must be made of soft-tissue dysplasia occurring in Recklinghausen's disease (11 cases). In our series, six CSTD were observed in patients with the well-known familial Recklinghausen's disease: two were localised and four were segmental with gigantism. The histopathology of these dysplasias was identical to other CSTDs and completely different to the neurofibromatosis commonly observed in Recklinghausen's disease. We saw five patients with no family history of Recklinghausen's disease and without any of the disease's early clinical features, who were followed-up for CSTD. In four patients the CSTD was localized; in one it was a dysplasia with gigantism with multifocal localisations. This child developed very severe Recklinghausen's disease (Figs. 19, 20).

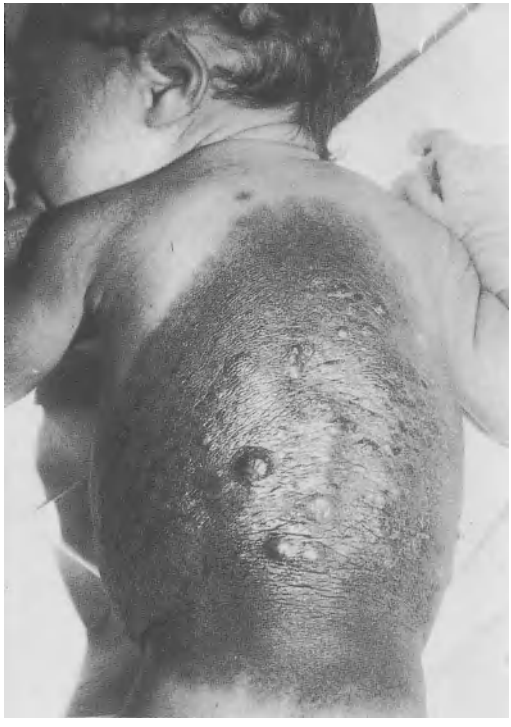


Fig. 18. Three-month-old girl. Pure metameric ectodermic CSTD: giant naevus

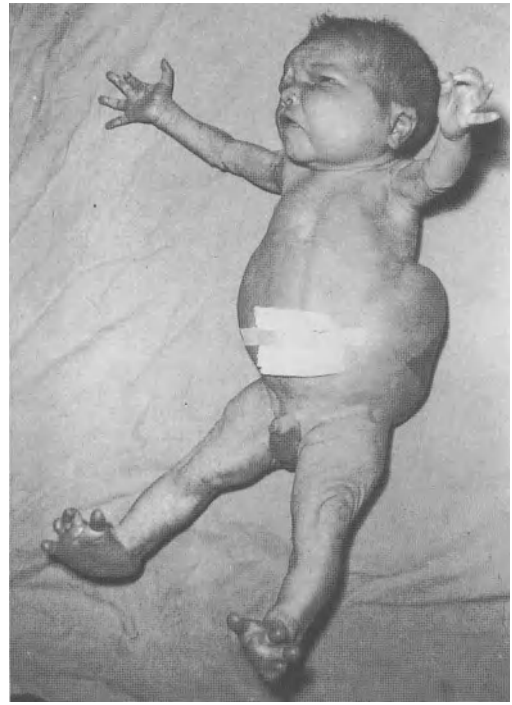


Fig. 19. At birth, CSTD of face and trunk, with distal gigantism

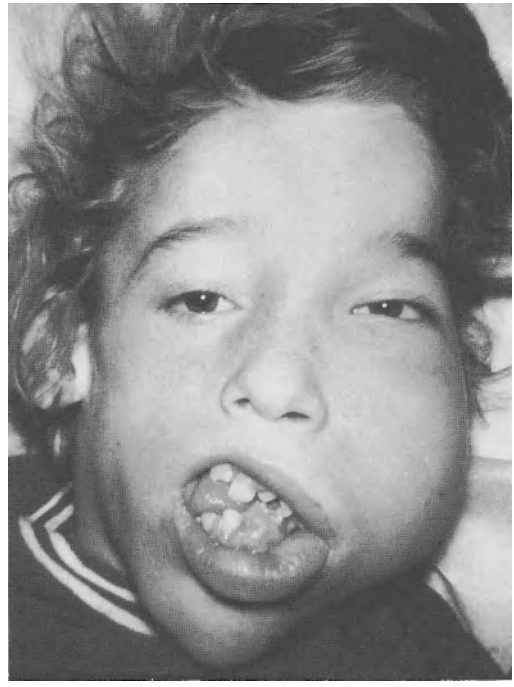


Fig. 20. The same patient at 12 years old, showing very severe Recklinghausen's disease

During the same period, 27 other patients with Recklinghausen's disease were observed in our department for the usual orthopaedic or tumoral symptoms but did not develop any signs of CSTD.

Comments

In spite of their apparent diversity, these 185 patients have striking similarities, which can be summarised as follows:

1. Anomalies are observed at birth and localisation remains identical throughout life, unique or multiple, localised or segmental. We have never observed dysplasia to occur in a new site in later life.
2. Growth of tissues remains stable, with similar rates for CSTD and body growth. Acute increases in volume are always transitory and caused by either an inflammatory process (usually at the site of lymphatic components) or a haemorrhage from a vascular tissue component. There is, however, an exception concerning certain angiodysplasias that frequently have an evolutionary process during the first few weeks of life. This is a well-recognised phenomenon in the natural history of haemangiomas. It suggests that the disturbed regulation of the growing vascular component of connective tissue can be expressed beyond the fetal life. This transitory process is, however, definitively exhausted 6–8 months after birth. The stability beyond birth is also true of dysplasia with gigantism. This was remarked by Barsky [5] in 1967 in regard to macrodactyly. He pointed out that, in this very rare anomaly (only 64 cases recorded in 140 years), the enlargement present at birth did not increase disproportionately to body growth ('static macrodactyly').
3. CSTDs are benign lesions. They include disproportionate growth of every type of ectodermal and mesodermal soft tissue, but do not involve any muscle or main deep vessel.

Aetiopathogenesis

It is well established that normal tissue is the product of the orderly distribution of differentiated cells and of the intercellular matrix. CSTD probably results from one of several cell regulation disturbances.

For any pathogenesis to be put forward, clinical and histopathological materials must be subject to investigation according to modern concepts of developmental biology. A brief summary follows of the three main stages necessary to the comprehension of CSTD: induction effect of the neural crest, growth factor mechanisms and cell biosynthesis.

Neural Crest

Le Douarin et al. [23, 25] clearly documented the morphogenetic role of neural crest cells in craniofacial organogenesis. They also stressed that at the initial stage of embryogenesis – at the 11th somite stage – crest cells loosing their neuron cell adhesive molecule initiate their migration into the somatopleural fold of the embryo, between the basement membranes of the neural tube and ectoderm. They migrate to numerous precise destinations according to specific pathways correlated with a structural glycoprotein environment, known as fibronectin. At the target site, neural crest cells differentiate into a variety of tissues including not only the peripheral nervous system, some endocrine and para-endocrine cells, but also lipocytes, pigmentary cells and the mesectoderm [9, 11, 45].

Growth factors

Since the identification in 1952 by Levi Montalcini [50] of nerve growth factor (NGF), the role of growth factors has been accentuated by observations from in-vitro cell cultures. The discovery by Stanley Cohen in 1962 [49] of an epidermal growth factor (EGF) from the male mouse submaxillary gland demonstrated that EGF is mitogenic for variety of epithelial and other tissues. However, the primary mechanism of action of EGF is not clear [14–16]. The fibroblast growth factor (FGF) isolated by Gospodarowicz in 1974 has been shown to have a strong mitogenic effect on fibroblasts, as well as endothelial cells, such as the internal wall of blood vessels and cornea. But FGF appears to be also active on different types of mesodermic cells. Not only is FGF action mitogenic, but it also allows cells to maintain their morphological characteristics and prevents their degeneration. Several other growth factors – tumour growth factor, platelet-derived growth factor (PDGF), etc. – have recently been isolated and have a very similar polypeptide structure. Growth factor is synthesised by the cell itself through an inactive precursor which must be activated by an activator enzyme. Activated GF is transported to the target cell by a specific protein carrier. It does not penetrate the cell to provoke a mitotic cycle, but binds with a specific receptor in the cell membrane. This process requires sufficiently numerous normal target sites.

Several GFs have an angiogenic effect, but this effect would appear to be non-specific. Consequently, we cannot explain why only some tissues are stimulated. It suggests that an interaction exists between the cells and their intercellular environment. Some experimental observations are of relevance: in-vitro cell culture on plastic fold is not stimulated by FGF, e.g., but the same culture on fibronectin is totally stimulated. It could also result from a modulation of target site during the development, as is suggested by other experimental observations that embryonic muscle cells of aorta attract more PDGF than the same adult cells.

Cellular Biosynthesis

Rapid development of in-vitro cell culture techniques have shown that the genetic information of cells does not change and that, for each one, codes for specific proteins are regulated and controlled. Moreover, cells have their own spatial organisation according to their environment and their genetic program [48]. A localised disturbance of any regulating factor between cells and their intercellular protein matrix [19–21] allows proliferation of well-differentiated cells, which retain their capacity to form specific tissues but are no longer controlled by the normal spatial regulating process. To put it another way, we may assume that it would be possible for a certain mutation inside a cell to provoke a faulty interpretation of the message and induce a disturbed 'biological pattern'. Likewise, a cell biosynthetic anomaly could produce a disturbed balance between anabolism and catabolism, with an excess of macromolecular synthesis or deficit of intercellular matrix (ICM) or of cell metabolic enzymes [36–37].

Such is, in summary, the state of present knowledge of early developmental biology. A consideration of our clinical material regarding CSTD in the light of this knowledge prompts some remarks.

1. The frequency of the cephalic localisation of dysplasia suggests an early disturbance of the neural crest. Other arguments which speak for the participation of neural crest arise from (a) the fibrolipomatous stroma observed in all dysplasias and (b) the association between ectodermal and mesodermal tissues in CSTD. Slavin and Baker [43] described a 'clinico-pathologic entity characterized by collation of non-encapsulated mature lipocytes that infiltrate local tissues, often associated with variable angiomatous, neural and collagenous components'. Concerning macrodactyly, Thorne and Posch [46] stress 'the voluminous amounts of adipose tissue containing various amounts of fibrous stroma. In several patients, instead of having enlarged blood vessels as would be expected, the arterial supply consisted of multiple small anomalous vessels.' Many CSTD have a strictly metameric distribution. Some ectodermal dysplasias have a typical neurogenic distribution (Fig. 21). As outlined above, we suggest that CSTD could closely approach the concept of a neurocrestopathy.

2. When NGF was first identified, the hypothesis was proposed that peripheral nerve hypertrophy could be the main factor of megadactyly. As long ago as 1942, Moor wrote: 'the fact that local hypertrophy is so constantly associated with peripheral nerve pathology, seems to indicate that there is a relationship between them. It is believed that the nervous system exerts some controlling action on the process of growth and that the impaired nerves fail in this function resulting in uncontrolled or uninhibited growth' [28]. Associated enlargement of peripheral nerves is in fact frequently encountered and in the past led to resection of these large nerves. The results were poor.

3. The special sensitivity of embryonal endothelial cells to growth factors and their angiogenic effect suggests a possible explanation for the frequency of a vascular component (angiodysplasia) in CSTD.

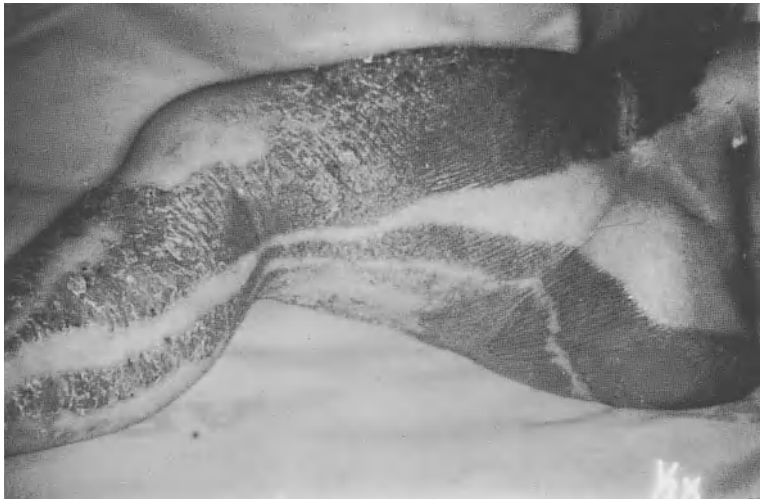


Fig. 21. Pure metameric ectodermal dysplasia

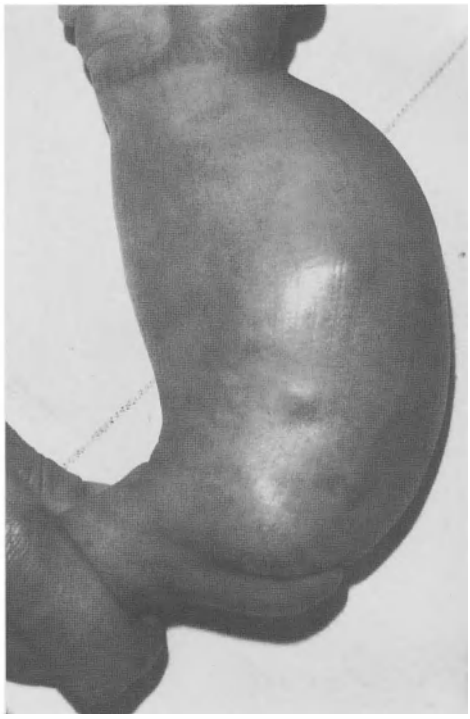
4. In-vitro sensitivity of structural glycoproteins, particularly fibronectin, to extrinsic effects is especially demonstrated with steroids, the antianabolizing and anti-fibroblastic effects of which have been proved [6, 17, 42]. The inhibition of collagen by steroids is likewise well established. The same mechanism probably explains the clinical effect of early steroid therapy of angiodysplasias and haemangiomas [8] during their initial postfetal phase of development.

5. A similar mechanism of cell dysregulation is observed in the rare, sarcoma-like congenital fibromatosis. If CSTD is the result of prenatal dysregulation of well-differentiated cells, the sarcoma-like congenital fibromatosis invariably appears at birth or during the first weeks after birth. The increased proliferation affects undifferentiated and immature fibroblastic cells. However diffuse and infiltrating the development of the tumour, definitive recovery is usually seen because of a spontaneous interruption of the cell proliferation process after the first weeks or months postnatally (Fig. 22–24). This suggests that, in this case, the same dysregulating process is affecting a remaining immature cell clone.

6. The pathogenesis of growth dysregulation in Recklinghausen's disease is totally unknown. It is suggested that the cell growth dysregulatory factors could have a genetic aspect. Also unexplained are rare recurrences, usually at puberty, of the dysregulatory process, which remains roughly proportional to growth. We have seen only one case of 'unstatic' dysplasia.

We believe that certain well-established data from fundamental cellular and molecular embryogenetic research suggest an – as yet incomplete – hypothesis to explain CSTD. There is no spontaneous animal model of this situation [3]. Our research protocol (Fig. 25) sets out the main sites of potential disturbances with control specimen of same localised normal tissues (Figs. 26, 27):

22



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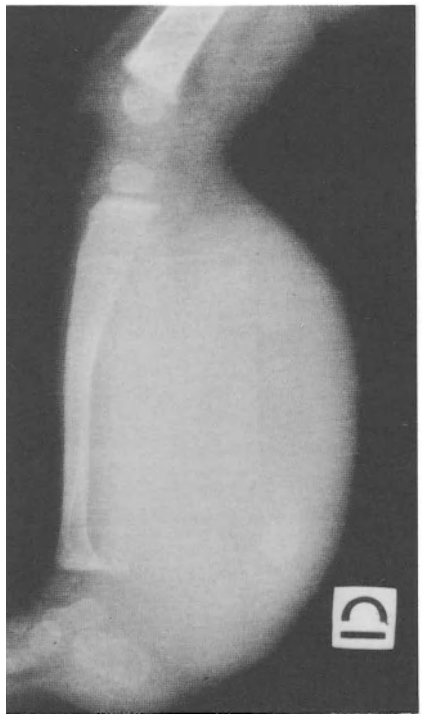

Fig. 22. 2-month-old boy. Congenital soft-tissue tumour of the leg

Fig. 23. Radiograph of the limb shown in Fig. 22

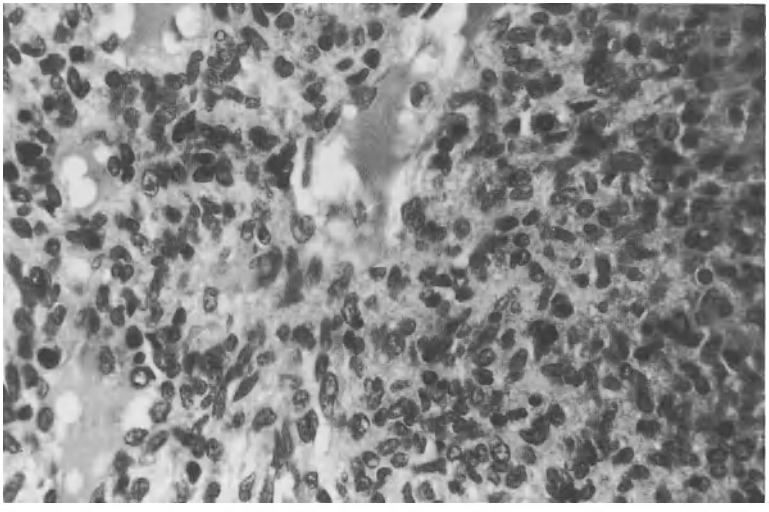

Fig. 24. Same patient as in Fig. 22: microphotograph. Sarcoma-like congenital fibromatosis

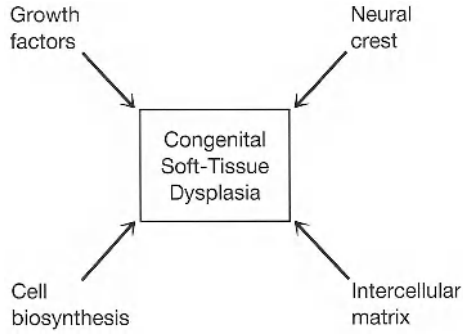

Fig. 25. Research protocol

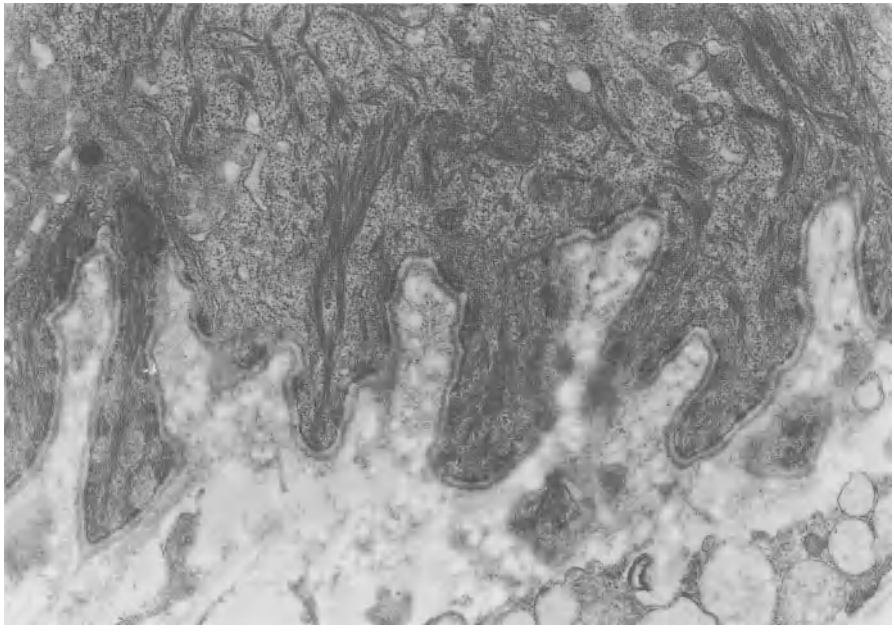

Fig. 26. Baby Dja., 1 year old. CSTD with right toe macrodactyly. Dermo-epidermic junction (× 22000). (By courtesy of Professor Da Lage)

1. Intercellular matrix anomaly (collagens and structural glycoproteins) or modification of cell environment
2. Localised cell mutations
3. Localised growth factor effect or receptor excess on target sites

It seems important to study CSTD tissue as early as possible after birth, because the disturbed cell proliferation mechanism will probably stop functioning shortly after birth [10].

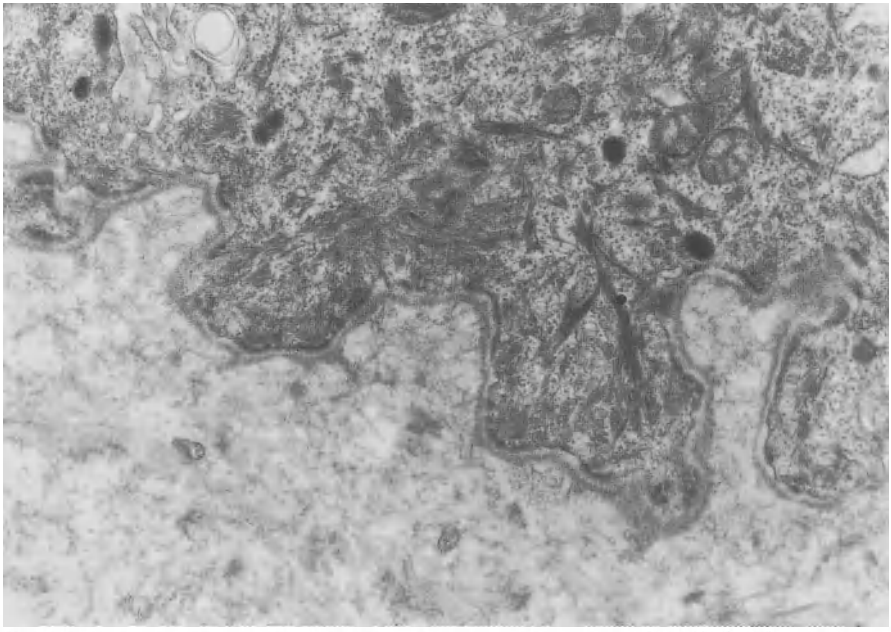

Fig. 27. The same patient as in Fig. 26. Left toe control specimen (× 34000). (By courtesy of Professor Da Lage)

Table 7. Protocol for clinical investigation of CSTD

Overgrown tissue or mass	Ultrasound CT scan
Skeletal dysfunction	Local, spine, skull, face, ± staged measurement
Vascular dysfunction	Angiogram (arteries and veins); Doppler (arteriovenous fistula); isotopic lymphogram
Visceral dysfunction	Renal, hepatic, ocular
Biological anomaly (of the neural crest)	Vanyl mandelic acid, vasoactive intestinal peptide, thyrocalcitonin

Clinical Investigation

Clinically, the concept of CSTD as an entity is used to categorise each case according to a full and rigorous protocol. Table 7 shows the protocol of the clinical study. It includes bulky tissues, tumour-like masses, skeletal, vascular and also visceral and potential endocrine dysfunction, especially according to the notion of segmentary and selective disturbance and possible neurocrestopathy.

Following this clinical investigation, it is obvious that the association of anomalies will occasionally suggest already known entities such as Recklinghausen's disease [2], Sturge-Weber syndrome [12, 31, 44], Bourneville's tuberous sclerosis, Klippel-Trenaunay-Weber syndrome [1], macrodactyly. However, in our experience, dysplasia of soft tissue appears preferentially unsystematised.

Stability of most CSTDs beyond their manifestations at birth or just after birth seems to be well established. Nevertheless, clinical follow-up will have to be rigorously carried out during infancy and childhood according to the new pathogenic concept. One male patient, presenting at birth with multifocal CSTD, had a delayed puberty. When he was 16 years old, a routine CT scan revealed an intracranial calcified area, suggesting the dysplasia to be the consequence of an associated early neural crest disturbance. Routine CT in another male patient, with hamartoma of the trunk and also a hemifacial hypertrophy, revealed a calcified diencephalic tumour.

Treatment

Treatment for CSTD must take into account the new concepts about this malformation entity. Of course, the diversity of anatomical and clinical phenomena excludes any systematisation. However, certain major facts must be taken into consideration before any therapeutic programme is embarked upon, especially surgery:

1. A dysplasic tumour takes the place of normal tissues. Resection will therefore lead to permanent loss, that later normal growth will not be able to make good.
2. Dysplasia usually involves both ectodermal and mesodermal tissue. Even when the skin is apparently normal, it always participates in the dysplastic process.
3. The dysplastic area is along the pathway of normal blood supply or lymph vessels. Any local resection may therefore interrupt the normal flow and may be responsible for blood or lymph stasis. This can stimulate over growth of tissue in the vicinity of the remaining dysplasia. This is often observed in the tongue or peripharyngeal area after partial resection of facial or cervical dysplasia, in the perineum and genitals after partial resection of thigh dysplasia, and in the retroperitoneal area or organs (rectum or bladder) after resection of lower limb angiodysplasia [4]. It is therefore imperative to confirm deep vessel integrity before any proximal or extended resection of the dysplasia.
4. CSTD is a benign malformation. It involves normally coded and differentiated cells without any risk of malignancy (except for some neurofibromatosis and melanotic tumours).
5. CSTD is a stable congenital anomaly (except in Recklinghausen's disease). There is no risk of recurrence or metastases.
6. Overgrowth after partial resection may occur at the site of localised or residual dysplastic tissues. This is usually secondary to an inflammatory process or local vascular stasis. The same effect can be seen after local trauma, especially if it affects the vascular component of a hamartoma.
7. Increased size of bone is relatively stable. The therapeutic approach is therefore entirely different from the usual approach in cases of length difference of acquired or congenital bone hyperplasia.

In conclusion, the treatment of CSTD is restricted and is often disappointing. The function must be considered more important than the cosmetic appearance. Therefore, indications for surgery should be limited and the surgery moderate. In our institution, we only perform full resection of localised or segmental CSTD when an autoplasty can be performed [34, 35]. When dysplasia extends over a full upper or lower limb we strictly limit our surgery to cases with significant functional handicap such as inability of the child to wear normal clothes. In these cases, we perform a staged remodelling resection and plasty, producing a fair functional but poor cosmetic result.

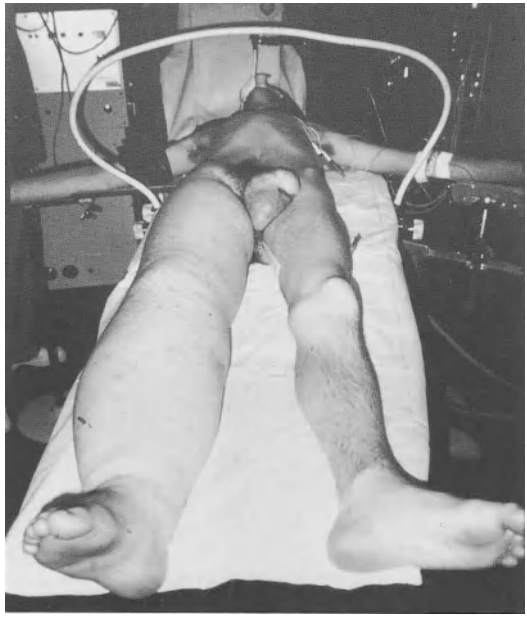

Fig. 28. 14-year-old male. CSTD of the right leg without angiodysplasia

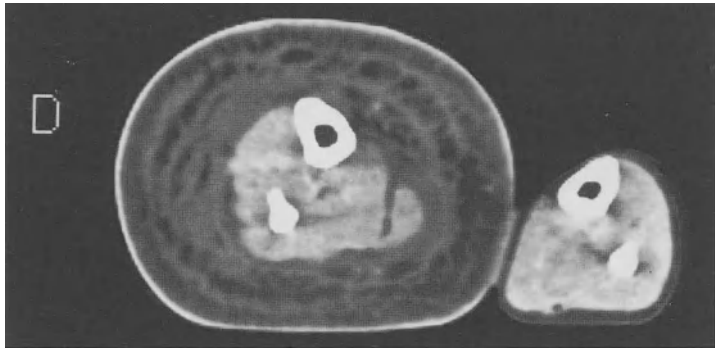

Fig. 29. The same patient as in Fig. 28. CT scan of both legs

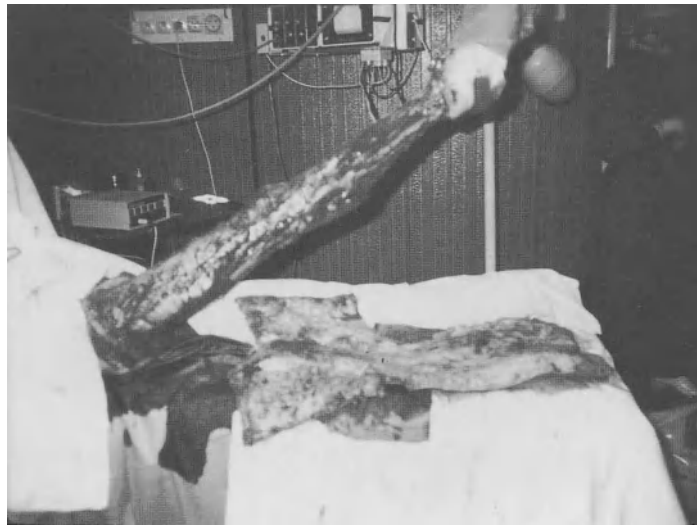

Fig. 30. The same as in Fig. 28, during surgery. Complete resection of soft tissues (11 kg), then autograft

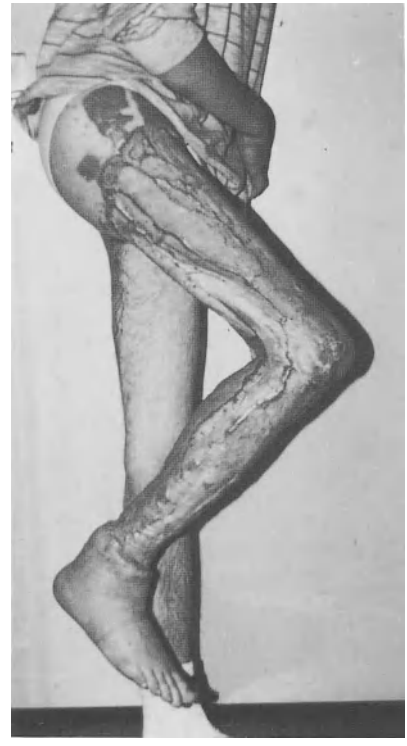

Fig. 31. The same patient as in Fig. 28, 6 months after surgery

Two cases of monstrous full lower limb CSTD were cured by total soft-tissue excision and primary auto-skin graft covering (Figs. 28–31).

Some dysplasia with gigantism, macrodactyly and macropodia, often associated with other sites of dysplasia, has required local surgery because of severe dysfunction. Several poor results from classical reconstructive surgery have led us to prefer determined functional surgery [22]. In some cases, fortunately rare, amputation followed by prothesis has been necessary (Fig. 32) and has been preferred to ambitious and fruitless reconstructive surgery.

Attention has recently been focused on some new techniques such as embolization [30] that result in significant improvement in some severe, predominantly angiodysplastic types of CSTD which are surgically uncorrectable (Figs. 33, 34). However, most CSTDs remain impossible to cure completely. Nevertheless, in spite of our inability to cure them, many of these unfortunate patients deserve more than mere curiosity for their anomaly or pity for their handicap. Our energies must be stimulated by the new concept suggested by the recent knowledge attained in fundamental embryology and cell biology. We must await identification of the initial mechanism of cell biosynthesis dysregulation before attempting to halt the process in utero. The treatment would then depend on prenatal diagnosis, which should now be possible using fetal ultrasonographic diagnosis.

Fig. 32. Only two patients of our series had limbs amputated. This one is the patient from Fig. 9, with normal activity after amputation and prosthesis

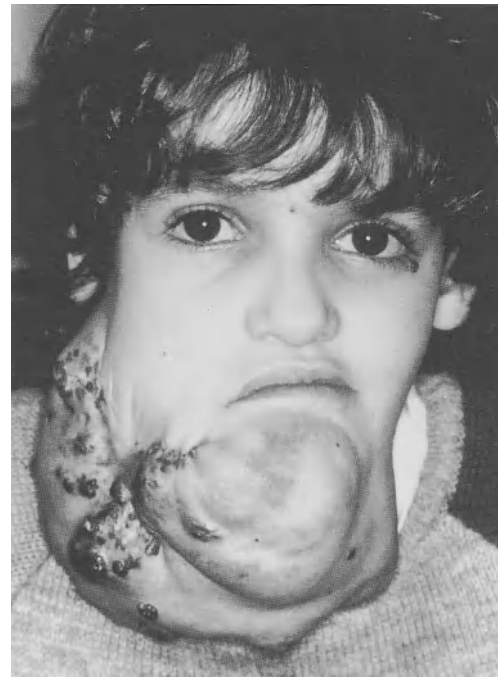

Fig. 33. Massive CSTD with angiodysplasia of the face and neck. Refused surgery. (By courtesy of Professor Merland)

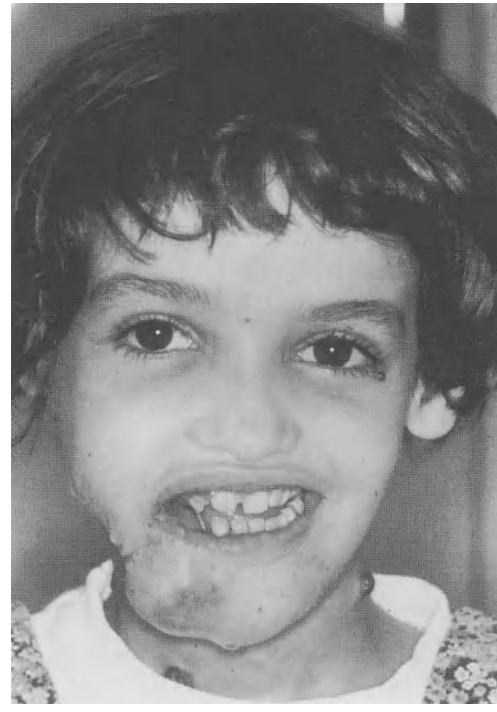

Fig. 34. The same patient as in Fig. 33, after embolization and block resection. (By courtesy of Professor Merland)

Acknowledgements. We wish to thank: N. le Douarin and J. P. Thierry (Institut d'Embryologie, Collège de France); L. Robert, A. M. Robert, G. Godeau (Laboratoire de Biochimie du Tissu Conjonctif, Centre National de Recherche Scientifique, No. 40); Y. Courtois (Institut National de la Santé et de la Recherche Médicale U. 118), and Mrs. Sengle (Institut de Zoologie, Grenoble). We are grateful to D. Sidi for critical reading of the manuscript.

Summary

We report 185 children with clinical manifestations of various conditions classically described as giant hamartoma, angiodysplasia, congenital hypertrophy, congenital trophoedema, localised gigantism (e.g. macrodactyly), etc. It is proposed to group all these conditions into a single entity: congenital soft-tissue dysplasia (CSTD).

According to recent advances in fundamental embryology and cell biology, CSTD appears to be a consequence of embryonal or fetal cell biosynthetic dysregulation. The concept of the CSTD entity leads to a common protocol for clinical investigation and a common therapeutic plan, with special reference to the stability and the benign nature of the condition.

Treatment should be confined to improving function rather than attempting to correct cosmetic deficits.

Résumé

Les auteurs rapportent 185 observations d'enfants présentant différentes situations cliniques connues et classiquement décrites sous les appellations d'hamartome géant, angiodysplasie, hypertrophie congénitale, trophoedème congénital, gigantisme localisé, macro- ou mégadactylie, etc. Ils suggèrent que ces anomalies localisées ou segmentaires, uniques ou multiples, plus ou moins associées les unes aux autres chez le même patient représentent une entité unique: la dysplasie tissulaire congénitale (congenital soft-tissue dysplasia; CSTD).

Selon les données les plus récentes de l'embryologie et de la biologie cellulaire fondamentale, CSTD semble être la conséquence d'une dysrégulation de la biosynthèse cellulaire embryonnaire ou foetale. Au-delà de l'intérêt de ce modèle clinique expérimental pour les progrès ultérieurs dans la connaissance de la biologie du développement des tissus des parties molles, cette nouvelle entité conduit à proposer un protocole d'investigations cliniques commun et une attitude thérapeutique commune dans tous ces cas, incluant certains syndromes cliniques bien connus (syndrome de Klippel-Trenaunay, de Sturge-Weber, maladie de Recklinghausen, etc).

Des remarques applicables à l'ensemble des CSTD doivent être prises en considération avant toute décision thérapeutique, en particulier la notion de stabilité et de bénignité de la dysplasie.

Le traitement doit se limiter au projet modeste d'une efficacité fonctionnelle plutôt qu'à l'ambition d'une restauration esthétique souvent décevante.

Zusammenfassung

Wir berichten über 185 Kinder mit unterschiedlichen Erscheinungen, die herkömmlich als Riesenhamartom, Angiodysplasie, kongenitale Trophoedem, örtlicher Gigantismus (z. B. Macrodaktylie) usw. gekennzeichnet werden. Wir schlagen vor, alle diese Erscheinungen als eine Entität zu verstehen: kongenitale Weichteildysplasie (congenital soft-tissue dysplasia, CSTD.

Nach jüngsten embryologischen und zellbiologischen Untersuchungen tritt die CSTD als Folge embryonaler oder fetaler biosynthetischer Zellfehlregulation auf. Das Konzept einer CSTD-Entität führt sowohl zu einem gemeinsamen Untersuchungsprotokoll als auch zu einem gemeinsamen therapeutischen Vorgehen unter besonderer Berücksichtigung der „Stabilität" und der Gutartigkeit des Zustandes. Die Behandlung sollte auf die funktionelle Verbesserung beschränkt bleiben, anstatt die Korrektur kosmetischer Defekte zu versuchen.

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Monoclonal Antibodies as Targeting Agents for Cytotoxic Compounds In Vivo: A Current Assessment

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Introduction

The idea of antibodies acting as magic bullets to target cytotoxic compounds selectively to specific sites in the body was introduced by Hericourt and Richet in 1895 [10] and Ehrlich in 1913 [7]. The use of hetero-antisera as a targeting medium has however, in many cases, been fraught with problems. These include difficulties in absorbing reagents to obtain sera of high specificity, and the irreproducibility of batches of antisera prepared in different animals [3, 13]. Despite this, several workers have successfully used radiolabelled polyclonal antisera for scintigraphic studies in patients with a variety of malignancies [2, 8, 16]. In addition, Order and Lenhard have used radiolabelled hetero-antisera to treat hepatocellular carcinoma and Hodgkin's disease [15, 20]. To avoid the problem of host antibody responses changing the pharmacokinetics of the targeting agent, they used antibodies prepared in a variety of different species.

With the ability to produce monoclonal antibodies, many of the problems associated with the use of hetero-antisera for in-vivo and in-vitro studies have been overcome [14]. However, despite many claims, that tumour-specific reagents have been produced, none of these has been substantiated [21, 25]. The availability of reagents that have a degree of specificity for different tumours has rekindled interest in the use of antibodies as targeting agents. A variety of studies have been undertaken showing the potential of radio-immunolocalisation of tumours in patients with different malignancies [17, 19]. In addition, anti-idiotype antibodies have been used therapeutically with some success in patients with B-cell lymphoma [18]. As yet, few studies have been described where monoclonal antibodies labelled with either drugs [24], toxins [30], or radionuclides [5, 12] have been undertaken. These have obviously been investigated in animal model-human tumour xenograft systems, and the most promising of these techniques for the eradication of solid tumours appears to be targeted radiation therapy. This review

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Progress in Pediatric Surgery, Vol. 22
Ed. by L. Spitz et al.

will attempt to cover some of the problems that have been encountered in our studies, in both animal model systems and patients, in trying to target ^{131}I to tumours derived from the neuro-ectoderm.

The Human Neuroblastoma-Mouse Xenograft Model System

The mouse monoclonal antibody UJ13A was produced following immunisation of mice with 16-week human fetal brain [1]. This antibody reacts with the majority of tissues derived from the neuro-ectoderm but does not bind to melanoma tissue. UJ13A was chosen for radio-immunolocalisation studies because the antigen recognised by the reagent is expressed in large amounts on human neuroblastoma cells. Radiolabelling of UJ13A with isotopes of iodine can be undertaken using either the chloramine-T technique or the iodogen method, without loss of antibody activity [11].

When radiolabelled UJ13A is injected into nude mice xenografted with human neuroblastoma, the antibody selectively localises to the tumour. This is not the case when an irrelevant antibody (FD44) not binding to neuroblastoma tissue is used (Table 1). Although there are considerable differences in the uptake of relevant and irrelevant antibodies between tumours in different mice, the median ratio of UJ13A: FD44 uptake was 7:1. No selective binding of UJ13A was found in any other tissue. This is not surprising as, in indirect immunofluorescence studies, the antigen recognised by the monoclonal antibody has not been detected in any murine tissues [1]. Calculation of the amount of UJ13A taken up into the xenografts shows that this was also extremely variable. Approximately 6% of the injected dose of conjugate per gram of tumour was detected in the human tissue after 24 h. Although no dosimetry studies using the gamma camera were undertaken on individual mice, analysis of the data from 25 animals killed at different

Table 1. Ratio of specific to non-specific monoclonal antibody uptake in human neuroblastoma xenografts and normal tissues in nude mice

Organ	Median	Range
Tumour	7.0:1	1.0:1 – 20.00:1
Liver[a]	1.0:1	0.9:1 – 1.15:1
Spleen[a]	1.5:1	0.7:1 – 2.00:1

[a] Other organs, namely, kidney, lung, adrenal, muscle, and brain gave specific: non-specific ratios within the same range as calculated for liver and spleen

37 nude mice xenografted with the TR14 human neuroblastoma cell line were injected with 15 μCi of ^{131}I conjugated to either 1.0 μg UJ13A or FD44. Animals were killed at set intervals and the ratio of specific (UJ13A) to non-specific (FD44) antibody uptake into equivalent weights of tissue was calculated. Results were pooled over a 9-day period as no statistical difference in the ratios found on different days could be determined

Table 2. Percentage of radiolabelled antibody UJ13A taken up into human neuroblastoma xenografts in nude mice

Days after injection	Percentage of injected dose ^{131}I/UJ13A per gram tumour			
	Mean	Range	Median	No. animals
1	9.1	0.8–20.6	6.0	3
4	7.9	1.4–26.0	6.1	7
5	6.6	2.3–23.0	4.8	9
7	5.1	1.3–16.6	2.4	6

times after antibody injection indicated that the half-life of the conjugate in tumour tissue is 2–4 days (Table 2).

Using increased quantities of ^{131}I-conjugated UJ13A (150 μCi/10 μg protein), regression of neuroblastoma xenografts in nude mice was observed [11]. Over a 21-day period, tumours of (approximately) 1.0 cm^3 regressed to 10% of their original volume. Repeated injection caused tumours to apparently disappear, but regrowth at the original site always occurred. Selection of cells that were negative for the UJ13A antigen did not occur during repeated administration of radiolabelled antibody to mice. No tumour regression was observed even when a 10-fold excess of non-radiolabelled antibody was injected into animals. Tumour kill could be blocked by prior injection of mice with a 50-fold excess of non-radiolabelled antibody 24 h before administration of the ^{131}I/UJ13A conjugate. Only ^{131}I/-antibody conjugates produced a therapeutic effect when administered to mice xenografted with human tumours: ^{125}I and ^{123}I/UI13A conjugates had no effect upon tumour growth. Emissions from ^{131}I are therefore most likely responsible for the tumouricidal effects of this antibody conjugate. No adverse physiological effects were seen in mice even when injected with 450 μCi radiolabelled antibody over a period of 160 days [13].

Radio-Immunolocalisation of Neuro-Ectodermally Derived Tumours Using Monoclonal Antibody UJ13A

General Protocol for All Patients

Ethical committee approval for these studies was obtained from each hospital involved and individual patient consent given for each scan. All patients were given Lugol's iodine solution (0.2 ml × 3 daily) for 3 days prior to radiolabelled antibody injection, and this was continued throughout the scanning period, so that uptake of free ^{131}I into the thyroid was blocked. All patients were skin tested for hypersensitivity to mouse immunoglobulin (Ig) by intradermal injection of 10 μg of UJ13A. Each patient received 100–300 μg of UJ13A radiolabelled with either 2.0–2.5 mCi ^{123}I or 0.9–2.3 mCi ^{131}I intravenously as a bolus. Scans were performed

with either a Scintag Berthold LFOV gamma camera or a General Electric Maxi camera linked to an Informatek Simis 3 or DEC PDP 11 computer respectively.

Neuroblastoma

None of the patients had a positive reaction to the skin test or demonstrated any adverse side effects at the time of antibody injection or subsequently. In our initial study, primary tumours were visualised in six patients who had a mass that had been demonstrated by other imaging modalities [9]. In the three in whom no primary tumour was detected by ^{131}I/UJ13A scan, two were "in complete remission", and no primary tumour had ever been detected in the third.

Ten other sites in this group of patients were demonstrated to take up ^{131}I/UJ13A. Of these, seven were known sites of metastatic disease. Two of the three remaining areas of antibody uptake were subsequently shown to be tumour sites that had not been identified by other imaging modalities. The final site was a false positive, never proven to be involved with tumour [9]. In addition, ^{131}I/UJ13A was not taken up by two sites that were demonstrated to be involved with tumour by other techniques.

All the sites at which tumour was visualised were evident by 24 h, although in those patients who underwent ^{131}I-labelled UJ13A scanning, clarity of images improved by the 3rd day as the blood pool levels decreased. Scans of the head showed virtually no antibody in the brain and orbital regions (Fig. 1). Thyroid uptake was effectively blocked by Lugol's iodine solution in all patients who com-

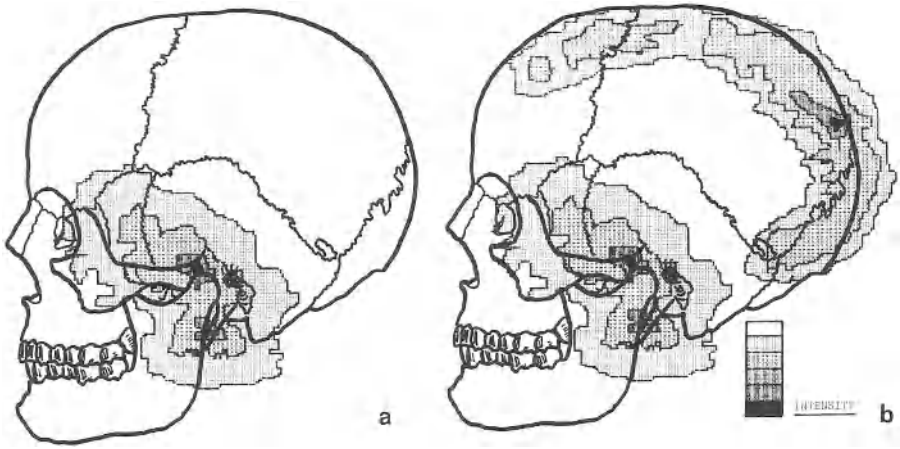

Fig. 1a, b. Isocontour maps of uptake of radiolabelled UJ13A into the head. **a** Normal image representing antibody in blood vessels and soft tissues of the neck. **b** Uptake of ^{131}I/UJ13A into the vault of the skull. Image taken 11 days after administration of 50 mCi ^{131}I/UJ13A. Considerable "flaring" on the image is noted, characteristic of the imaging of ^{131}I. In neither case is antibody found in the eye or brain, because of the brain and retinal blood barriers

plied with the suggested oral regimen. Visualisation of adrenal glands not thought to be involved with tumour was observed in three patients. Non-specific uptake of ^{131}I/UJ13A into liver and spleen was a consistant finding in all scans, although the degree of uptake was found to be variable.

In these studies, it was not possible to determine accurately the percentage of radiolabelled antibody targeted to tumour sites, as these were not resected directly after scintigraphy. No comparison could, therefore, be made between the amount of radiolabelled antibody taken up into patients' tumours and that taken up into human neuroblastomas xenografted into mice.

Scintigraphy of Brain Tumours

Although the UJ13A antigen is expressed on many normal neural tissues, the experience gained with neuroblastoma patients indicates that the antibody does not cross the blood-brain and retinal blood barriers respectively [31, 32]. The specificity of the reagent as determined by indirect immunofluorescence studies on frozen sections is different to the 'operational specificity' observed in vivo. Breakdown of the blood-brain barrier has therefore to occur for radiolabelled antibody to gain access to intracranial tumours. This may occur to varying degrees in either the same or different tumour types [32]. Patients should first receive a 99m-Technetium scan as a prerequisite to show blood brain barrier breakdown before attempting radioimmunolocalisation of intracranial malignancies.

In our first study using radiolabelled UJ13A alone, a good correlation was achieved between antibody scans and [99m] technetium images, although the time when the optimal image was obtained differed for the two agents [23]. Resection data, however, showed that only a small proportion of the injected antibody was targeted to tumour (Table 3). This contrasts to the 6% of radiolabelled UJ13A per gram of tumour targeted to neuroblastoma xenografts in mice (see Table 2). In addition, analysis of antibody uptake within a tumour showed that more radiolabel was associated with necrotic tissue and cyst fluid than with viable tumour areas.

In view of these findings, it was decided to investigate further the specificity of these scintigraphic images using additional radiolabelled antibodies. This is particularly pertinent to brain tumours, as it has been known for 30–40 years that once blood-brain barrier disruption occurs brain tumours can be imaged using non-selective radiolabelled proteins such as albumin [28]. Two patients were given radiolabelled antibody conjugates that, according to frozen section data, should not bind and thus not localise to tumours. In both cases, positive images were obtained by scintigraphy. A secondary carcinoma was imaged with ^{131}I/UJ13A, and a primary glioma with HMFG2 [29]. This reagent, of the same isotype as UJ13A, was raised against milk fat globule membranes and human epithelial cells, and on frozen sections does not bind to gliomas (20/20 tested).

To investigate these findings further, a second group of patients were given both UJ13A to which ^{131}I was attached and the irrelevant antibody HMFG2 to which ^{125}I was coupled. After surgery, analysis of resected tissue showed a very

Table 3. Percentage of injected dose of radiolabelled antibodies found in tissue resected after radioimmunological studies

Patient	Tumour sample	Percentage of injected dose/gram of tumour		
		^{131}I/ UJ13A $\times 10^{-6}$	^{125}I/ HMFG2 $\times 10^{-6}$	Ratio UJ13A: HMFG2
1	A	79.04	79.83	0.9
	B	90.24	84.33	1.07
	C	109.80	93.84	1.17
2	A	29.95	26.74	1.12
	B	36.38	31.09	1.17
	C	10.19	8.93	1.14
3	A	6.07	8.67	0.77
	B	26.90	23.39	1.15
	C	31.74	28.95	1.11
4	A	1.55	2.01	0.77
	B	2.16	2.76	0.78
	C	4.04	5.38	0.75
	D	2.58	3.44	0.75

Patients were injected with both relevant (UJ13A) and irrelevant (HMFG2) antibodies radiolabelled with ^{131}I and ^{125}I respectively. Following scintigraphy studies, tumours were resected and the percentage of antibody per gram of tumour was determined. The ratio of ^{131}I/^{125}I was determined as a reflection of the selective uptake of UJ13A into primary brain tumours

low percentage uptake of radiolabelled antibody per gram of tumour, and the ratio of UJ13A: HMFG2 in the tissue was approximately 1.0 (Table 3). Thus, no specific uptake of antibody into relatively large primary malignancies could be demonstrated. It is not, at present, clear whether this is also the case for neuroblastomas and other tumours, or whether the nature of the blood-brain barrier compounds difficulties in obtaining selective antibody uptake into intracranial malignancies. Certainly Mach et al. [16] have demonstrated specific anti-carcinoembryonic antigen uptake in patients with carcinomas of different types. Unfortunately, many scintigraphy studies using antibodies have not, for ethical or other reasons, incorporated the use of irrelevant antibodies.

Targeted Radiation Therapy for Patients with Neuroblastoma: A phase 1 Study

Study 1 (Fig. 2)

Following radio-immunolocalisation studies in patients and a small toxicity study in which primates were administered high doses of ^{131}I/UJ13A, a phase 1 study

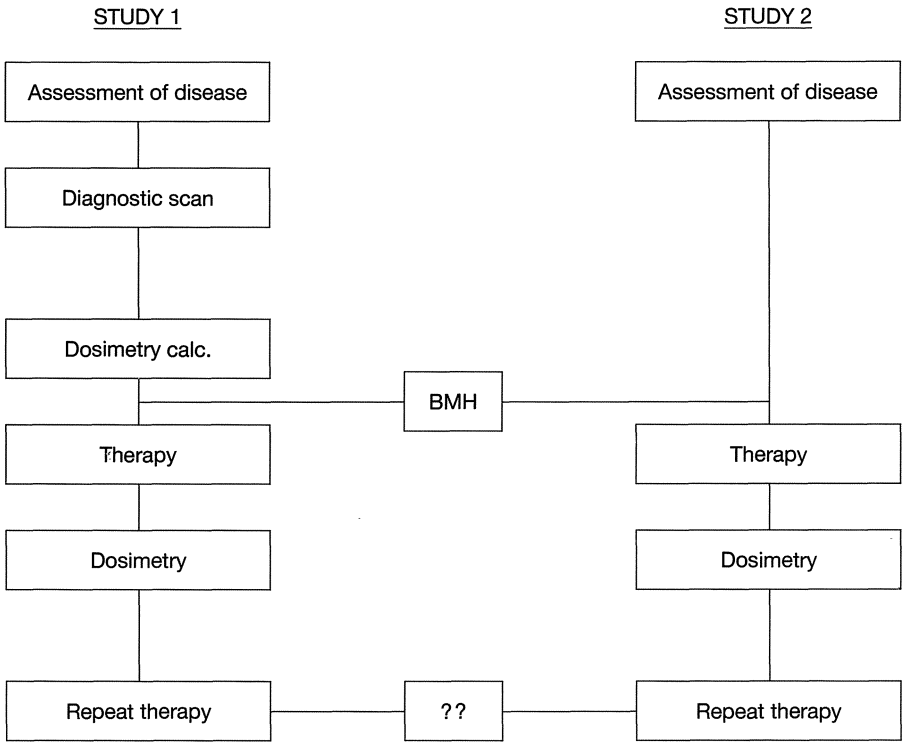

Fig. 2. Protocols of original phase 1 study (study 1) and modified phase 1 study (study 2) to investigate the toxicity of ^{131}I/UJ13A given to patients with neuroblastoma. *BMH,* bone marrow harvest

was begun in children who had either not responded to or had relapsed after conventional chemo-radiotherapy. Ethical committee approval was obtained from all hospitals involved and patient/guardian approval sought after full explanation of the purpose of the study. To ensure that the risk to individuals was kept to a minimum at all times, it was decided to undertake diagnostic scans on all patients, so that the radiation dose to tumour, liver, spleen, and bone marrow could be calculated. In addition, the total body dose of radiation could be determined from the gamma camera images and the biological half-life of the conjugate in the blood. From this data it was hoped to check that the dose of ^{131}I/UJ13A that was to be given to a patient would not result in radiation damage to any organ.

Antibody preparations for patients 1, 2, 3 and 5 were undertaken at the ICRF laboratories, where UJ13A was radiolabelled in small batches (1.0 mC/30 μg protein). This was to ensure that conjugates were essentially free of aggregates and contained less than 5% free iodine. Moreover, radiolabelling in this way reduces radiolysis of the conjugates and keeps to a minimum the radiation dose to personnel handling the material. Antibody preparation for patient 4 was undertaken, by

Amersham International, in a single-step procedure. All preparations were administered to patients as soon as possible after radiolabelling and were shown to contain Ig molecules that had not been damaged by the procedure.

Patients

Patient 1 (JS) presented with stage IV neuroblastoma in April 1982. Radiographs showed the presence of a mediastinal mass and analysis of bone marrow aspirates and trephines indicated the presence of tumour cells. Catecholamine levels in the urine were found to be elevated. Following six courses of OPEC (VM26, cis-platinum, vincristine, cyclophosphamide; Fig. 3) a thoracotomy was performed and mediastinal lymph nodes removed. Viable tumour was identified in these nodes. After two further courses of OPEC a recurrence of the paraspinal mass was noted and a bone scan showed residual 'hot spots'. Two further courses of OPEC were followed by biopsy of cervical lymph nodes, bone marrow and a lesion in the femur. The cervical lymph node clearly showed the presence of viable tumour. In February 1983 JS underwent a diagnostic UJ13A scan (2 mCi ^{131}I/180 μg UJ13A) and 4 weeks later it was decided to administer 35 mCi ^{131}I bound to 18 mg protein.

Side effects of therapy were minimal. A transient rise in the patient's temperature to 39°C was noted. Mild nausea followed and the patient was lethargic for 36 h. White blood cell and platelet counts did not fall significantly following administration of the conjugate. The patient was well at the time of antibody administration and remained so for 5 months. CT scans were not performed before and after ^{131}I/UJ13A therapy, making objective assessment of any benefit to the pa-

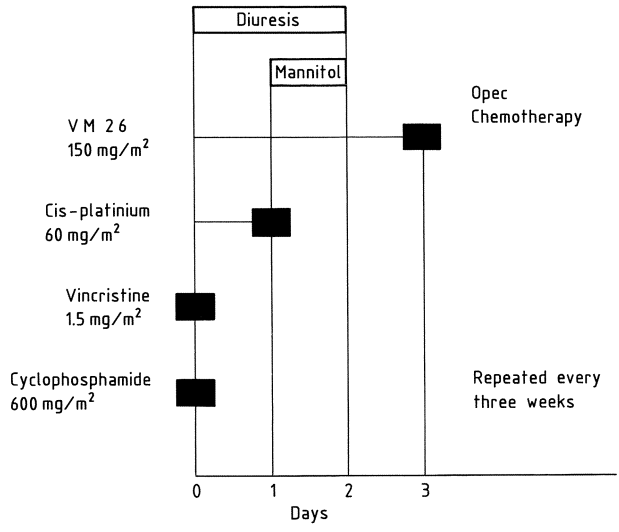

Fig. 3. Protocol of OPEC chemotherapy given to children with stage III/IV neuroblastoma

tient impossible. At relapse, the therapeutic procedure was repeated but despite a negative skin test the radiolabel was rapidly excreted. No therapeutic benefit could therefore be expected. Serum samples were not analysed to see if the dramatic change in the pharmacokinetics of antibody handling were due to the presence of mouse Ig-specific antibodies.

Patient 2, aged 6, presented in August 1981 with stage IV neuroblastoma. Following one course of CVA/DTIC (cyclophosphamide, vincristine, doxorubicin adriamycin), dimethyl-triazeno-imidazole-carboxamide), she was given ten courses of OPEC chemotherapy (Fig. 3). She remained well until late 1982 when she again presented with active disease. In January 1983 she was given two courses of total body irradiation (TBI; 2×50 rads), DTIC ($200\,mg/m^2$) and doxorubicin ($30\,mg/m^2$) and was given a tracer amount of radiolabelled antibody for scintigraphic studies. Dosimetry calculations indicated that a therapeutic dose of 50 mCi ^{131}I/UJ13A should deliver no more than 60 rads to the bone marrow. As with patient 1, a slight rise in body temperature and transient nausea were noted on antibody administration. Six days later the patients blood count fell rapidly. A hypocellular bone marrow was found on aspiration and the patient had to be supported by transfusions.

Scintigraphy studies after therapy showed localisation to tumour throughout the abdomen and pelvis. At this time it was noted that the patient's thyroid showed ^{131}I uptake. It was subsequently ascertained that the patient had failed to take the Lugol's iodine prescribed to block ^{131}I uptake. However, calculations revealed that less iodine was present in the thyroid than in tumour tissue, indicating that the biodistribution of the ^{131}I had been markedly changed following conjugation to immunoglobulin. No other dosimetric studies were possible on this patient and no therapeutic benefit was achieved. The patient did not recover bone marrow function and died 12 weeks after therapy.

Patient 3 was a 2.5-year-old boy who had shown a partial response to 11 courses of OPEC (Fig. 3). Bone marrow aspirates showed 3%–5% tumour cell contamination and bone scans indicated abnormalities in the vault of the skull and tibia. To avoid the problem of irreversible aplasia resulting from targeted radiation therapy, bone marrow was harvested, purged of tumour cells with monoclonal antibodies and magnetic microspheres, and cryopreserved. Following diagnostic scans the patient received 55 mCi ^{131}I/UJ13A. No immediate side effects of therapy were noted, but 1 week after administration of the conjugate, white blood cell and platelet counts dropped markedly. The patient was supported with transfusions (red blood cell and platelet) and haemopoietic function recovered after 5 weeks without the need to give the cryopreserved bone marrow. Scintigraphic studies demonstrated a significant radiation dose to liver and spleen (approximately 800 rads). However, no elevation in liver function tests (serum glutamic oxalo-acetic transaminase, serum glutamic pyruvic transaminase, lactate dehydrogenase) was noted. The whole-body dose to the patient was calculated to be 61 rads.

The patient received benefit from the procedure as his bone marrow cleared of tumour cells for 8 months (determined by histological and monoclonal antibody

studies on multiple bone marrow aspirates). Furthermore, the tumour sites in the vault of the skull and tibia were noted on radiological examination to be improved (see Fig. 1). On relapse the patient was re-treated with ^{131}I/UJ13A therapy, but, as with patient 1, the pharmacokinetics of antibody handling had changed and the conjugate was rapidly excreted from the body.

Patient 4, aged 7, with stage IV neuroblastoma, began OPEC chemotherapy in August 1982. During the second course of therapy, an anaphylactic reaction to VM26 was observed. After one further attempt at administering VM26 was made (OPEC course 3), this drug was replaced by VP16. Following three courses of this treatment the patient relapsed and was given two courses of TBI (2×50 rads), DTIC (200 mg/m^2) and doxorubicin (30 mg/m^2). Four weeks later, the patient was given a scanning dose of ^{131}I/UJ13A for dosimetry studies and bone marrow was harvested, purged of tumour cells and cryopreserved. Although it was planned to continue the phase 1 study with a dose of 60 mCi, only 45 mCi conjugate was available. This was given 6 weeks after the diagnostic scan. A moderate anaphylactic reaction to mouse Ig was noted but was controlled by corticosteroids. This occurred despite the patient's having had a negative reaction to the skin test. The biological half-life of the conjugate in this patient was extremely short (less than 24 h). After this period, only 1.0 millicurie of the injected dose remained in the patient and therefore no tumoricidal effect could be expected. The study was not repeated due to the presence of mouse Ig-specific antibodies in the patient's serum.

Conclusions from Study 1

1. Toxicity to bone marrow was noted at a dose of ^{131}I/UJ13A of approximately 50 mCi, although this may be dependent on the amount of prior therapy.

2. Little therapeutic benefit was observed in patients 1, 2 and 4 where large tumour masses were present. This may be due to the small amount of conjugate taken up into primary tumours (see above, pp. 37–39). Access of antibody to tumours via the vasculature may be a limiting factor in considering targeted therapy to relatively large tumour masses.

3. A response to targeted therapy was noted in patient 3 who had diffuse chemo-resistant disease. In this instance, access of antibody to tumour is maximized. Patients with minimal disease – that is, highly radiosensitive – are those who will benefit most from targeted radiation therapy.

4. To maximize information gained from these studies, a thorough investigation into the patients' status should be made prior to targeted therapy. This was difficult in this group of children due to their rapid relapse and poor general condition.

5. Administration of diagnostic amounts of radiolabelled UJ13A to determine tumour and normal tissue uptake can only be detrimental to the patient. This can lead to the development of mouse-specific antibodies in the patient's serum and this is suggested to dramatically affect the biodistribution of the conjugate in vivo. In addition to more rapid blood clearance, an anti-mouse response may lead to greater levels of ^{131}I/UJ13A being targeted to the reticulo-endothelial system, including bone marrow.

6. Bone marrow should be harvested, purged of tumour cells and cryopreserved to overcome unexpected bone marrow toxicity occurring in heavily pretreated patients.

On the basis of these conclusions, we have begun a second phase 1 study in which patients do not receive diagnostic scans prior to therapeutic administration of radiolabelled UJ13A. In addition, a full assessment of the extent of the patient's disease prior to targeted radiation therapy is made (bone scan, CT scan, ultrasound, urine catecholamine determinations, and serum measurements of mouse Ig-specific antibody and circulating antigen). One patient has so far been entered into this protocol.

Study 2 (Fig. 2)

Patient 5 was a 7-year-old boy who was diagnosed as having stage IV neuroblastoma in July 1984. He presented with difficulties in walking, ataxia, abnormal eye movements and limb pain. Investigations at this time showed elevated urinary catecholamines (homovanillic acid), a paravertebral mass on radiography, and multiple bone abnormalities seen on bone scan. A right suprarenal mass and tumour in the left lobe of the liver were noted on ultrasound and neuroblasts that were UJ13A-positive were identified in the bone marrow. Between July and November, the patient was given six courses of OPEC chemotherapy (see Fig. 3). In November, a laparotomy revealed an inoperable tumour which, on biopsy, appeared mainly calcified and necrotic but contained small foci of viable neuroblastoma. After four further courses of OPEC chemotherapy a CT scan revealed little change in the size of the primary tumour. However, in May 1985 a repeat CT scan showed an increase in the retrocrural mass of lymph nodes, suggestive of tumour recurrence. Bone marrow was harvested, purged of tumour cells (0.1%–1.0% contaminated by immunohistology) and cryopreserved.

The patient received 50 mCi ^{131}I/UJ13A (6.0 mg protein) on the 25th June 1985. No acute adverse side effects were noted and no fall in blood count was observed. Scintigraphy studies indicated little antibody uptake in the area shown by CT scan to be involved with tumour. The patient continued to decline after antibody therapy, suggesting that no benefit was received from the procedure. More patients will have to be treated on this protocol before conclusions about toxicity and the effectiveness of therapy can be made.

This patient further illustrates a major problem associated with targeted radiation therapy to primary tumour masses. Access to relatively large, partially necrotic tumours from the vasculature appears highly variable between patients. In diagnostic studies, uptake of radiolabelled UJ13A into neuroblastomas has been variable between patients, with some imaging well and others only imaging via a 'negative filling effect' on the scan. The reasons behind these differences remain unclear. Obviously, one possible explanation is the degree of tumour vasculature present, although this cannot fully explain the differences observed. Our current imaging study for neuroblastoma patients is to investigate the relative qualities of

two agents, radiolabelled antibody and the radiopharmaceutical meta-iodobenzylguanidine (MIBG). Occasionally in this study, patients have imaged with MIBG but not at all with ^{131}I/UJ13A. This might suggest that the tumour vasculature can be selectively 'leaky' to molecules of different size. In this instance, molecules of less than 1000 molecular weight (mol. wt.) pass through the capillary bed of the tumour, whereas large Ig molecules (150000 mol. wt.) are restricted. A similar phenomenon has been observed on imaging primary brain tumours: in some cases a brain tumour has been imaged using 99m technetium (less than 1000 mol. wt.) but not using radiolabelled antibody [23]. Further studies using $(Fab)_2$ and Fab monomers of 100000 and 50000 mol. wt. respectively may clarify some of the difficulties in targeting antibodies to primary brain tumours.

Conclusion

The studies undertaken to date have been somewhat disappointing in terms of the concept of the 'magic bullet'. From data being obtained currently, it would seem that, if targeted radiation therapy has a role in the treatment of malignant disease, it will be in the eradication of small tumour clumps. Furthermore, unless the problems associated with changes in pharmacokinetics of antibody handling on multiple injections are solved, further restrictions will be mandatory. However, the idea of targeted radiation therapy remains important even when viewed in this limited context. The long-term side effects of this type of treatment may be far less than those associated with TBI. It is possible that targeted radionuclide therapy could replace TBI in protocols giving high-dose chemo-radiotherapy as a consolidation procedure [22].

The use of targeted radiation therapy in body cavities has been explored by Epenetos et al. [5]. Following from these studies, Coakham et al. [4] have used ^{131}I/antibody therapy intrathecally in patients with malignant disease. One of three patients currently studied has shown a response to this type of therapy. This person presented with malignant meningitis arising from a pineocytoma, a tumour that is highly radiosensitive. This observation gives further credence to the suggestion that small clumps of tumour are those most amenable to antibody targeted therapy. Further work may reveal a role for this in the treatment of metastatic medulloblastoma and leukaemia/lymphoma where there is CNS involvement. This could be important, as external-beam craniospinal irradiation (18–24 Gy) currently given to children has been shown to result in patients' having a considerably diminished IQ [27]. On a more speculative basis, targeted antibody therapy may be useful if directly introduced either into residual tumour or the tumour bed at the time of surgery.

All of these observations point to the conclusion one might expect from the history of malignant disease, namely that instant answers do not exist, but with sufficient time and effort a therapeutic advantage may be gained via the use of monoclonal antibodies conjugated with either radioisotopes or other toxic compounds.

Summary

Monoclonal antibodies have proved useful in the in vitro diagnosis of tumour type. Radiolabelled antibodies have also been investigated as targeting agents for the in vivo diagnosis of tumour metastasis. These studies have revealed the potential of using 'targeting agents' to identify tumours, but in addition have exposed some of the problems associated with the technique. This review describes our experiences using radiolabelled antibodies for the identification and treatment of tumours arising from the neuro-ectoderm. Based on a small number of 4 patients studies, we conclude that there are limitations on the use of radiolabelled antibodies for targeting isotopes to primary tumour masses. In addition, we outline a possible important role for antibodies in targeting therapeutic agents to minimal residual disease and diffuse tumours presenting as micro-metastasis.

Résumé

Les anticorps monoclonaux se sont révélés très utiles pour le typage in vitro d'un tumeur. Les anticorps marqués à l'iode radioactif ont aussi été examinés pour savoir si la cible serait aussi atteinte lors du diagnostic in vivo de métastases. Ces études ont prouvé l'utilité de ces marqueurs pour l'identification des tumeurs mais ont aussi révélé les problèmes inhérents à cette technique.

Cet article décrit nos expériences avec les anticorps marqués à l'iode radioactif pour identifier et traiter les tumeurs neuroectodermiques. Sur la base d'un petit nombre de 4 cas, nous en avons conclu que l'usage d'anticorps marqués à l'iode radioactif pour placer des isotopes dans les tumeurs primaires reste limité. En outre, nous faisons état du rôle important de transporteurs que pourraient jouer les anticorps pour délivrer des substances thérapeutiques au niveau de tumeurs résiduelles très petites ou de micrométastases.

Zusammenfassung

Monoklonäle Antikörper haben sich bei der in vitro Typisierung eines Tumors bewährt. Es wurde auch untersucht, ob radioaktiv markierte Antikörper bei der in vivo Diagnose von Metastasen als „targeting agents" eingesetzt werden könnten. Die Studie hat diese mögliche Verwendung bestätigt und gleichzeitig die damit verbundenen Probleme gezeigt. Wir berichten über die Verwendung von radioaktiv markierten Antikörpern bei der Erfassung und Behandlung von ektodermalen Tumoren. Aus unserer Erfahrung mit einer kleinen Anzahl von 4 Fällen stellen wir fest, daß die Verwendung radioaktiv markierter Antikörper zum Transport von Isotopen in Primärtumormassen eingeschränkt bleibt. Darüber hinaus erwähnen wir die Möglichkeit, daß Antikörper eine große Rolle beim Transport therapeutischer Substanzen in kleineren Resttumoren und Mikrometastasen spielen könnten.

Acknowledgements. This work was supported by ICRF, Bristol Brain Cancer Research Fund, the Newman Foundation and the Welton Foundation. We thank R. Richardson, G. Davies, S. Bourne, F. Gibson, L. Heath, B. Gregory and D. Golten for the excellent technical assistance. In addition, we thank the radiographers, doctors and nursing staff at Great Ormond Street, Frenchay Hospital, Bristol, and Our Lady's Hospital for Sick Children, Dublin. We are also grateful to S. Watts for typing the manuscript.

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Bulk Disease as the Major Problem in the Cure of Paediatric Sarcomas

P. N. Plowman

It is a misconception particularly prevalent amongst European paediatric oncologists that, because sarcoma has a propensity to metastasise, therefore only systemic therapy has a major role in management or is logical [1, 2].

The term "tumour bulk" is an umbrella term covering two related but necessarily distinguishable aspects of cell mass. The first relates to total cell burden (the number of malignant cells in the body), whereas the second relates to particular problems with large, bulky, conglomerate, and perhaps widely locally infiltrating tumour masses – usually, but not invariably, the primary.

Total Cell Burden and Chemoresistance: Theoretical Discussion

Skipper and colleagues elucidated many of the fundamental principles upon which modern cancer chemotherapy is based [3, 4, 5]. These workers demonstrated in animal tumour models that, after intermittent bolus cytotoxic chemotherapy, the cytocidal effect on the tumour cells is logarithmic (i.e. a certain dose x killed a constant fraction of cells irrespective of the number present at commencement of chemotherapy), *but* that there is always an inverse relationship between cell number and curability by chemotherapy. The conclusion appeared to be that chemotherapy would be curative if the presenting tumour mass/bulk/cell number was small enough for all the cells to be killed (or at least brought below critical threshold). During the same period, other workers demonstrated that the situation was much more complex: the growth fraction (the proportion of potential stem or clonogenic cells) in the tumour often being small, some of these cells resting (interphase or G_0), and some cytotoxic drugs being cell-cycle phase-specific, thus affecting cytocidal efficacy both with regard to tumour and normal tissue stem-cell kill.

Inherent in Skipper's conclusions is the problem of drug resistance, for otherwise chemotherapy that killed a fixed fraction of tumour cells with each course would eventually, normal tissue stem cells "willing", always be curative. Although some cells may adopt "Lamarckian tactics" to overcome the cytocidal effects of cytotoxic drugs to which they do not immediately succumb, nevertheless, the majority of resistant tumour cell clones appear to arise by "Darwinian" spontane-

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Progress in Pediatric Surgery, Vol. 22
Ed. by L. Spitz et al.

ous mutation followed by favoured selection. There is considerable evidence in mammalian cell systems that spontaneous/sporadic mutation to phenotypic drug resistance occurs more readily in a malignant cell line of genetically unstable cells than in a normally dividing and homeostatically regulated, regenerating human tissue (e.g. bone marrow, gut epithelium [6–9]. Goldie and Coldman estimate the rate of spontaneous mutation towards drug resistance in tumours as having a frequency of 10^{-5} to 10^{-6}. This estimate is of course dependent upon drug, cell environment, cell line and so on. However, the Goldie-Coldman theory of chemo-resistance [10, 11] is as good a contemporary model as any other of the development of tumour chemo-refractoriness and will be discussed further here. It is known that human tumours kill patients when there are approximately 10^{12} cells in the patient (perhaps 1 kg total mass of tumour), and that clinically 'early' palpable or radiologically visible (imaged) cancer is associated with a total cell burden of 10^8–10^{10} cells in the patient. Even with the most sensitive biochemical markers (e.g. AFP and βHCG for germ cell lineage tumours) human cancer detection is insensitive to a cell burden of less than 10^5 cells.

This being the case, a spontaneous mutation rate to drug resistance of 10^{-5} to 10^{-6} augurs badly for cure if cancer is usually clinically detected with a cell burden of 10^8–10^{10}. The Goldie equation $P \propto e^{-\alpha N}$ (P = probability of cure, α = mutation rate, N = tumour bulk) summarises the relationship of cure chance to cell number and mutation rate.

However, there are various 'tricks' to be played for therapeutic advantage – for example, combinations of drugs (in a manner analogous to the use of combination drugs in the chemotherapy of tuberculosis) – to reduce the emergence of resistance. If the patient presents clinically with 10^{10} cells and one in a million (10^{-6}) is the chance of drug resistance to a single 'effective' cytotoxic drug, then 10^4 cells are going to be potentially resistant in that patient and these will grow selectively if 'less fit' surrounding cells are dying due to drug action. Combinations of drugs or early sequential use of drugs will reduce the chance of double or triple or even quadruple drug-resistant cells arising (e.g. MOPP chemotherapy for Hodgkin's disease). However, the use of these multiple non-cross-resistant drugs must be early, before the regrown tumour is itself composed of cells already resistant to the first drug. In this latter case, one is back *in statu quo ante* – or perhaps even worse. An alternative to combination cytotoxic chemotherapy is a very highly effective single agent, particularly if the mutation to drug resistance is a multi-step process; is this why bulky Burkitt lymphoma has been cured by cyclophosphamide alone, or is it because the α value is low in these cells?

In the last paragraph I suggested that the delayed introduction of non-cross-resistant therapy might worsen the cure chance: why? Firstly, the type of resistance developed to drug A may not be completely different to that giving resistance to drug B. Secondly, if drug A is a mutagen, it may increase the genetic instability of even those cells that are resistant to its cytocidal actions. Thirdly, the resistant cells to drug A will multiply during drug A therapy and $P \propto e^{-\alpha N}$ applies to drug B at the level of N encountered when drug B is first administered. It is fairly universally true throughout human cancer medicine that tumours that grow

through, or even respond and then relapse through, first-line chemotherapy will not respond well to second-line drugs.

Recently, multidrug-resistant phenotypes (pleiotropic drugs resistance, PDR) have been described as a spontaneously arising phenomenon in mammalian cells and the first described PDR phenomenon appears to be a property of the altered cell membrane [9, 12].

Goldie and Coldman have published computer programmed models of optimal chemotherapeutic strategies. They assume that tumours are chemocurable if no permanently resistant cell lines are present. However, the chance of cure rapidly diminishes with the appearance of a single resistant cell line (R_1) if there is only one effective therapy (T_1) available, or with the emergence of a double resistant line (R_{1-2}) if two equally effective therapies are available (T_1 and T_2). T_1 and T_2 may be two single cancer drugs or two non-cross-resistant drug combinations. In their model, they have programmed in known human cancer characteristics, assuming, for example, a presenting mass of 10^{10} cells, a tumour doubling time of 36 days, a two-log cell kill with each once 3-weekly bolus chemotherapy, and a natural resistance mutation frequency of 10^{-5} to 10^{-6}. They assume that T_1 and T_2 are equally effective therapies but cannot be given simultaneously. Analysis of their model predicts that alternating cycles (T_1, T_2, T_1, T_2, etc.) will be superior to sequential use (T_1, T_1, T_1, T_1, T_2, T_2, T_2, T_2, etc.) because the latter scheme allows the development of a doubly resistant clone more readily than the first scheme. Thus, whilst continual use of T_1 alone may allow a dramatic clinical remission (remembering that a clinical 'complete remission' may be less than a 99.9% cell kill of 10^{10} cells – i.e. leaving 10^7 cells behind), but within the surviving R_1 cells, the R_{1-2} cells will develop more advantageously [10, 11].

The conclusions from these works are that one must maximise therapy in the early period of treatment using different non-cross-resistant modalities (to maximal advantage). Thus, whilst the tumour is still responding to T_1 (used to maximal advantage), T_2 (used to maximal advantage) must be brought in – and T_3, if it exists – before returning, without delay, to T_1. If, for example, T_1 is transiently highly myelosuppressive and T_2 transiently causes chemical conjunctivitis, then the therapeutic ratio may be enhanced by such alternation of T_1, T_2, T_1, T_2; indeed, T_1 and T_2 alternating courses may be condensed in time, as their side effects are dissimilar and recovery from T_1 is not essential prior to T_2, etc. Condensing T_1, T_2 alternate courses in time reduces the tumour cell multiplication between cycles and is again advantageous.

Conglomerate Bulky Masses of Cancer

Malignant solid tumours usually present because of symptoms from a bulky primary tumour mass. Local and regional cancer treatment (that is, cancer surgery and radiotherapy) have cured a substantial fraction of patients with most types of cancer for the greater part of this century to date. Although the additional adjuvant chemotherapy has, certainly in the paediatric field, further increased survival

for some patients (including those with recurring paediatric tumours), and has represented a major advance in cancer treatment, regional treatment nevertheless also has cure potential by itself. In adult cancers, where adjuvant chemotherapy is less well established and usually not employed, there is no doubt that the size of the primary tumour mass negatively influences the local control rate and cure rate by both surgery and radiotherapy. This is best documented for breast cancer, head and neck cancer and melanomata, but is also true for bladder or colorectal cancer or even bronchial carcinoma. Not only is the surgeon unable to obtain clear and generous margins around cancers that are widely infiltrating surrounding tissues, but it is also widely acknowledged that, in cases of head and neck cancers involving cartilages or bone, such invasion immediately reduces radiocurability. The same is probably true for other tumours, and in the paediatric field a parameningeal rhabdomyosarcoma with extensive bony destruction of the base of skull is rarely sterilised by even combined chemo-radiotherapy.

So here the problem is not only of cell numbers with the problems of $P \propto e^{-\alpha N}$ as described above, but also the added problem of sterilising a big conglomerate mass of tumour cells, often poorly vascularised and often infiltrating viscera, bone, cartilage, etc., or else causing critical normal tissue compression.

It is usually true that tumour angiogenesis is deficient and larger masses of tumours containing relatively hypoxic cells with poor nutrition and living in acidotic conditions often develop necrotic centres. However, many cells within such a tumour survive and, although hypoxic and resting in G_0, nevertheless retain the clonogenic capacity which would become active should their environment improve. Even under the adverse conditions, with their high radioresistance (as hypoxic cells are anything up to three times more radioresistant than non-hypoxic cells) and chemoresistance (at least in the sense of lack of drug penetration), they remain a formidable problem.

The growth of a bulky primary tumour is often slower than that of its small bulk metastases elsewhere in the body, both because of an enhanced cell-loss factor (although the cell-loss factor for sarcomas appears less than for carcinomas [13]) and because the impaired nutrition due to deficient angiogenesis is more growth-retarding or exaggerated when the tumour bulk is larger. Although all human tumours appear to grow along a retarded exponential (obeying Gompertzian kinetics), the mathematical modelling of a solid tumour's growth nevertheless involves more retardation constants or more complex formulation than that of a fluid phase malignancy (e.g. leukaemia), almost certainly because of this nutrition deficit.

With all these problems for radiotherapy and chemotherapy with the big single mass of cancer, perhaps surgery is important even if macroscopic (although smaller bulk) disease is left behind. This principle of debulking surgery even in the presence of metastatic peritoneal disease is well established in ovarian cancer [14] as primary therapy. In the paediatric field it is also well established, but is often delayed and sandwiched into a chemotherapy regime: e.g. delayed nephrectomy after chemotherapeutic clearance of lung secondaries in a child presenting with stage IV Wilms' tumour. This last example appears entirely logical and, whilst the

primary, bulky renal mass is still responding, might be expected to further reduces the chance of an emergent R_{1-2} clone in the kidney or renal bed. However, De Vita [15] does not agree on this point 'Attempts to improve responses to chemotherapy by "debulking" operations to reduce tumour mass and favourably alter cell kinetic characteristics have not been successful in increasing cure rate... Since mutation towards resistance is mass related, patients with large masses of cancer prior to debulking already have a high likelihood of having developed at least one and probably more than one resistant cell line. If these lines have metastasised widely prior to reductive surgery, reducing the mass, while it may improve response to chemotherapy, will not likely improve curability...' I would suggest that whilst these comments may theoretically be correct, they are counter-intuitive given the problems with conglomerate masses per se and the obviously greater number of cells (by several log orders) in one site than in any other (and $P \propto e^{-\alpha N}$), particularly when these are considered together with the known cure potential of surgery for early stage disease – to take again the responding Wilms' IV tumour exemplified above.

With radiotherapy there is no access problem, as the ionising radiation reaches every cell in its path irrespective of blood supply, visceral infiltration etc. It is also true that, when viewed alongside single anticancer drugs, radiotherapy remains the most powerful anticancer agent known (surgery excluded). However, it is still a regional therapy, and, although the ionising radiation reaches all the cells, it is not equally effective in all. The hypoxia problem in particular leads to radioresistance.

The objective of a radical radiotherapy course is to achieve a high total dose delivered. This objective is compromised if the surrounding normal tissues are sensitive to radiation damage and restrict the therapist's dose prescription. The radical objective is also compromised if the volume that requires irradiation (i.e. tumour plus extensions) is large, as, in general, large volumes of the body can be irradiated to modest doses but only small volumes to radical high doses. The shrinking field technique (i.e. reducing the volume irradiated after a moderate dose equivalent, boosting only the more resistant tumour centre to a high dose) is now an established and logical technique [15]. The use of initial chemotherapy, which both reduces the tumour size somewhat and improves vascularity/nutrition to the tumour before radiotherapy, is also established and logical.

Actually, returning to the Goldie-Coldman model, I view radiotherapy as regional T'_2 for sarcomas, whilst vincristine – actinomycin D – cyclophosphamide (VAC) type chemotherapy is both regional and systemic T'_1. As I will argue below, the proven improved local control rates for the alternating T'_1, T'_2, T'_1 approach for Ewing's sarcoma and rhabdomyosarcoma occurring in the face of high death rates due to metastatic disease (which has only undergone VAC, i.e. T'_1 only) ought to be instructive. This is particularly so when we consider that most of these children present with a bulky primary tumour and invisible (to clinical and radiological/imaging investigations) metastases, and yet die from the latter.

Whilst initial chemotherapy may obscure the immediate need for local therapy in each individual child to therapists considering their options early in the course

of the disease, nevertheless, the data reviewed below cry out the necessity of early, adequate local therapy.

Rhabdomyosarcoma: Clinical Management

The distribution of primary sites of paediatric rhabdomyosarcomas includes orbital (9%), other head and neck (34%), and genitourinary sites (30%) [16]. The majority of patients present because of bulky primary masses and without evidence (clinically, imaging, bone marrow sample) of metastatic disease. The discussion to follow is confined to these apparently non-metastatic cases. Certain tumour sites give a better prognosis (e.g. orbit, anterior facial, paratesticular) than others (e.g. parameningeal, prostatic) and this is important with regard to intensity of recommended therapy (see below).

Radical surgery, usually comprising extensive surgical procedures (e.g. amputation, orbital or pelvic exenteration, etc.), was historically the first successful method of treatment. Such early surgical series reported long-term survival of up to 48% of patients with orbital tumours and 73% of patients with bladder tumours [16]. However, the surgery involved was usually extremely mutilating.

The introduction of radical radiotherapy for these patients soon led to the recognition that local control could be achieved in a high percentage of cases by high-dose (50–55 Gy – conventionally fractionated for a paediatric population) and wide-field radiotherapy. Thus, for orbital primaries, radical radiotherapy could achieve a 90% local control rate (and two-thirds survival), whilst avoiding enucleation/exenteration [17]. Radiotherapy to this dose equivalent will itself have sequelae in a growing child and these can be serious.

In the early 1970s adjuvant combination cytotoxic chemotherapy – notably, once 3-weekly vincristine, actinomycin and cyclophosphamide in dosages sufficient to give a moderately severe myelosuppression at days 9–15 with count recovery by days 17–21 – made an impact on local control and survival. Firstly, these three agents, all lifted from the top of the single-agent activity table for this tumour, were (as expected) more effective in combination than singly. Secondly, the drugs could initiate cytoreduction and so help the radiotherapist, often hampered by poorly vascularised and large hypoxic conglomerate tumour masses. Lastly (and this has still not been clearly worked out), it is possible that, together with chemotherapy, lower doses of radiotherapy are necessary (see below). In the last decade, doxorubicin (adriamycin) has been acknowledged as another first-line drug and in some centres it replaces actinomycin in the above-mentioned triple drug regimen. Additionally, recent years cyclophosphamide and other alkylating agents have been recognised as potent mutagens whose contribution to sterility and second malignancy (notably leukaemia) in the late follow-up of cancer patients is great. These last observations have bearing on my current recommendations on adjuvant chemotherapy for low-risk cases of rhabdomyosarcoma.

The synthesis of the understanding of the therapeutic potential and unwanted sequelae of surgery, radiotherapy and chemotherapy in the 1970s led to best con-

ventional treatment recommendations for rhabdomyosarcoma, and such recommendations are still valid:

1. Radical resection of easily excised tumours, followed by radiation (if resection margins showed incomplete excision), followed by adjuvant VAC for 1 year or more.
2. Initial chemotherapy (2–3 cycles of pulse VAC only), followed by surgery or radiotherapy or both, after which pulse VAC is continued for one year or more. This approach is used for lager invasive tumours or those that are not so easily resectable at presentation.

Several groups have now a greater than 10-year experience with such treatment policies and have reported adequate numbers of patients for analysis of such policies and some variations from these themes.

The Children's Solid Tumour Group (CSTG), comprising a collaborative group from St. Bartholomew's Hospital and the Royal Marsden Hosptial, London, reported 73 patients treated broadly according to the above policies. The extent of the local disease at presentation was found to be the major prognosticator of outcome. Children with tumours confined to the tissue of origin had a predicted 5-year survival rate of 86%, whilst this survival rate was 21% for children where there was extension outside the tissue of origin [18]. The best survival rates were seen in children with tumours of the orbit, with a predicted 5-year survival rate of 94%. The survival for children with tumours in other head and neck sites was 50%, but these could be clearly divided into a group with superficial tumours (e.g. parotid, anterior facial) with no bone erosion and a good outlook, and a group with extensive spread around the base of skull or sinuses and usually extensive bone destruction, who had a very poor outlook (the so-called parameningeal group). Boys with paratesticular tumours and girls with vaginal tumours had 5-year survival rates of 81% and 67% respectively, whereas children with primaries at other pelvic sites did much worse, with only 31% surviving at 5 years. Age did not appear to influence outcome. Embryonal histology appeared a more prognostically favourable microscopic diagnosis than alveolar histology [18].

A later analysis of CSTG data discloses new information. Of 102 children presenting to CSTG participants over a 13-year period and with a minimum of 2 years' follow-up, 54 have relapsed. Of the 54 relapsers, the primary site was the first site of relapse in 35 patients (65%), whereas distant metastatic disease was the cause in 19 (35%; Fig. 1). The relapse rate at the primary site is considerably higher in this CSTG series than in the comparable American (IRS) series (see below). It seemed that radiotherapy was given less routinely in the CSTG series, being withheld from cases that the physician in charge felt to be at low risk. Of the 35 relapsers at the primary site 15 cases had received no radiotherapy, two cases received less than 20 Gy, a further four cases received less than 40 Gy and the other 14 cases received over 40 Gy (Fig. 2). Looking at this CSTG data the other way around, 64% of patients not receiving radiotherapy to the primary site relapsed locally, whereas 31% of patients receiving radiotherapy relapsed locally (I. E. Kingston and P. N. Plowman, unpublished CSTG data). The local relapse

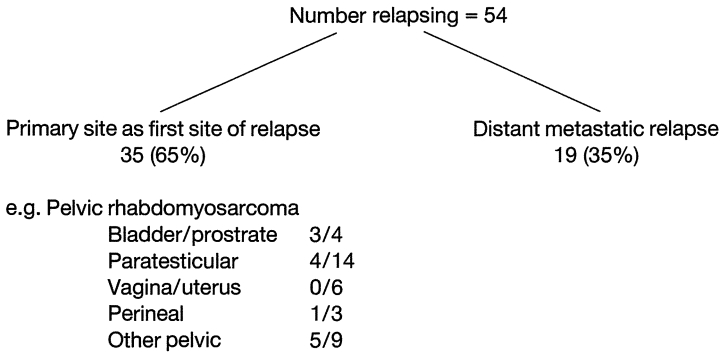

Fig. 1. Analysis of sites of relapse in 102 children presenting with rhabdomyosarcoma 1970–1983

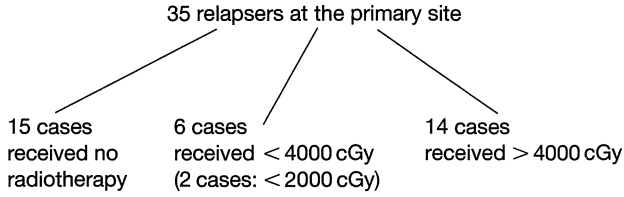

Fig. 2. Analysis of relapses at primary site according to radiotherapy dosage

rate in the comparable IRS trials employing routine radiotherapy is considerably lower (M. Tefft, personal communication, 1985).

The American Intergroup Rhabdomyosarcoma Study (IRS) has collected and analysed data concerning large numbers of children treated on protocols based broadly on the above treatment principles. In 1982 the IRS reported 202 children with primary rhabdomyosarcomas of head and neck sites so treated. The relapse-free survival rates were 91% (21/23) for orbital primaries, 46% (20/44) for those with parameningeal primaries and 75% (27/36) for those with tumours in other head and neck sites. Of 33 relapsers, 19 relapsed locally, and 15 of these 19 had presented with 'parameningeal' tumours [19]. These data represent a clear demonstration of the extreme difficulty of local control of parameningeal primaries, also reflected in the CSTG data.

The IRS data on bladder and prostatic tumours is also important. In their first study, IRS-1, 64 patients were treated broadly according to the above cited principles. Nineteen of the 64 patients relapsed, none of whom were in the group of eight patients whose disease was localised to the tissue of origin and completely excised. Ten of the 19 relapses occurred with tumours of the pelvis; one other relapser is documented as peritoneal, and a further one as having multiple sites [20]. Thus 10–12 of the 19 patients relapsed locally in this study; local control was also a problem in the CSTG experience (see Fig. 1). Hays et al. [20] conclude:

1. Pelvic exenteration (anterior in most cases), when combined with local radiotherapy and appropriate chemotherapy, results in high rates of survival. It may also be successful in the salvage of patients in whom other surgical (or non-surgical) approaches have failed. The sequelae of anterior exenteration, however, make it desirable to attempt to find other forms of therapy.
2. Partial cystectomy must be perfect (i.e. tumour excision without microscopic residual or nodal involvement) to be successful. If it is incomplete or nodes are involved, lethal relapse usually follows.
3. The primary chemo-radiotherapy approach was inferior to pelvic exenteration with respect to overall survival in the IRS-1 series, but this group did not employ the most intensive pulse VAC regimen used in the most successful primary chemo-radiotherapy series. Finally, Hays et al. concluded that patients can be salvaged by exenteration after failure on a primary chemo-radiotherapy regimen if the decision for surgery is not delayed.

However, radiotherapy to high dose equivalent to the bladder may lead to late bladder dysfunction, even haemorrhagic cystitis, occasionally necessitating cystectomy; radiation enteropathy also occasionally occurs. In an attempt to avoid radiation complications, the IRS group initiated a study (IRS-2) of primary chemotherapy in the treatment of children with bladder-prostate tumours [21]. This study (29 cases) represented an attempt to avoid, firstly, pelvic exenteration and, secondly, the irradiation of pelvic organs. Limited, but significant, success was achieved for the first aim, because 11 patients (38%) of the total group (52% of survivors) had functional bladders and survive without recurrence. However, with regard to the second aim, results were disappointing as only 2/29 (7%) achieved a successful outcome without either radiotherapy or tumour excision, and only 3/29 (10%) without radiotherapy or exenteration. An update on a larger number of patients treated by the IRS group with primary pulse VAC chemotherapy for bladder-prostate tumours has shown that 90% of such patients will later require radiotherapy, and that the survival of those coming to radiotherapy later rather than earlier is worse (M. Tefft, personal communication, 1985). I currently believe that unless a lesion arises in the bladder dome and is amenable to complete excision by partial cystectomy, radiotherapy must be given and placed early in the treatment programme.

A primary chemotherapy approach was also attempted for 81 children with rhabdomyosarcoma (arising in all body sites) by the European International Society for Paediatric Oncology (SIOP) [1]. This study comprised initial pulse VAC chemotherapy, after which, in responders, chemotherapy was continued without local therapy, whilst non-responders moved to radical local therapy. There were 15 poor responders who went to local therapy and 33% survived. In the good VAC responder group the survival was only 39%. The local relapse rate is not documented, but in the discussion section of the paper it is stated that no patients with bladder or prostate primaries achieved a complete response to chemotherapy alone. With such an extremely low overall survival rate (37%) and with such a high implied local recurrence rate in pelvic primaries, this author finds illogical

SIOP's continued advocacy [2] of the strategy of primary chemotherapy only, particularly when the IRS and CSTG data support a combined modality programme for high survival rates. All the existing data on the management of bladder/prostate rhabdomyosarcoma suggest that a regime of primary and radical surgery plus radiotherapy plus chemotherapy is best, that a primary chemo-radiotherapy regime is often safe with surgery as a salvage procedure if necessary, but that a primary chemotherapy regime is quite frankly dangerous. The only exception to this might be small bladder dome tumours with a favourable histology.

However, is it really essential to reach doses in the region of 50–55 Gy, as advocated by early IRS protocols? In an article from Memorial Sloan Kettering Institute, 58 patients with embryonal rhabdomyosarcoma were analysed for local control versus radiation dose received [22]. This analysis is difficult: 58 patients are hardly enough for a significant analysis, and the study is further complicated by the use of different chemotherapy regimes and by the use of chemotherapy concomitant with radiotherapy (a practice many of us avoid, not only because of the radiosensitisation by actinomycin D and doxorubicin but also, in bladder-prostate cases, because of the chemical cystitis provoked by cyclophosphamide catabolites). Nevertheless, in Jereb et al.'s study [22], radiation doses of 30–40 Gy seemed as effective for local control of microscopic disease and doses of 40–50 Gy seemed as effective for control of bulky tumours as higher doses.

In the much larger IRS-1 analysis, doses below 40 Gy were associated with higher local relapse rates in older children and those with bulky tumours.

From the experience gained in the IRS trials, several important conclusions can be drawn and have been summarised by Donaldson [23]:

1. Prognosis worsen with increased tumour burden/staging.
2. For localised tumours, amenable to complete resection, margins clear of tumour microscopically: in the IRS Group 1, post-operative radiotherapy is unnecessary if the patient is given pulse VAC chemotherapy.
3. Pulse VAC chemotherapy is not superior to two-drug (vincristine and actinomycin D) chemotherapy for patients with only microscopic residual disease after surgery and to whom post-operative radiotherapy is given.
4. Four-drug (VAC plus doxorubicin) chemotherapy is not superior to VAC for those with advanced local tumours.
5. Any recurrence, local or metastatic, is associated with a poor prognosis.

To these five conclusions of Donaldson we could add a sixth, again drawn from IRS data, notably the update on IRS-2 (cited above):

6. Delayed radiotherapy reduces the chance of local control, and this conclusion entirely accords with Goldie-Coldman theory outlined in the introduction.

So where to do we go from here? I would suggest and advocate that the most important advances in the management of rhabdomyosarcoma in European children are that such children should be treated in cancer centres with disciplines other than paediatrics represented. Secondly, two-drug adjuvant chemotherapy (viz actinomycin D and vincristine only) should be introduced for cases with a

good prognosis (small bulk completely excised, or only microscopic residuum post-operative that has received 40 Gy plus). The avoidance of systemic alkylating agents from adjuvant chemotherapy regimens of young children with good prognosis is important. Thirdly, the early use of radiotherapy seems important, and conventionally fractionated dosages of 40 Gy for microscopic disease and 50 Gy for macroscopic disease are now advocated rather than higher dosage – this slight dose reduction will prove important with regard to late tissue morbidity, particularly in younger children. Except where early complete surgical excision has been achieved, radiotherapy remains vital. The more widespread availability of megavoltage electron sources and modern radiotherapy planning techniques are also important means of reducing normal tissue morbidity. Radiotherapy will remain a critical part of therapy, particularly as we attempt to reduce the chemotherapy by omitting the alkylator from pulse VAC in the good-risk children.

Donaldson's fifth conclusion, that any relapse is associated with a poor prognosis, is salutary and borne out by the CSTG also. Finally, therefore, before advocating any reduction in intensity of surgery, radiotherapy or chemotherapy for any patient, we must always remember that we are dealing with a considerably nastier tumour than uncomplicated Wilms' tumour or early-stage Hodgkin's disease with a favourable histology, and that, by and large, we have but one chance to cure the patient.

Ewing's Sarcoma: Clinical Management

Ewing recognised that the tumour that bears his name was 'highly susceptible to radium' [24] and radiotherapy has since been used to achieve local control in this disease. Higher total dosages of radiotherapy appear to be associated with higher local control rates. Thus, Fernandez observed a local control rate of 44% in 25 patients with doses of 40–60 Gy to the primary tumour but a 67% local control rate in 15 patients whose primary received 60–70 Gy [25]. Similarly, Chabora observed four local relapses among eight patients whose primary tumour had received 45 Gy or less but only two among nine patients whose primary had received 60 Gy or more [26].

In the 1970s, combination cytotoxic chemotherapy further increased the local control rate, improving overall survival by this means and by reducing the incidence of metastases [27].

Surgery with removal of the bone bearing the primary tumour has long been recommended for 'dispensable' bones (fibula, rib, clavicle) and radical excision of the whole rib bearing a Ewing's sarcoma – as a planned procedure sandwiched into a multimodality treatment programme – has been clearly demonstrated to improve local control [28]. Following the demonstration of poor local control of primary pelvic Ewing's sarcoma treated by chemo-radiotherapy alone, a more aggressive surgical approach has been advocated [29] and indeed there was a move (now arrested) back towards amputation for limb primaries on the other side of the Atlantic.

Table 1. Local recurrence incidences of Ewing's sarcoma: treatment results from Bart's/GOS and the IESS (the latter retabulated from [32])

	Number of patients	Local recurrence only	Local and distant recurrence	Total local recurrence
Bart's/GOS				
Limbs	20	1	2	3
Pelvis	16	6	5	11
Ribs	15	4	3	7
Others	9	4	2	6
IESS [32]				
Limbs	161	3	14	17
Pelvis	59	0	9	9
Ribs	14	1	0	1
Others	31	1	1	2

The problem of bulk disease in Ewing's sarcoma is an important issue. Thomas et al. [30] cite data from the Intergroup Ewing's Sarcoma Study (IESS) which demonstrate that patients with tumours of less than 10 cm diameter have a statistically significant longer disease-free survival than those with larger primary tumours. Jurgens et al. [31] found that patients with tumour volumes below 100 ml had a 75% relapse-free survival at 40 months, as compared to a 10% relapse-free survival at 40 months where the presenting primary mass was greater than 100 ml. Central and proximal primary masses (particularly pelvic) tend to be bulkier at presentation.

Thus analysis of local control rates and survival according to site of primary tumour have become the most important means of separating out results of treatment. The treatment results from St. Bartholomew's Hospital/Great Ormond Street Hospitals for Sick Children (Bart's/GOS) show a much poorer local control rate for pelvic than for limb primary tumours, and rib primaries also fare worse (Table 1). All these Bart's/GOS results are inferior to the results of the more aggressive chemotherapy IESS programme [32] (Table 1), although the 0/59 local recurrence rate cited by Perez et al. for pelvic primaries is at variance with a previous publication citing a 4/25 local recurrence rate [33], and many workers concur that the pelvis is a high-risk site for local recurrence [27, 34–37].

Among the Bart's/GOS patients, 12 out of 16 had primary tumours greater than 10 cm in diameter; indeed, we have CT scan measurements of pelvic primaries of up to 17 cm diameter at presentation, whereas for limb primaries, 10 patients out of 23 presented with masses greater than 10 cm in diameter. However, we have been displeased with our local relapse rates in pelvic Ewing's sarcoma and,

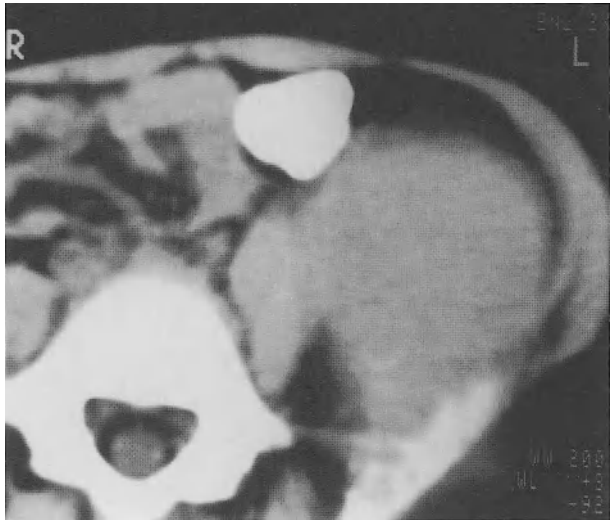

Fig. 3. CT scan cut at level of top of iliac crest showing a mass of Ewing's sarcoma

following publications of aggressive surgical resection of such primaries [29], it is now our policy to initiate therapy with chemotherapy and then, where possible, to proceed to surgical resection and follow this with radiotherapy before returning to adjuvant chemotherapy. Figure 3 shows the CT scan appearance of a Ewing's sarcoma of the iliac wing in a 7-year-old girl. The plain radiograph (Fig. 4a) shows well how the lesion is destroying the iliac bone. Following tumour shrinkage by chemotherapy, the child underwent radical surgical removal of the iliac bone (Fig. 4b). At this operation, the small bowel was temporarily moved out of the pelvis by use of an absorbable mesh [38] so that, post-operatively, a radiation dose in excess of 50 Gy could be given to the area at risk without fear of radiation enteropathy. This child's tumour was approximately 15 cm in diameter at presentation and she is currently 15 months from diagnosis and disease-free. She is amongst the first of the children receiving more aggressive local therapy for pelvic Ewing's sarcoma at this hospital.

In the limb primary tumour group local control has been less of a problem, with only one purely local relapse out of 20 patients in the Bart's/GPS series, (despite ten out of 23 with more than 10-cm-diameter primaries) and three out of 161 in the IESS series (Table 1). However, the radiation dose of 60 Gy advocated by the early workers [25, 26] together with the 'whole bone' radiation policy has led to unwanted late sequelae and second tumours within the high-dose zone. Thus, Lewis et al. [39] considered in 1977 that young children with lower limb primaries would be better amputated *ab initio* because of subsequent discrepancies in leg length. Given the enormous psychological blow that amputation creates, and given the high local control rates with chemo-radiotherapy, can the conclusions of Lewis et al. be substantiated? Jentzsch et al. [40] did not confirm them. In a larger

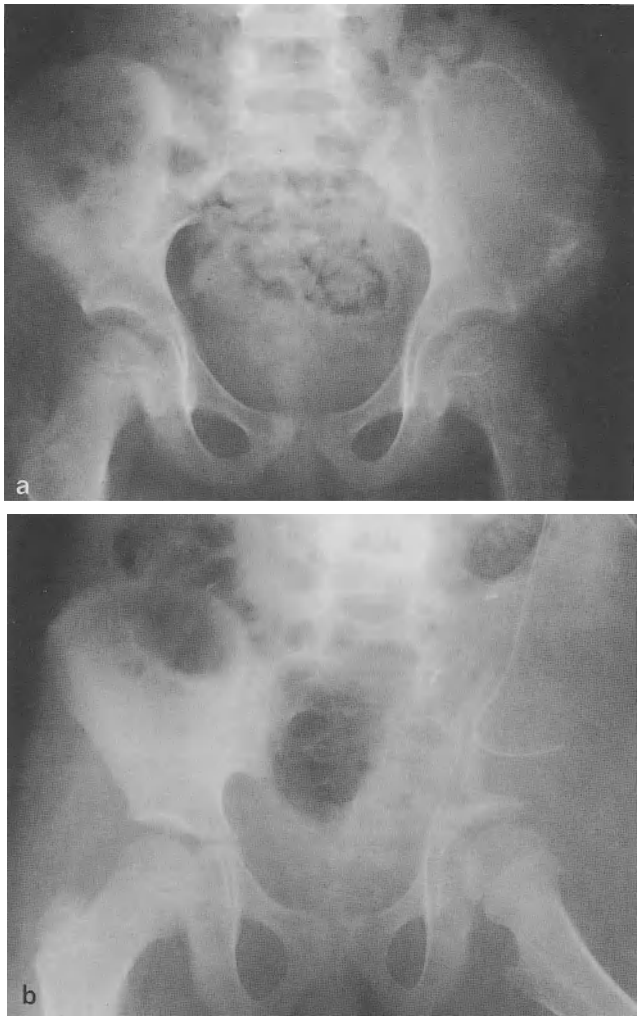

Fig. 4. a Plain radiograph of pelvis of child with a large Ewing's sarcoma of the iliac bone. **b** Plain radiograph of pelvis following chemotherapy and surgery; same patient as in Figs. 3 and 4a

study, Jentzsch et al. found that the majority of survivors of Ewing's sarcoma of the leg had minor functional limitations and small leg-length discrepancies. Thus our current policy of limb conservation seems justified.

Recent recommendations from IESS are reflected in my own practice and again will lead to lesser degrees of leg shortening, because it now appears to be safe to shield one or even both epiphyses of a long bone if these lie well away from the primary [32, 41]. Furthermore, with modern chemotherapy it is probable that

60 Gy is unecessary; 50 Gy for small bulk disease and 55 Gy for large bulk disease is my current recommendation, to be given by a shrinking field technique [42].

As regards Ewing's sarcoma of the rib, the Bart's/GOS series has a disproportionately large number over other institutions, due largely to a young child population that has presented to GOS in recent years. Our local control rates have been inferior to the IESS. In one American report, Thomas et al. found that seven out of eight patients who underwent complete surgical excision of the primary rib lesion remained disease-free, compared to four out of 12 after biopsy or only partial excision [28]. Our current protocols employ radical rib resection after initial 2–4 cycles of chemotherapy. Post-operative radiotherapy is essential where there is tumour residue at operation and may be indicated anyway. One of our local relapsers was a child whose operative histology was reported her to be clear of tumour at the resection margins; radiotherapy was withheld and she later relapsed locally and died. Once again it must be emphasised that the risk of relapse must be assessed at a tumour's first presentation, as the initial cytoreduction caused by primary chemotherapy may often obscure the need for radiotherapy and mislead clinicians into witholding essential local therapy.

The Sloan Kettering results in Ewing's sarcoma are worthy of note as they have used aggressive multimodality therapy (surgery, radiotherapy, chemotherapy) [43]: Five out of 48 patients who did not have post-operative radiation therapy had local recurrence as had six of 11 who did not have post-operative radiation therapy and all are dead. The difference is statistically significant ($P = 0.002$)... Treatment with all three modalities: pre-operative chemotherapy, surgery and post-operative radiotherapy results in higher survival rates as compared to those treated with two modalities only.

A further study from Sloan Kettering demonstrated that delayed radiotherapy in Ewing's sarcoma led to a significantly lower local control rate than radiotherapy sandwiched early into the chemotherapy (M. Tefft, personal communication). This again accords with the Goldie-Coldman model (see above).

The inferior local control and indeed distant control/survival figures at Bart's/GOS as compared to IESS have forced us to increase the aggressiveness of local therapeutic policies, both surgical and radiotherapeutic. It is also now clear that pulse VAC (or doxorubicin-VAC) chemotherapy is inferior to some of the more intensive American regimes.

Osteogenic Sarcoma

The problem of bulk disease in limb osteogenic sarcoma was until recently not a subject that would have merited discussion here, as amputation was the ablative therapy for the primary tumour and no other therapy was established. The major problem was, and still is, metastatic relapse. However, during the last 10 years several workers have claimed that adjuvant chemotherapy based on high-dose methotrexate alters the natural history of osteogenic sarcoma [44, 45]. There is no doubt that such drug regimes may cause substantial tumour-cell death in a large

conglomerate mass of primary osteogenic sarcoma, and indeed Rosen's group have found it useful to give pre-operative chemotherapy and to then gauge the efficacy of this therapy by the degree of tumour necrosis in the operative specimen [46]. Subsequent adjuvant chemotherapy following tumour resection is then based on the tumour responsiveness.

Two randomised controlled trials have recently been reported that appear to confirm the early workers' claims that adjuvant chemotherapy in osteogenic sarcoma increases survival [47, 48].

Pari passu with these adjuvant chemotherapy studies has been the surgical interest in limb preservation by transmedullary operations. As the medullary spread of osteogenic sarcoma is limited, transmedullary operations are theoretically safe (c.f. Ewing's sarcoma), and with the recent availability of new orthopaedic implants, limb preservation is now contemplated in most children with this sarcoma in a limb.

What militates against limb preservation is the familiar problem of bulk of disease. Regarding tumours with extensive soft-tissue extension, we have seen two children suffer local relapses after conservative surgery, and I am aware of similar problems occuring at the Middlesex Hospital and in Lyons (personal communication). Pre-operative chemotherapy may undoubtedly assist the surgeon in performing a surgical clearance of the tumour at limb-conserving surgery. The Los Angeles protocol is the most interesting protocol on trial at present, however, for not only is pre-operative chemotherapy being given, but also synchronous pre-operative radiotherapy using large-dose fractions [49]. As I have argued elsewhere regarding bladder cancer, whilst there is a real objection to large-dose fractions in radical treatment schemes where a high total dose is the main objective, there is no such objection to them in pre-operative treatment regimes where the normal tissues are only being taken to partial tolerance [50] – if there are good reasons in the first place for wanting large fractions to treat the tumour. Anecdotal experience with centrally placed and unresectable osteogenic sarcoma is that large-dose fractions are needed. Although radical radiation for this sarcoma was not a successful technique, partial tolerance prescriptions together with pre-operative chemotherapy for bulky primary tumours (for which there is a chance of limb preservation) once again leads us to the conclusion that multimodality therapy is required to overcome the problem of bulky sarcomas.

Summary

Bulk disease is a problem in all the major paediatric sarcomas. It is the pre-eminent problem in parameningeal rhabdomyosarcoma but only a recently recognised problem in limb osteogenic sarcoma (only since the advent of limb-conserving surgery). In all cases where a large bulk of sarcoma threatens to relapse locally, multimodality therapy (surgery, radiotherapy, chemotherapy) stands a better chance of sterilisation than individual modalities of therapy, and such multimodality therapy stands its best chance when it is used early, that is, all three

modalities are used at the beginning or shortly after commencement of the treatment course.

Résumé

Le problème majeur posé par la plupart des sarcomes de l'enfant est un problème d'envahissement, à noter le cas du rhabdomyosarcome paraméningé mais aussi l'apparition depuis peu seulement (en fait depuis que l'intervention chirurgicale permet de conserver un membre), du problème du sarcome ostéogène. A chaque menace de récidive locale d'un sarcome, le traitement combiné (intervention chirurgicale, irradiation et chimiothérapie) donne de meilleures chances qu'un traitement unique, à la condition expresse de le commencer tôt.

Zusammenfassung

Die Ausdehnung ist ein großes Problem bei den meisten Sarkomen im Kindesalter. Es ist das allergrößte Problem bei dem parameningealen Rhabdomyosarkom und wird zusehends zu einem Problem bei dem Osteosarkom der Gliedmaßen (eigentlich erst seit den Fortschritten der erhaltenden Chirurgie). In allen Fällen, in denen ein ausgedehntes Sarkom droht, lokal zu rezidivieren, ist eine kombinierte Behandlung (Chirurgie, Radiotherapie, Chemotherapie) erfolgversprechender als Monotherapien, dies allerdings unter der Voraussetzung, daß sie von Anfang in dieser Form durchgeführt wird.

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The Care of the Child Facing Death

R. Lansdown

To say that death is the twentieth-century taboo is now a cliché but this does not diminish its truth. With the decrease in infant mortality (Table 1), together with an increase in survival rates of many conditions of later childhood, the death of a child is now sufficiently rare to produce an embarrassed reluctance to communicate on the part of other people, leading to a potentially devastating sense of isolation on the part of the family of one who is sick. Here can be seen two contexts within which to consider the care of children facing death: the social and the family. The work of various organisations – Cruse, for example – is part of a movement eroding the taboo nature of death and the phenomenon, having been acknowledged, can now be left. The context of the family, and to a lesser extent the school and hospital, will remain central to the rest of this paper.

Seeing the child within a family context means remembering that all members of the family contribute to children's care and also have their own needs. One reading of this position might lead to the conclusion that all help should be within a family therapy framework. There are objections to this, however, the main one being that the notion of therapy in this context is to be questioned, since it carries with it an assumption of systemic dysfunctionality. Families of very sick children

Table 1. Infant mortality in England and Wales per 1000 live births (source: the Registrar General's Statistical Review)

1906–1910	117.1
1911–1915	108.7
1916–1920	90.9
1921–1925	74.9
1926–1930	67.6
1931–1935	61.9
1936–1940	55.3
1941–1945	49.8
1946–1950	36.3
1960	21.8
1970	18.2
1974	16.3

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Progress in Pediatric Surgery, Vol. 22
Ed. by L. Spitz et al.

might at times fall into this category, but the overall aim of a supportive team should be to prevent the dysfunctionality rather than to treat it. What is more, there are at least three good reasons for offering support to different combinations of a family and to individuals. One is the phenomenon of mutual pretence, a concept discussed at length by Bluebond-Langner [2]. The notion behind mutual pretence is that parents and children wish to protect each other, so adults tell children that they are ill but not seriously so and children ask their parents no questions, appearing to be unconcerned. When this is recognised on all sides it need not hamper the psychological care of child and family. Mary was an 8-year-old facing a leg amputation. At one point her parents told the social worker and psychologist working with them that Mary had to stay strong to keep them going. Mary in her turn confided that she knew she had to put up an unworried front to prevent her mother having a second breakdown. Because everyone concerned could voice their fears the family were able to receive help with parents and daughter being seen separately. When the pretence remains unacknowledged the strain imposed on everyone is enormously magnified.

A second reason is the fact that many parents gain most support not from professionals but from other parents. Only they are perceived as truly understanding parental feelings, only they can pierce the barriers society seems to impose on those whose plight it cannot comprehend. To this end, parent groups are set up. With a social worker colleague I have run many such groups and have found that, while they do not meet everyone's needs, they go a long way to helping at least a minority of parents.

A third reason for not seeing families together all the time is that adults and children are at different stages on developmental timetables. The most obvious timetable is related to the concept of death [5]. Children as young as 3 years are likely to use the word dead, but misunderstandings abound to the complexity of the concept; one of our first tasks when working with a child is to try to discover where the child is 'at'. Kane [3] has postulated that there are nine components making up the total concept (Table 2).

Ever since the pioneering work of Anthony carried out in Britain in the 1930s [1] it has been generally accepted that 7–8 is the age by which children have developed the concept fully. However, the most recent study to be published in this country, Lansdown and Benjamin [4] suggests that, while one can be reasonably sure that almost all 7–8 year olds of normal intelligence will have a good grasp of the meaning of the word 'dead', one must also be aware that much younger children can have a full concept. In the Lansdown and Benjamin study about one-third of the 5-year-olds seemed to be well aware of all Kane's components.

Equally important is the stage the child has reached in the timetable of formation of a concept of illness. One such developmental sequence is given in Table 3. The crucial stage is number 4. When children realise that their illness can kill other children the truth strikes home. Before then their parents might have told them that they had to undergo their treatment because otherwise they would die, but then parents are always saying things like 'I'll kill you if you touch that again' and they do not really mean it.

Table 2. Components of the concept of death (adapted from [3])

Component	Average age at which component incorporated
Realisation of existence of death	3
Separation from the living	5
Immobility of the dead	5
Irrevocability of death	6
Causality of death	6
Dysfunctionality of the dead	6
Universality of death	7
Insensitivity of the dead	8
Appearance of the dead	12
Personification of the agent of death[a]	–

[a] Studies in Europe in the 1930s suggested that children personified the agent of death (e.g. the Great Reaper), but Kane's work [3] did not support this for American children

Table 3. Stages in the concept of illness

1. I am ill but I will get better
2. I am very ill but I will get better
3. I have an illness that can kill but I will get better
4. My illness can kill my contemporaries
5. I may die very soon

This developmental sequence can equally well be used as a framework for children with degenerative conditions, like muscular dystrophy; the importance of stage 4 is just as great as it is for children who call themselves sick. Either sick here, last word of this line, should be changed to ill or all the ill words in Table 3 should be changed to sick to give consistency.

There is a need to tailor intervention to the child's place on these sequences. Christopher, for example, talked about dying when he was five. He said confidently that he expected to be a pilot when he grew up and he thought he might be shot down. A year later his illness had progressed. In his own words, 'one tumour is enough, two is too many'. At this time he was able to see and to discuss the possibility that his too numerous tumours could kill him.

In the early stages of a possibly fatal illness, then, it is not generally appropriate to focus on death, unless of course the child leads the conversation in that direction. Rather, it is better to offer as much information about treatment and

about the nature of the illness as the child can cope with. Similarly, parents are likely to respond initially to an approach which is heavily loaded with hard information.

From then on the art of helping lies in listening. Children will sometimes give obvious cues. Very occasionally they will ask directly. 'Am I going to die?' More often they will indicate their needs for communication obliquely, like the 12-year-old with leukaemia who continually asked her hospital teachers for extra biology lessons, with a focus on studying blood. Or children will report dreams and nightmares: 'I was in a big hole and my mum and dad came and looked down at me.' These are all clear requests for someone to tune in to their thoughts and feelings, for someone, not necessarily to give them answers, but to explore their thoughts with them, to help them by this exploration to come to a better understanding of their current anxiety.

There can be such a tuning in even to children too young to have more than a hazy notion of dying. For them the fear is of separation. As one boy said to his mother, 'I don't want to be an angel. I don't want to go to heaven, I shall miss you and daddy.' They can be helped by a reassurance that they will not be alone, that someone will always be with them – providing, of course, that such a promise can be kept.

A frequently asked question is whether or not a child should be told that death is imminent. One school of thought says this is a non-question because all children who are dying know this, no matter how young they are. Others argue that telling anyone such awful news will inevitably upset them. In my experience, telling children, taking into account their conceptual level, does not distress them and in many cases can actually allay anxiety. And once everyone knows that everyone else knows, there can come a great enhancement of the value of non-verbal communication; the hug means so much more.

In conclusion, it must be emphasised that caring for dying children is not the sole preserve of the professional counsellor, social worker or psychologist. Children will choose whom they communicate with, and they may choose a student nurse, a teacher, a parent, a doctor, another child. What is important is that the person who is chosen is able to seek support for him or herself and can be part of a team, formal or informal, offering help.

Summary

With the decrease in infant mortality, together with an increase in survival rates of many conditions of later childhood, the death of a child became a relatively rare event. The concept of death developing in a child from its 3rd year of life on renders sensitive care necessary. Caring for dying children is not the sole preserve of the professional counsellor, social worker or psychologist. Children will chose whom they communicate with. It is important that the person who is chosen is able to seek support for him- or herself and can be part of a team offering help.

Résumé

Etant donné la baisse de la mortalité infantile et l'augmentation des survies dans le cas de beaucoup d'affections des enfants plus agés, la mort d'un enfant est devenue un événement assez rare. A partir de l'âge de 3 ans, un enfant est capable de concevoir la mort et il est donc nécessaire d'aborder cette question avec les ménagements et la sensibilité qui lui sont dus. L'assistance aux enfants mourants ne doit pas être réservée uniquement aux conseillers professionnels, aux assistantes sociales ou aux psychologues. Les enfants choisiront eux-mêmes les personnes avec qui ils veulent communiquer. Il faut que la personne choisie puisse bénéficier à tout moment de l'aide nécessaire et être intégrée à l'équipe offrant son aide.

Zusammenfassung

Mit dem Rückgang der Säuglingssterblichkeit und dem Ansteigen der Überlebensrate bei vielen Erkrankungen in der späteren Kindheit ist der Tod eines Kindes ein relativ seltenes Ereignis. Da die Kinder jedoch schon mit 3 Jahren anfangen, den Tod zu begreifen, muß diese Frage mit der notwendigen Feinfühligkeit behandelt werden. Die Betreuung sterbender Kinder sollte nicht ausschließlich Fachkräften, Sozialarbeitern oder Psychologen vorbehalten werden. Die Kinder werden sich selbst eine Bezugsperson aussuchen. Diese Person muß unter allen Umständen die Möglichkeit haben, sich Rat zu holen und kann in einem Hilfeteam integriert werden.

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Hepatobiliary Tumours of Childhood: Investigation and Management

Adrian D. Joyce and Edward R. Howard

Introduction

Primary liver tumours represent 15% of abdominal tumours in childhood. Approximately two-thirds are malignant, and effective diagnosis and treatment depend upon a logical protocol of investigation. Bile duct tumours are extremely rare and they are included in this chapter because their investigation and management is similar to those of hepatic neoplasms.

Most of these tumours present within the first 2 years of life and surgery, which may include resection of up to 85% of the liver substance, is necessary for the majority of both benign and malignant lesions. However, the cure rates for malignant tumours have been poor, and in the 30% of cases of hepatoblastoma that are surgically resectable less than 60% of the children survive. Nine per cent of the whole group die within 12 months of presentation. Recent reports suggest, however, that some malignant tumours may respond to cytotoxic agents, and drug treatment combined with surgery may help to improve the poor cure rates achieved in the past.

This review will be illustrated with the case histories of the 22 children treated for hepatobiliary tumours during the last 5 years at King's College Hospital, London (Table 1).

Table 1. Analysis of 22 cases of hepatobiliary tumours in children presenting to King's College Hospital 1980–1985

Benign		Malignant		
Hamartoma	3	Primary:	Hepatoblastoma	7
Haemangioma	3		Hepatoma	3
Adenoma	1		Rhabdomyosarcoma	1
Inflammatory	1	Secondary:	Neuroblastoma	3
Total	8		Total	14

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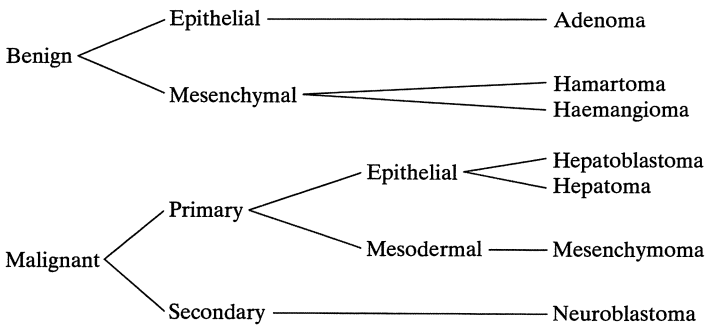
Progress in Pediatric Surgery, Vol. 22
Ed. by L. Spitz et al.

Table 2. Pathological classification of hepatic tumours of childhood



Pathology

Primary Hepatic Tumours

Primary tumours of the liver in children arise from either hepatocytes or supporting mesenchymal structures. The following outline includes the more common hepatic tumours of childhood (Table 2; Fig. 1).

Benign

Haemangiomas

Vascular neoplasms are the commonest benign paediatric liver tumours and 90% are discovered before the age of 6 months. Two histological subtypes have been described by Ishak [31] as haemangio-endothelioma and cavernous haemangiomata. The former are composed of many small vascular channels lined by one or more endothelial cells identical to the skin lesions similarly named. Although they are usually localised, these can be multiple lesions in 30% of cases consistent with a multifocal process (Dehner and Ishak 1971). Cavernous haemangiomata are composed of varyingly sized vascular spaces lined by a single layer of endothelial cells which may contain thrombus. Many tumours show features of both types of histological lesion. In the first 12 months of life, haemangiomata may undergo rapid enlargement followed by stabilisation and subsequent regression. Enlargement is accompanied by arteriovenous shunting which may cause high output cardiac failure or even rupture of the vascular mass [55, 60]. The cardiac failure may be unresponsive to treatment and a mortality rate of 50% within 2 weeks of onset has been reported in young infants [16]. Trastek et al. [70] reported a retrospective series of 49 cases of cavernous haemangiomas exceeding 4 cm in diameter. Thirteen underwent a surgical procedure and four developed post-operative complications. The remaining 36 were treated conservatively, and, although four lesions increased, none developed haemorrhage or intensification of symptoms [70]. The triad of hepatomegaly, high output cardiac failure and cutaneous haemangioma is strongly diagnostic of hepatic haemangioma.

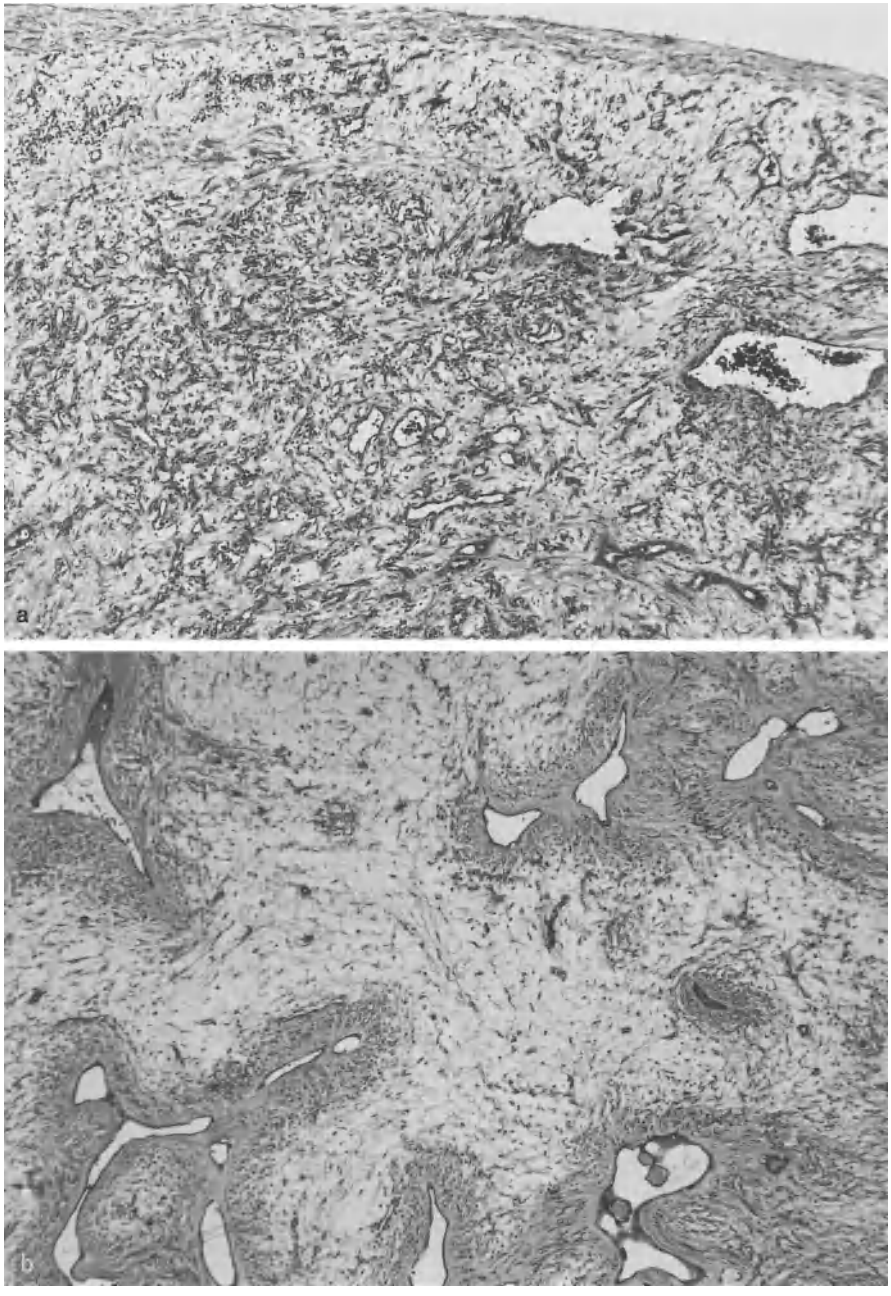


Fig. 1a, b. Section of liver showing **a** haemangioma composed of small vascular channels lined by flattened endothelium (×16); **b** mesenchymal hamartoma composed of a loose connective tissue and islands of thin-walled blood vessels with scattered bile ducts

Mesenchymal hamartoma

This was first described by Maresch [46]. It is a benign cystic lesion lined by grey smooth spaces containing clear fluid or mucoid material [17], and typically presents within the first 2 years of life. The tumour is usually confined to one lobe and may be pedunculated. Microscopically there is a mixture of mesodermal and endodermal structures in a loose connective tissue stroma with characteristic fluid-filled spaces without an endothelial lining. Some are associated with raised α-fetoprotein levels, thought to be produced by proliferating hepatocytes [33]. They are entirely benign and enucleation may be possible.

Other Benign Tumours

Additional benign lesions encountered in the liver are:

Adenoma
Focal hyperplasia
Epidermoid cysts
Lymphangioma
Benign cysts

Adenomas and focal nodular hyperplasia may present in childhood. These lesions are extremely rare and comprised only 2% of hepatic tumours in the survey of the American Academy of Pediatric Surgical Section [21]. They usually present with asymptomatic hepatomegaly, although adenomas have been associated with glycogen storage disease [30]. Adenomas show a homogeneous yellow tan colour, and, in view of the histological difficulty in distinguishing them from well-differentiated hepatomas, resection is recommended [13, 31].

Focal nodular hyperplasia can occur at all ages, but usually appears in children between 7–14 years of age. Histology shows micronodular cirrhosis with regenerative nodules and although resection is not necessary it may be advised if there is doubt over the histological diagnosis [13, 58].

Malignant

The epithelial tumours, hepatoblastoma and hepatocellular carcinoma, are the commonest primary hepatic malignancy, representing about 2% of all malignant

Table 3. Reported associations with childhood hepatic tumours [3, 10, 15, 22, 36, 72]

Anomalies	Congenital liver disorders	Other associations
Hemihypertrophy	Biliary atresia	Osteoporosis
Haemangioma	Neonatal hepatitis	Polyposis coli
	Von Gierke disease (glycogen storage disease)	Androgen therapy
	Lipid storage disease	De Toni Fanconi syndrome
	Hereditary tyrosinaemia	

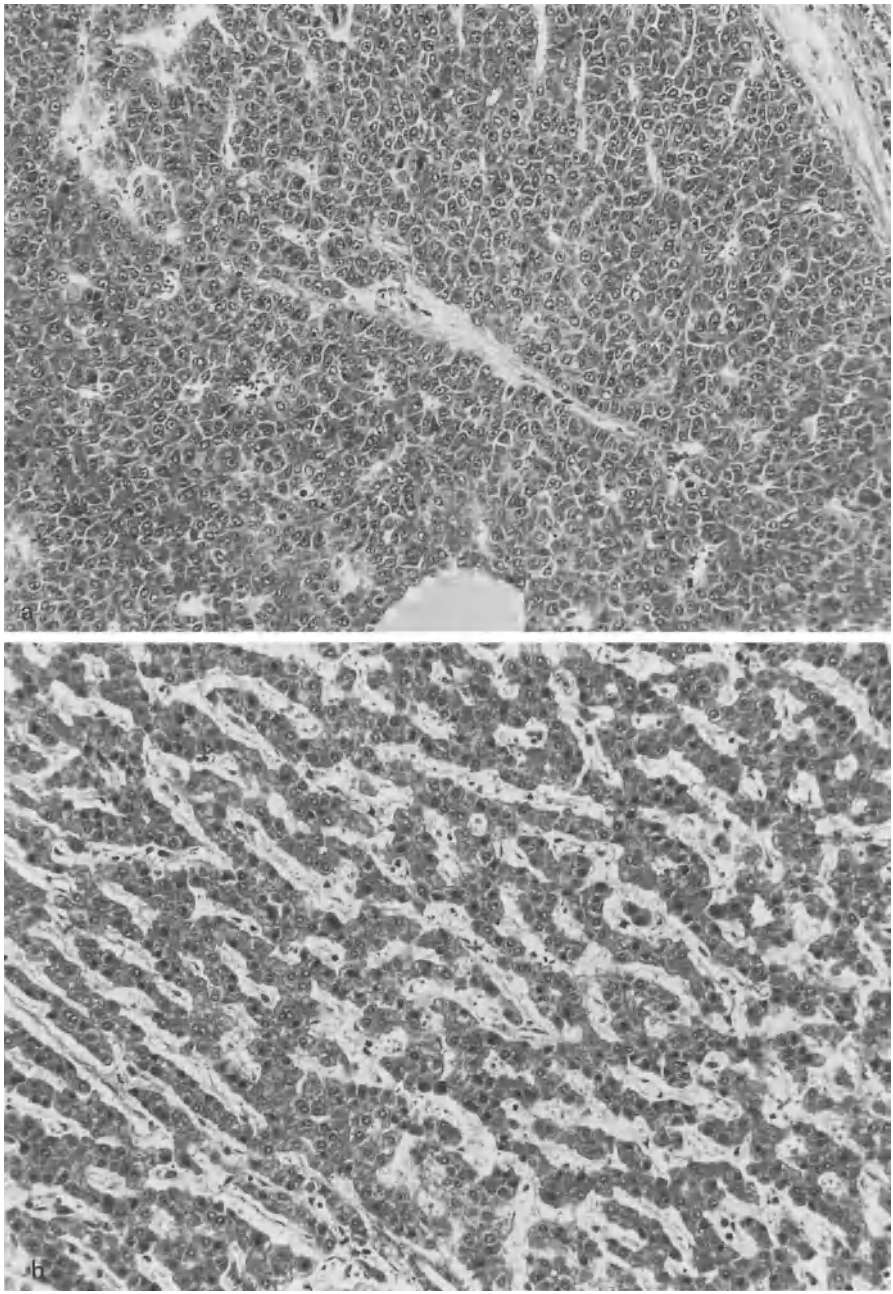


Fig. 2. **a** Section of hepatoblastoma of fetal type composed of pleomorphic cells with abundant cycloplasm arranged in a nodular pattern with bands of fibrous tissue (× 40). **b** Section of hepatoma composed of well-differentiated hepatocytes; although it resembles normal liver, no normal architectural features are seen (× 40)

lesions seen in childhood. Liver tumours have been associated with certain congenital liver disorders, extrahepatic anomalies and metabolic disorders. An epidemiological relationship to geographical location has been reported [25] (Table 3; Fig. 2).

Hepatoblastoma

This is the third most commonly encountered intra-abdominal malignant neoplasm in infants and generally occurs in children less than 3 years of age. Although two forms are recognised, epithelial and mesenchymal, the prognosis is not related to histology [32]. Regardless of the histological type, hepatic tumours involve the right lobe in approximately 75% of cases; in our series all tumours except one were located there. Metastasis to other parts of the liver occurs by direct extension, probably via intrahepatic vascular or lymphatic channels. Extrahepatic spread involves the regional nodes in the porta hepatis, while the lung is the commonest site of distant metastasis.

Hepatocellular carcinoma

Hepatocellular carcinoma, by contrast, are rare in children under 3 years of age, but account for 20% of all primary hepatic tumours reviewed over 57 years at the Children's Hospital Medical Center, Boston, Massachusetts [39]. There are various childhood diseases which predispose to cirrhosis but these do not appear to place the child at risk for hepatocellular carcinoma. An exception is the chronic form of hereditary tyrosinaemia, a rare inborn error of metabolism, in which it is estimated that 30% of the children will develop hepatoma [72]. Histologically these tumours are identical to the adult form but recently a variant has been recognised [11]: this fibrolamellar carcinoma has a relatively high rate of resectability and improved survival. Overall the prognosis for hepatoma patients remains poor, with a mortality of 90%.

Mesenchymoma

This malignant tumour was first defined by Stout in 1948 [66]; the macroscopic appearance is of a single cystic tumour mass, and microscopically it is composed of mesenchymal cells with prominent nuclear pleomorphism and frequent mitoses. A collection of 14 cases culled from the literature in 1982 revealed a survival rate of 33% of nine patients after resection [61].

Metastatic Disease

Secondary involvement of the liver by paediatric tumours resulting in hepatomegaly is not uncommon, resulting in the following lesions:

Neuroblastoma
Nephroblastoma
Lymphoma
Leukaemia
Histiocytosis X

It has been recognised that a particular subgroup of disseminated neuroblastoma has a good prognosis [12]. Such children were classified as stage IVS by Evans who described a subset of children with disseminated disease presenting with a large, rapidly growing liver [18]. The primary lesion may not be easily demonstrable, but these patients have elevated urinary catecholamines and positive bone marrow aspirate, and 30% present with metastatic skin lesions. The majority of patients in this subset are young infants less than 12 months of age, although children of any age can be included in the criteria. Evans [19] reviewed 17 patients with stage IVS disease. Eleven patients survived, 55% having spontaneous regression of all or part of their disease. Death usually occurred in the 1st month from local disease. In view of the fact that spontaneous regression is likely to occur, careful consideration should be given to treatment modalities. Children with rapidly enlarging livers are at risk of renal impairment, caval compression or respiratory embarrassment due to tumour bulk, and coagulopathies may also occur. Treatment should be designed to induce regression, using low-dose irradiation or limited chemotherapy. Surgery is reserved for those who need urgent intervention for the relief of symptoms and for the resection of the primary tumour after regression to prevent local recurrence at the primary site [54].

Bile Duct Neoplasms

Benign Inflammatory Tumours

One case in our series presented with obstructive jaundice secondary to a benign inflammatory tumour of the common duct beneath the porta hepatis. These tumours have a yellow-brown surface and are composed of a mixture of acute and chronic inflammatory cells in a dense fibrous tissue matrix. Their aetiology is unknown, but the excessive inflammatory reaction may be a sequel to a local irritation by a chemical or infective focus. Treatment consists of radical excision and reconstruction with a Roux-en-Y portoenterostomy and is usually curative [62].

Rhabdomyosarcoma

This malignant mesenchymal tumour represents 10–15% of all solid tumours in children [67]. Lack, in a review in 1981, emphasised that this is the commonest primary tumour of the extrahepatic biliary tract and should be considered in the differential diagnosis of obstructive jaundice in childhood. The average age of presentation is 4.5 years; 40% have local or distant metastases and the average survival time is 6 months (Fig. 3). Unlike rhabdomyosarcomas in other sites, treatment by radical resection is technically difficult and treatment should include adjuvant radiotherapy and chemotherapy. In 1983 we excised an embryonic rhabdomyosarcoma in a 3-year-old girl which arose from the common bile duct and extended to the bifurcation. Resection was followed by Roux-en-Y loop reconstruction and post-operative chemotherapy. The child is alive and well 2 years later. Mihara and colleagues [47] describe a similar successful resection for a gall bladder tumour.

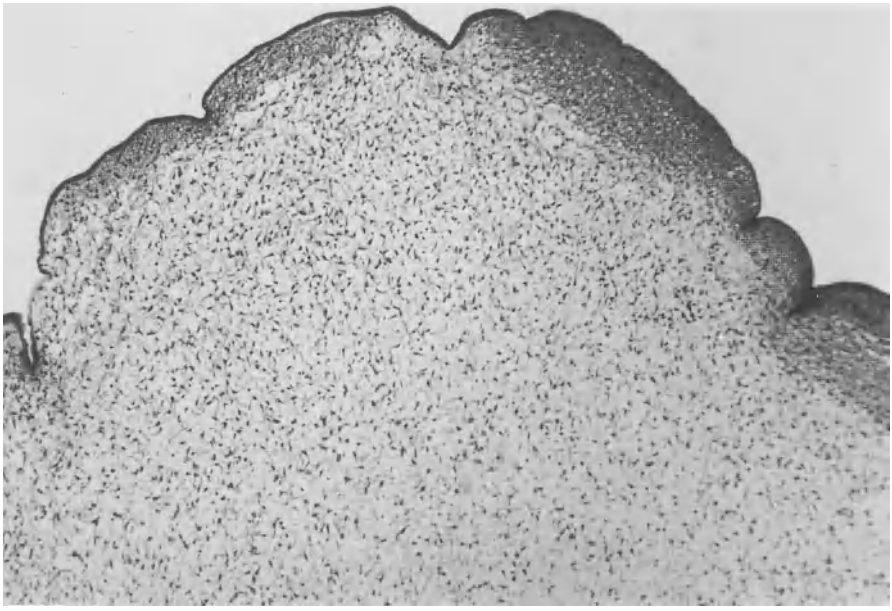


Fig. 3. Section of a polypoid rhabdomyosarcoma found at operation to arise from the common bile duct. The tumour is composed of a loose stroma containing embryonic rhabdomyoblasts covered by cuboidal epithelium (×16)

Clinical Aspects

Symptoms

Most children present with an asymptomatic abdominal mass, although 25% of the children with malignant neoplasms present with abdominal pain and weight loss indicative of advanced malignant disease [32]. The presenting symptoms of the 22 children at King's College Hospital are shown in Table 4.

The degree of hepatomegaly is often severe and 60% presented with a mass in the right upper quadrant which extended to below the level of the umbilicus (Fig. 4). The differential diagnosis of such a mass is represented in Table 5.

Abdominal pain may be caused by ischaemic infarction or haemorrhage within the tumour resulting in capsular pain. Many of the patients are anaemic and thrombocytopenic.

Malignant liver tumours, especially hepatoblastomas, have been associated with virilisation in young males due to abnormal production of human chorionic gonadotrophin (HCG) [7, 26, 32]. Testosterone elevation is the result of testicular Leydig cell hyperplasia stimulated by HCG. These hormonal levels may as be used as markers of tumour activity after treatment.

Table 4. Symptoms at presentation of the 22 children to King's College Hospital

Symptom	Benign ($n = 8$)	Malignant ($n = 14$)
Mass	4	7
Pain	2	6
Vomiting		1
Malaise	1	3
Jaundice	2	2
Precocious puberty		1
Cong. heart failure	1	

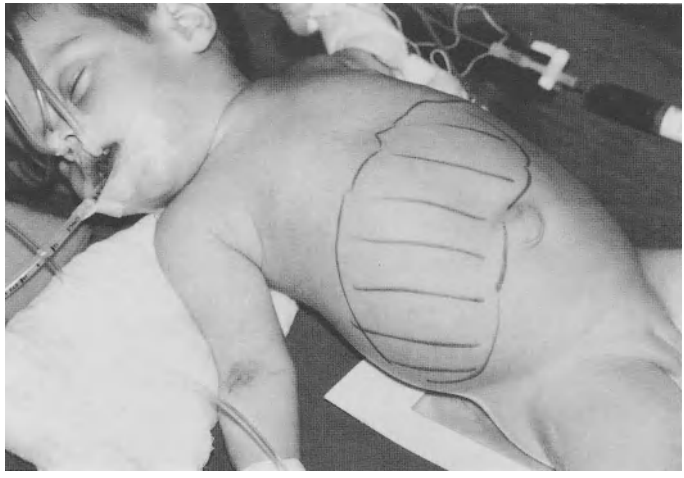


Fig. 4. Female infant of 8 months with a large hepatoblastoma of the right lobe which was successfully resected. Three years later she has shown no evidence of recurrence

Occasionally the benign vascular tumours present with spontaneous intraperitoneal haemorrhage, often associated with minor trauma which can be fatal [60]. A survey of the literature in 1983 revealed 21 reports of spontaneous haemorrhage from cavernous haemangiomas in both adults and children [1, 59, 60, 70]. The majority were fatal.

Diagnosis

This is made on the history, physical examination and certain biochemical and radiological investigations. Anaemia is the commonest abnormality; in most cases alteration in the liver function is only found where tumours are encroaching on

Table 5. Differential diagnosis of a mass in the right upper quadrant

Mass	Diagnosis
Renal	Neoplasm Cysts
Adrenal	Neoplasm
Hepatic	Abscess Neoplasm Cyst
Choledochal	Cyst

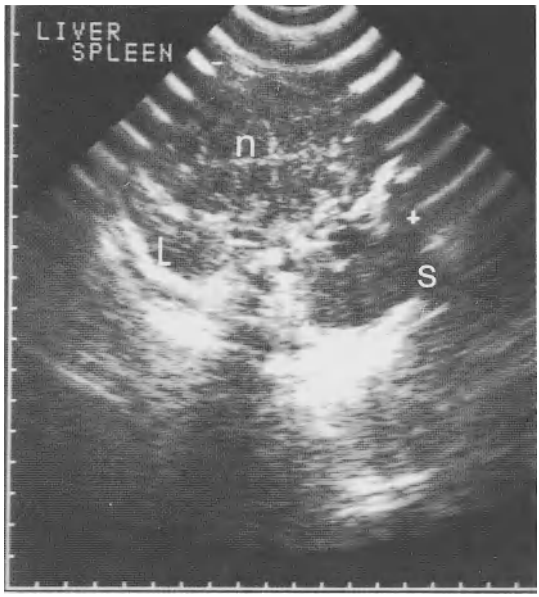


Fig. 5. Typical ultrasonogram of a large neoplasm of the right lobe of the liver. The spleen is slightly enlarged. *n*, Neoplasm; S, spleen; L, liver

the porta hepatis or in patients with pre-existing liver disease. Jaundice is normally considered a contra-indication to major liver resection, particularly in patients with little evidence of bile duct obstruction or cholangitis [51]. Serum α-fetoprotein levels have been more useful as a diagnostic tool [2, 44]. α-Fetoprotein, produced by proliferating embryonic hepatocytes, is normally present in the blood of the fetus and infants in the first few days of life. This α-globulin is elevated in two-thirds of malignant hepatic epithelial neoplasms and some benign

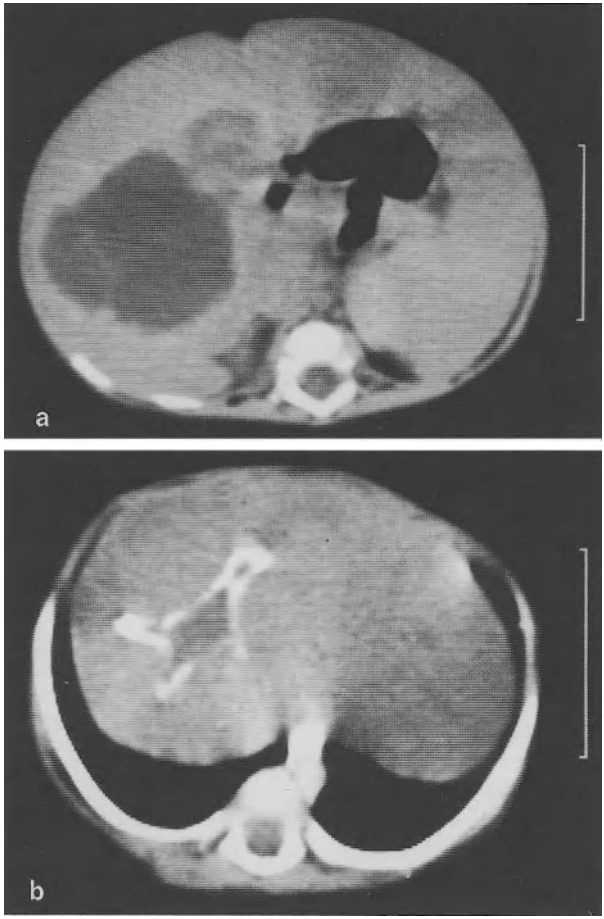


Fig. 6. a Computed tomogram showing a large necrotic hepatoblastoma. **b** Repeat examination after embolism and injection of contrast medium now shows the lesion to be well defined and contrast medium outlines the capsule

vascular tumours [21, 33]. It is also found in the blood of patients with yolk sac tumours and teratomas. When present, α-fetoprotein is an accurate tumour marker, and serial estimations are used to measure the efficacy of treatment [44].

Although chest radiology is the initial method of examination to exclude metastases, CT scanning is far more sensitive in this respect [48]. It is important to establish the accurate location, size and relationships of hepatic tumours, but despite the information given by ultrasonography and CT, selective angiography still has an important diagnostic role [53]. Ultrasonography has been recommended as a screening procedure in children with hepatomegaly and usually helps to localise the lesion, but it has limitations with regard to defining the anatomical location and the extent of the tumour (Fig. 5) [35, 37]. Although CT is not totally

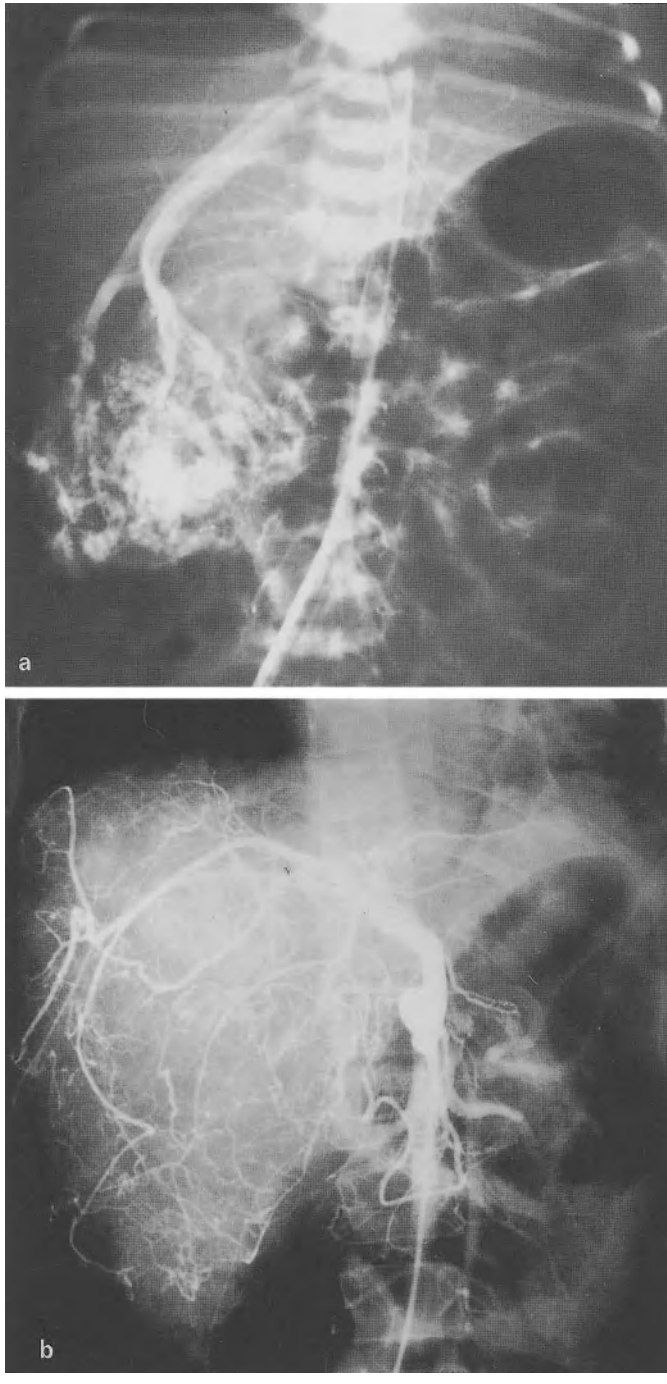


Fig. 7a, b

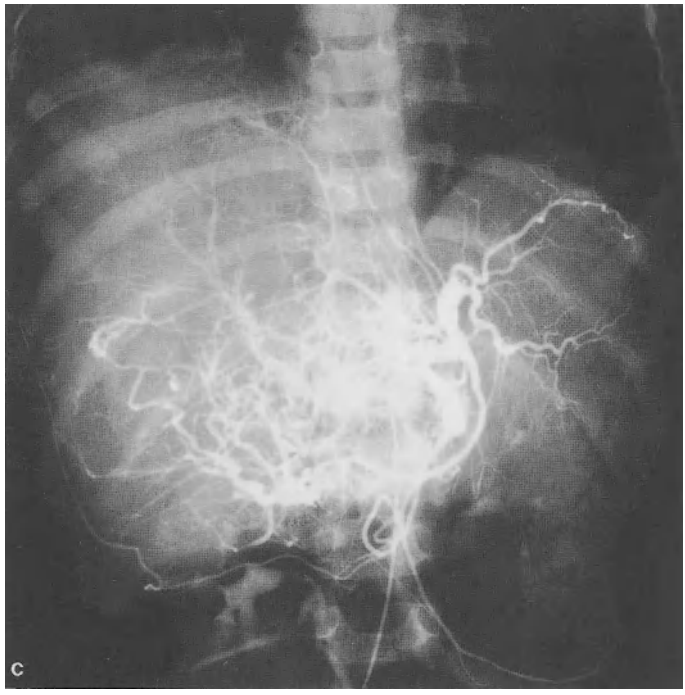


Fig. 7a–c. Examples of angiography in different types of hepatic tumour. **a** Venous phase angiography of a cavernous haemangioma showing arteriovenous shunting which was responsible for high-output cardiac failure. **b** Hepatoblastoma of the right lobe. The left lobe is free of tumour and seen in the upper right-hand corner of the figure. Tumour resected. **c** Rhabdomyosarcoma in central position. Tumour inoperable

reliable in assessing tumour extent, it is thought the number of false positive diagnoses will be rare so that there will not be an overestimation of the disease [4] (Fig. 6). These techniques also enable the clinician to monitor small benign lesions if a conservative policy is adopted and to assess the response of the lesion to treatment with the hope of selecting patients who may benefit from 'second look' laparotomy.

Opinions vary on the role of angiography, but we consider that selective coeliac arteriography gives important information on tumour pathology, resectability and the surgical anatomy of the hepatic vasculature, especially as hepatic neoplasms derive their blood supply almost exclusively from the arterial system rather than from the portal venous system (Fig. 7). The recent introduction of digital subtraction angiography allows the examination time and the dosage of contrast medium to be reduced and gives improved visualisation of the portal venous anatomy [23]. At present we rely on the venous phase of the arteriogram to detect the portal vein (Fig. 8). Tumour assessment by inferior venacavogram may be misleading as it is difficult to distinguish between extrinsic compression

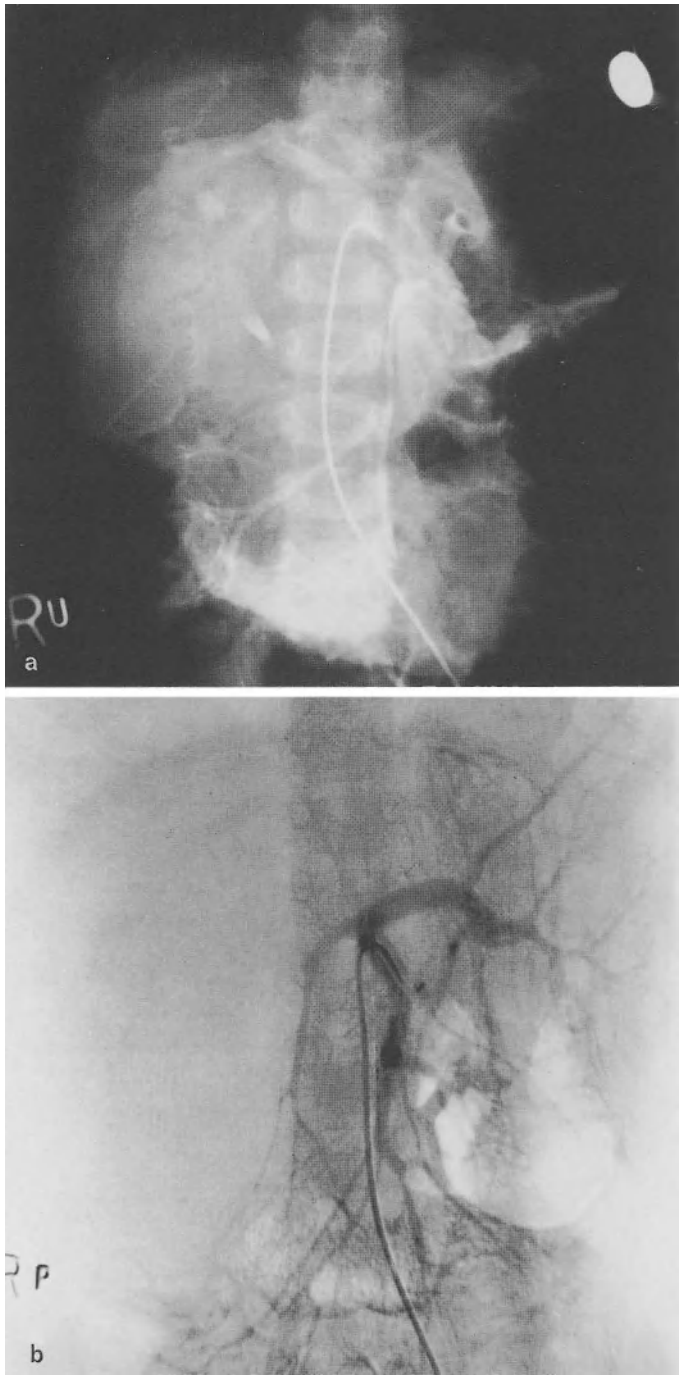


Fig. 8

and invasion by the tumour. Indeed, the only true guide to resectability may be assessment at laparotomy [24]. Similarly, isotope liver scans are limited in value as they lack specificity and often fail to illustrate the full extent of the disease.

Percutaneous liver biopsy may not be totally reliable and hepatic haemangiomata have been regarded as a contra-indication to needle biopsy [34]. Recently, fine-needle aspiration biopsy has been performed in some centres [8, 71] without complications, but it is advocated that this technique should be performed under CT guidance and should not be the main diagnostic tool. Sampling errors can occur with needle biopsy and one case referred as having a mesenchymal hamartoma on the strength of needle biopsy proved at resection to have an obvious hepatoblastoma. The risk of seeding onto the anterior abdominal wall should not be ignored: one of the children with hepatoblastoma underwent successful trisegmentectomy resection, but later developed seedling metastases along the needle track.

Treatment

Hepatic Tumours

It is generally accepted that surgical excision is necessary for the cure of primary malignant neoplasms of the liver, although a single case of spontaneous regression of childhood hepatoma was reported by Lee [41] following incision biopsy. Resection is also necessary for the majority of benign neoplasms. Small haemangiomas (< 3 cm) may be managed conservatively with regular ultrasonographic follow-up, surgery being reserved for those with either expanding tumours or complications – for instance, high-output cardiac failure or haemorrhage.

Hepatic Artery Ligation

Treatment regimens for haemangiomas have included steroids [27], radiotherapy [56], hepatic artery ligation and resection [40]. Hepatic artery ligation alone is very effective in the majority of cases with cardiac failure and we suggest the following course of management:

1. In the absence of complications, infants are simply monitored until stabilisation and involution occurs.
2. Infants less than 6 weeks of age in cardiac failure undergo hepatic artery ligation because of the high mortality associated with this age group.
3. Infants over 6 weeks of age receive steroids, digoxin and diuretics. Failure to respond to treatment within 2 weeks is an indication for hepatic artery ligation.

Careful observation both during and after treatment is essential to detect progress or relapse of the cardiac failure. Surgical excision can be contemplated

Fig. 8. Venous phase angiogram (**a**) and digital subtraction angiogram (**b**) showing the portal vein and extrinsic compression of the right venous system by tumour. The left vein is normal and the tumour resected

Table 6. Types of resection performed for 21 hepatic tumours in children

	No.	Tri	RL	LL	Wedge	En bloc	Inoperable
Hamartoma	3	1	1	1			
Haemangioma	3	1	2				
Adenoma	1		1				
Hepatoblastoma	7	7					
Hepatocellular carcinoma	3	1					2
Rhabdomyosarcoma	1				1		
Neuroblastoma	3					3	

Tri: trisegmentectomy; RL: right lobectomy; LL: left lobectomy

for patients with localised lesions in a single lobe and the rare cases of intraperitoneal haemorrhage. In the absence of liver disease, sepsis or shock, hepatic artery ligation can be performed with minimum morbidity even in a sick infant [40, 49].

Resection

Eighty-five per cent of the liver may be safely resected, and improvements in anaesthesia and the post-operative care of these patients have greatly minimised the hazards of surgery. A significant portion of the liver will have been regenerated by 1 month and full regeneration is seen in 3–6 months. The procedure performed for the respective diagnoses are detailed in Table 6.

In two cases (one hepatoblastoma and one hepatocellular carcinoma) the preoperative arteriogram revealed the lesion to be inoperable because of the presence of tumour beyond the falciform ligament or extension around the porta hepatis. Embolisation of the right hepatic artery was therefore performed, and in the patient with hepatoblastoma, chemotherapy was instituted. Follow-up angiography revealed that tumour reduction had occurred, and at 'second look' laparotomy a trisegmentectomy was possible.

Transcatheter hepatic artery embolisation using Gelfoam has been established as an effective treatment method for hepatic tumours [9, 50]. It can be used to decrease the vascularity and size of a tumour pre-operatively and thus limit intrahepatic spread during operative manipulation and also as a palliative treatment for patients with inoperable tumours. Post-embolisation vomiting, pain and fever may occur but these usually settle with symptomatic treatment. Specific complications can arise from the embolisation of extrahepatic structures including the gastroduodenal artery, resulting in peptic ulceration and pancreatitis. From the surgical viewpoint hepatic artery embolisation may result in local sepsis, but, more specifically, there is an increased inflammatory response which makes subsequent surgery more demanding.

In many cases a laparotomy is performed because a histological diagnosis is necessary to exclude a malignancy. Our standard incision is a right subcostal ex-

tended across the midline to form an inverted chevron. Fifty per cent of the resections require a thoracic extension through the eighth intercostal space to produce a T-shaped incision when access to the inferior vena cava and the hepatic veins is difficult. We use the standard resection technique described by Starzl and Putnam [63].

We do not use haemodilution or hypothermia anaesthesia, nor do we employ biliary intubation. In hepatic lobectomy the structures in the porta hepatis are identified and Pringle's manoeuvre (temporary clamping of the structures in the free edge of the lesser sac) with or without hepatic artery ligation used to control peri-operative haemorrhage. The liver is divided using the finger-fracture technique with ligation of individual bleeding points. Only one patient, a neonate, suffered a peri-operative circulatory arrest and quickly responded to prompt resuscitative measures, without complication.

Post-operative Management

Recently there has been a greater appreciation of the metabolic and haematological consequences of major liver surgery [43]. Intravenous administration of dextrose, albumin and fresh frozen plasma are standard in the initial post-operative management of these patients, with careful monitoring of the prothrombin time, serum albumin and blood glucose. The aim is to anticipate any deficit in these parameters. It has been suggested that the coagulopathy and fall in serum albumin is due to increased fibrinolysis and the loss of plasma proteins at the resection site rather than any primary deficit in liver function [65]. Serum alkaline phosphatase and transaminases are often transiently elevated, as is the serum bilirubin level. It appears that a markedly elevated bilirubin level after surgery is a poor prognostic sign [6]. A report in 1983 showed that 12 of 16 patients with a bilirubin level more than ten times above the norm in the immediate post-operative period died – the majority from liver failure [69]. Our long-term assessment of these patients post-operatively includes technetium isotope liver scans to assess regeneration and the serial measurement of α-fetoprotein in the α-fetoprotein-positive tumours in conjunction with chest radiology and ultrasound to detect recurrence. Pritchard et al. [52] emphasise the value of α-fetoprotein monitoring in determining the tumour response to therapy and for the early detection of metastases. Initially the α-fetoprotein levels are determined weekly until there is an exponential decline and then fortnightly until normal. Any sequential rise merits investigation including computed tomography of the lungs and abdomen to detect any local or distant recurrence (Figs. 9, 10).

Any suggestion of intra-abdominal recurrence warrants a 'second look' laparotomy with a view to further tumour resection. Hermann and Lonsdale [29] were the first to report the conversion of tumour from inoperable to resectable after combination therapy which resulted in a 5-year cure.

Other centres are describing similar successes [5, 73], and two patients in our recent series have progressed well after a second procedure, the longest survival being 3 years after removal of recurrent tumour.

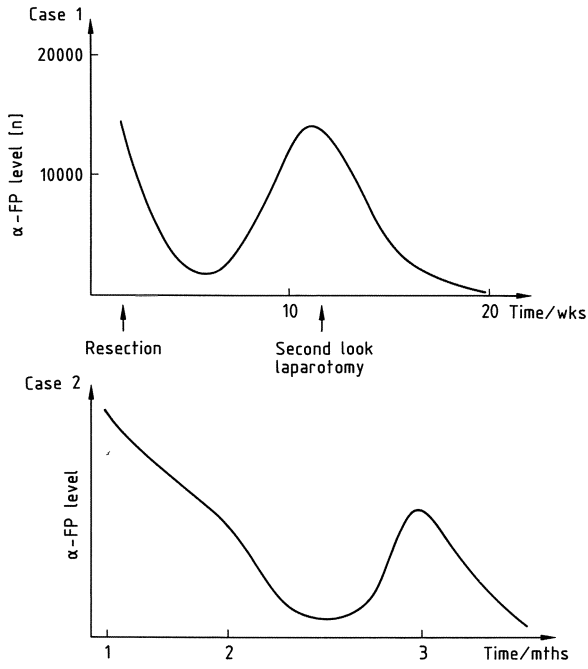


Fig. 9. The value of α-fetoprotein monitoring.

Case 1: A 13-month-old infant underwent trisegmentectomy for hepatoblastoma. Sequential rise in α-fetoprotein noted post-operatively; CT examination revealed local recurrence in the caudate lobe which was successfully resected at second look laparotomy.

Case 2: A 3-year-old girl presented with an inoperable hepatoblastoma at initial laparotomy *(1)*. Following hepatic artery ligation and chemotherapy, tumour reduction occurred allowing trisegmental resection *(2)*. A further rise in α-fetoprotein 5 months later *(3)* was related to the presence of three pulmonary metastatic deposits. Cis-platinum therapy effected a further fall in α-fetoprotein levels

Chemotherapy

Cure rates after surgical excision in patients with hepatoblastoma and hepatoma are reported as 60% and 33% respectively, but over 50% of patients have unresectable disease at diagnosis. In the past, long-term survival has not been affected by chemotherapy, immunotherapy or radiotherapy, but recently several authors have demonstrated a reduction in tumour size of both primary and secondary deposits using chemotherapy in children with hepatoblastoma in an attempt to increase the percentage of children likely to benefit from surgery [57, 68]. From a variety of chemotherapeutic agents initially involving vincristine, actinomycin and cyclophosphamide, alone or in combination, doxorubicin (adriamycin) has proved to be the most effective agent in a cumulative dose of 400–500 mg/m^2 [73]. At this dosage the risk of cardiotoxicity is generally minimal.

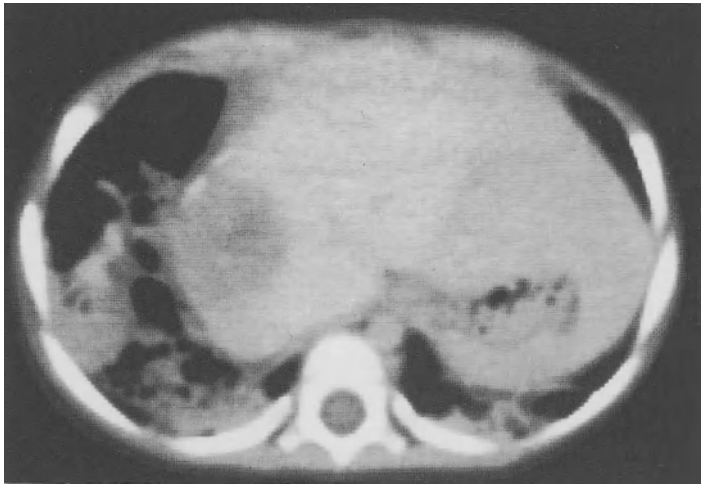


Fig. 10. Computed tomography showing local recurrence after trisegmentectomy. This investigation was preceded by a rise in α-fetoprotein levels. The recurrence was successfully resected

Results in the chemotherapeutic treatment of hepatoma have been less rewarding, but in 1982 members of the Child Cancer Study Group reported their results of combination therapy in the treatment of children with malignant hepatoma [20]. The overall response in 12 out of 27 adequately treated patients with measurable disease is extremely encouraging, with a median survival of 18 months. Not surprisingly, many of those who appear to respond well to chemotherapy are those children with the better hepatic function who survive long enough to have the full course of treatment. Not only does radiotherapy inhibit liver regeneration but these patients are also more sensitive to chemotherapy, and treatment regimens may therefore have to be modified.

Bile Duct Tumours

Benign

These are commonly inflammatory tumours of uncertain aetiology and best treated by local excision and reconstruction. Excision is curative. The cholangiographic diagnosis is usually secure enough to proceed to laparotomy with facilities available for frozen section histological examination. If normal ducts can be palpated above the lesion, the ducts can be divided and a 40-cm Roux-en-Y loop fashioned retrocolically up to the porta hepatis and anastomosed using a 5/0 Prolene mucosa-to-mucosa suture. No biliary stents are employed. Occasionally resection is hazardous because of the dense adhesions to the portal vein, as was the situation in one of our cases. We therefore intubated the common duct after biopsying the lesion and at subsequent laparotomy a Roux-en-Y bypass procedure was possible above the tumour although the lesion was still unresectable.

Malignant

It is hard to comprehend the origin of rhabdomyosarcomas of the bile duct in a site normally devoid of voluntary muscle. It has been suggested that they arise from embryonal mesenchyme capable of differentiating into rhabdoblasts [38]. In contrast to the current successes seen in the treatment of rhabdomyosarcoma in other sites [28], the biliary tract tumours have a dismal prognosis. Local invasion of the hepatic artery or portal vein often makes curative surgery impossible [42]. Should the lesion be operable, combination therapy with surgery, local radiotherapy and chemotherapy yields the best survival rates.

Summary

The most commonly encountered complications include wound infections, subphrenic collections and bile leaks from the cut liver surface. Stress ulceration of the stomach or duodenum is also not uncommon. Inadvertent bile duct damage has also been reported after major resection in children.

The results of surgery for benign lesions are very good and usually depend simply on technical expertise. The results for malignant lesions, however, remain poor. Six series, including our own experience, reported in the last 5 years have shown an overall survival rate of 43% for patients whose tumours were resected for cure. It is difficult to compare results as authors differ in their presentation of results, but details of the series are listed in Table 7. There were no definite prognostic factors to be drawn from these series other than that children with the fibro-

Table 7. Survey from the published literature 1980–1985of the results of surgery for 188 malignant hepatic tumours in children

	n	Resected for cure (*n*)	Alive disease-free (*n*)
Filler and Hagen [22]	22	13	7
Thompson et al. [69]	10	10	5
Mahour et al. [45]	38	10	3
Lack et al. [39]			
HC	32	17	3
HB	54	34	13
Giacomantonio et al. [26]	22	16	11
King's College Hospital (1985)	10	5	3
Total	188	105 (56%)	45 (43%)

HC: Hepatoma; HB: hepatoblastoma

lamellar variant of hepatocellular carcinoma fared better than those with other hepatomas.

It is a sad fact that overall 56% of patients in these series presented with unresectable disease. Mahour et al. [45] described seven patients with unresectable disease who were treated by either chemotherapy alone or in combination with radiotherapy, followed by 'second look' laparotomy and resection. Five of these patients were alive and disease-free for a minimum of 2.5 years after surgery. Thus it is necessary to adopt an aggressive approach to these tumours if one is to see any improvement on the overall figures.

Résumé

Les complications les plus fréquentes sont les plaies infectées, les rétentions sous-diaphragmatiques et les bilirragies provenant de la section du foie. On trouve aussi assez fréquemment des ulcères de stress, gastriques ou du duodénum. On a aussi fait état de lésions par inadvertance du conduit biliaire aprés une résection importante chez des enfants.

Les résultats obtenus par l'intervention chirurgicale dans le cas d'affections bénignes sont très bons et, seule, une bonne technique est requise. Les résultats dans le cas d'affections malignes, par contre, restent peu encourageants. Six études, dont la nôtre, ont fait état, au cours des 5 dernières années, d'une survie moyenne de 43% dans le cas des patients ayant subi une résection de la tumeur. Il faut dire que les résultats sont difficiles à comparer car leur présentation varie d'un auteur à l'autre, mais le tableau 7 donne tous les détails. Ces études n'ont fourni aucun facteur pronostique fiable si ce n'est que le cancer en amande a un pronostic meilleur que les autres carcinomes hépatocellulaires.

Ces études ont aussi fait une triste constation: 56% en moyenne de ces tumeurs sont inopérables. Mahour et coll. ont décrit sept cas de tumeurs inopérables qui ont été traités par chimiothérapie uniquement ou irradiation adjuvante puis qui ont subi une laparotomie et une résection. Cinq de ces patients ont eu une survie d'au moins 2 ans et demi après l'intervention chirurgicale. Seule, une décision thérapeutique agressive permettrait donc d'obtenir un début d'amélioration de ces chiffres.

Zusammenfassung

Die häufigsten Komplikationen sind Wundinfektionen, subphrenische Abszese und Gallenaustritt aus der Schnittfläche der Leber. Stressinduzierte Ulzeration im Magen oder Duodenum kommen auch relativ häufig vor. Es wurde auch über versehentliche Verletzung der Gallengänge während großen Eingriffen bei Kindern berichtet.

Die Ergebnisse der Chirurgie in den gutartigen Fällen sind sehr gut und hängen lediglich von der technischen Fertigkeit ab. Bei bösartigen Erkrankungen

jedoch bleiben die Ergebnisse unbefriedigend. Sechs Untersuchungen, die im Laufe der letzten 5 Jahre durchgeführt wurden, darunter auch unsere, haben von einer Gesamtüberlebensrate von 43% im Falle einer Tumorresektion berichtet. Es ist allerdings schwierig, die Ergebnisse zu vergleichen, da sie von den einzelnen Autoren verschieden ermittelt werden. Die einzelnen Ergebnisse der Untersuchungen sind in Tabelle 7 aufgeführt. Diese Ergebnisse lassen keine prognostischen Faktoren klar erkennen, außer, daß Kinder mit einem fibrolamellaren Leberzellkarzinom deutlich bessere Chancen haben als diejenigen mit einem anderen Hepatom.

Die Ergebnisse ermöglichen eine traurige Feststellung: 56% der Patienten insgesamt haben einen inoperablen Tumor. Mahour et al. berichten über 7 Patienten mit einem inoperablen Tumour, die entweder mit Chemotherapie allein oder mit Chemotherapie und Radiotherapie und darauffolgender „second look" Laparotomie oder Resektion behandelt wurden. 5 dieser Patienten lebten beschwerdefrei mindestens 2,5 Jahre nach dem Eingriff. Es ist also unerlässlich, diese Tumoren mit aggressiven Methoden zu behandeln, wenn man anfangen will, diese Gesamtzahlen zu verbessern.

Acknowledgement. Especial appreciation is due to Isolde Harris who guided the manuscript through numerous drafts into its final form.

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Wilms' Tumour: Trials and Tribulation

D. C. S. Gough

> ... For though the father sets the price,
> the children pay the cost.
> *Don McLean*

As the treatment of any medical condition becomes more effective, it is difficult to make further progress in management. Where there is general agreement over the role of treatment modalities, the subject of trials and their design, which might give further insight into therapy, becomes more important; yet for rare lesions individual units are unable to gain sufficient accrual of patients to perform what would be regarded as an acceptable clinical trial. Where the subject under investigation has a very low incidence in the population, it may be impossible to organise a comparative clinical trial as such on a national basis, as is the case in the United Kingdom for patients with Wilms' tumour. Areas with larger populations, such as the United States or mainland Europe, have been able to arrange trials comparing two treatments concurrently, but, with large numbers of patients in different centres, the control of the study and assessment of individuals does become a serious problem. Central collation of data, as in the United Kingdom Children's Cancer Study Group (UKCCSG), often reveals minor irregularities in treatment protocols when close scrutiny is made of each case, which are insufficient to withdraw a patient from the study but may explain some of the minor variations in results. The dangers of assessing current therapy against historical data are well illustrated by the different results obtained from the same chemotherapy protocol for stage II, stage III, and stage IV patients with Wilms' tumour in the first national study in the United States, and the poorer results from the second national study [1].

For all the success there has been in the management of patients with Wilms' tumour, anxieties about individuals will still occur, and groups for whom treatment is still unsatisfactory will emerge. The form that this dissatisfaction may take is variable, and it has been possible recently to define patients who need less treatment than has been historically prescribed, and those who might benefit from more.

The answers are not yet clear; we still see darkly into the glass, and it is this uncertainty that lies at the heart of the tribulation we feel as doctors and that we see expressed in the eyes of parents. One thing is certain, however, and is the guiding light of all clinicians involved with these patients: that, without treatment, the tumour is relentlessly progressive and the patients will die, but treatment will radically influence the natural history of the disease.

As treatment has become multimodal, the relative value of each part of the therapy has become indistinct and the reasoning behind current practice more dif-

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Progress in Pediatric Surgery, Vol. 22
Ed. by L. Spitz et al.

ficult to follow. I feel it necessary to state some of the therapeutic foundations, slowly build current treatment around this base, and describe the relative merits of surgery, radiotherapy, and chemotherapy.

Surgery

The fact that surgery influences survival in patients with Wilms' tumour has been known for nearly a century, but it is worth re-emphasising the central role of surgery in the management of this tumour. Surgery alone, without any other form of treatment, will cure a maximum of 25% of patients with long-term survival, but recurrent disease in the abdomen or lungs will ultimately appear in the remainder. If, however, the tumour remains unresectable in stage I–IV patients, then, whatever alternative combination of therapy is used, no cure is to be expected. Resection of the primary tumour is central to survival in this disease [2].

Surgical mortality has been reduced to 1.5% in all major centres and the most dangerous intra-operative complication is a venacaval tumour embolising into the pulmonary artery. This usually, but not always, causes a major cardiorespiratory collapse under anaesthesia, and within minutes the patient is usually dead. Time has allowed emergency Trendelenburg operation to remove the embolus from the pulmonary artery, but those who have survived such an episode can be counted on the fingers of one hand. Torrential bleeding and unwitting ligation of the wrong renal vessels are the other causes of mortality reported.

Surgery is now safer than chemotherapy when crude analysis is made of the cause of death in this condition, the most recent reports suggesting more than 2% mortality from drug treatment. The surgeon faced with an enormous abdominal mass may justifiably feel apprehensive; failure is no longer expected, but the hazards are still the same. He may consider treatment to reduce the size of the tumour, and perhaps also reduce the risks of surgery. There is nothing to suggest that such a policy is in any way hazardous to the long-term outcome and, where intracaval tumour is present, it may well be the safest course for the patient. Many centres in Europe have established this practice of chemotherapy preceding surgery as routine and it forms the basis fo the International Society of Paediatric Oncology (SIOP) trials. Needle biopsy may be used to initially confirm the diagnosis, as there is no current evidence suggesting an increase in local or distant metastases. Pre-treatment may well be preferable to laparotomy disclosing an unresectable tumour. Because of duodenal, caval, or aortic involvement, the tumour is found to be inoperable in 10% of patients where surgery is the primary therapy, and recent analysis of this group indicates they have a poor prognosis, with only 50% of patients surviving in the long term (DCS Gough, unpublished observations). The factors responsible for this poor prognosis may be the aggressive biological nature of the disease, metastases seeded by the initial trial of the tumour mobilisation, or other factors of which we know little. All one can say is that patients found to be initially inoperable, who then have local and systemic therapy followed by successful secondary surgery, have a survival rate of 50%; this has been confirmed by current UKCCSG studies.

Surgeons also need to be aware that current staging is based on pathology, and information as to the lymph node status of the patient is vital for treatment planning. Some form of lymphadenectomy should be carried out at the time of extirpative surgery, but there is no evidence that radical abdominal lymphadenectomy confers any benefit on the patient. Metallic surgical clips, once the radiographic hallmark of the tumour surgeon, are disliked by those trying to interpret postoperative CAT scans for tumour recurrence, and are no longer needed to guide the radiotherapy portals. The general opinion is that these clips should be abandoned, but in difficult situations such as the control of adrenal veins, they can be so useful...

The importance of careful examination of the contralateral kidney as part of an exploratory laporotomy is accepted by all, but in fact few fully mobilise the contralateral kidney to inspect its posterior surface: only 30% of those participating in Medical Research Council (MRC) trials did so (Gough DCS, unpublished observations). As it is not routine practice in many centres, it is difficult to draw any conclusions as to the merit of this extra interference, but those who do not usually bother may like to note that others who do make such a practice routine occasionally find small tumours on the posterior but not the anterior surface of the kidney. Moreover, the commonest site of abdominal recurrence in stage I and stage II cases is the contralateral kidney. If these factors encourage more surgeons routinely to inspect the posterior surface of the other kidney, it will at least give more uniform data for trial coordinators!

It is difficult to make definite statements on the subject of bilateral tumours, as the individual's experience is usually quite shallow and strongly coloured by a single case. In general, the survival of patients with bilateral tumours is good compared to stage IV cases, with survival of 87% being reported as long as 8 years ago [3]. Some would suggest that the biological nature of these tumours is usually different to that of unilateral cases. Where the second tumour occurs concurrently, the generally accepted approach would be to remove the larger tumour completely, performing radical nephrectomy, and locally resect or perform partial nephrectomy on the side of the smaller lesion if this is anatomically possible. Where this would be hazardous to the patient's survival, it would be quite acceptable to perform radical nephrectomy on the side of the larger tumour and concentrate local and systemic therapy on the remaining tumour-bearing kidney. Leaving a tumour in situ in unilateral cases will always meet with failure, but following this course in bilateral cases has been reported to meet with some clinical success [3, 4]. As to more radical surgery, although giants have always walked the earth, and bench surgery and bilateral nephrectomy with transplantation after periods of dialysis therapy have undoubtedly met with some limited success, lesser therapies are still a safer option for the majority of us and, probably, our patients, for the failures of new and radical therapies usually go unreported and the successes as a rule have only short-term follow-up.

The simpler solution of surgical removal is attended by the difficulty of removal of the tumour intact and there should be no doubt in the surgeon's mind that a complication such as tumour rupture during removal does seem to confer a

worse prognosis in some respects. Recurrence is more common in patients whose tumour ruptures during removal, although this does not seem to affect the overall survival rate [5]. Recurrence-free survival at 8 years was reported as 51% in cases without rupture and 27% in cases with rupture. The overall survival was 63% of all patients treated, and no difference was noted in either group.

Intra-operative rupture is a fairly common occurrence, and there can be little doubt that pre-operative therapy reduces this risk (Table 1). From the SIOP studies it is clear that pre-treatment with radiotherapy (2000 cGY) or vincristine can reduce this complication. Those who argue against pre-operative therapy point to the one in 20 patients whose pre-operative diagnosis is inaccurate, half of whom have benign disease and therefore unnecessary toxic therapy [6]. For this and other more obscure reasons, both British and American workers persist with surgery as the initial therapy, and look for post-operative success with chemotherapy and radiotherapy only in patients with proven malignant disease.

The most fundamental determinants of survival and therapeutic response are the histological characteristics of the tumour and the stage of the disease at presentation; and both UKCCSG and National Wilm's Tumour Study (NWTS) patients are staged as in Table 2. One patient in ten has a tumour with anaplastic or sarcomatous elements, and this unfavourable histology leads to a greater risk of recurrence or metastases, poorer response to chemotherapy, and decreased chance of survival. There is a further, much smaller group of patients with a tumour type that metastasizes to bone, and survival with this tumour type is most unusual. If bone metastases occur, the patient will not survive.

Because of the higher risk of recurrent disease in patients with unfavourable histology, most protocols advocate more intensive therapy, treating such cases as

Table 1. Intra-operative tumour rupture

SIOP I	32%	Primary tumour resection
NWTS I	16%	Primary tumour resection
MRC II	16%	Primary tumour resection
SIOP I	4%	With pre-operative radiotherapy
SIOP II	5%	With pre-operative chemotherapy

NWTS: National Wilms' Tumour Study

Table 2. Staging of Wilms' tumour (abridged)

Stage I	Renal capsule intact – complete removal possible
Stage II	Renal capsule penetrated – complete removal possible
Stage III	Spill, lymph node involvement, incomplete removal possible
Stage IV	Metastases at presentation
Stage V	Bilateral disease at presentation

stage IV, with three-drug chemotherapy and local radiation to known tumour sites. The UKCCSG trial has tried to avoid post-operative radiotherapy to these patients, relying on the proven presence of intra-abdominal disease some 16 weeks from diagnosis to determine whether radiotherapy is to be given. The disease is to be confirmed by second look laparotomy, but surgical compliance with this regime is not universal. The rationale behind this approach to treatment is to avoid routine post-operative radiotherapy to the abdomen, with its permanent effects on bone growth, only irradiating after positive evidence of intra-abdominal disease. It is also felt that, without radiotherapy, chemotherapy is less likely to be interrupted.

The clinical pattern of recurrence shows that recurrence is now rare at abdominal sites alone (Table 3) and it was felt appropriate to recommend reoperation in patients with stage III tumours and unfavourable histology. Perhaps the natural surgical conservatism has been justified, as only one patient out of eight has been found to have residual disease. On the other hand, this could be turned round to suggest that seven patients have so far been spared post-operative radiotherapy by negative relaparotomy (Table 4)!

The surgical management of unfavourable histology cases remains a vexed question and second look surgery is unpopular in surgical circles. One must be quite clear that a definite question is being asked: for instance, can some cases be spared radiotherapy at the cost of reoperation? Only further study along this path will lead to an answer.

Table 3. Pattern of recurrent disease (from [7])

Number of patients	164
Relapse in lung only	22
Relapse in lung and abdomen	13
Relapse in abdomen only	4
Relapse in liver only	2
Relapse in bone only	1

Table 4. Unfavourable histology stage II/III (second look laparotomy at week 19)

Case judged suitable for second look	14
Cases explored	8
Negative findings	7
Positive findings	1
Mortality	0

Radiotherapy

Despite radical surgery, survival from Wilms' tumour was still considered poor until the advent of radiotherpy. Combinations of surgery and post-operative irradiation of the tumour bed resulted in 50% long-term survival [8]. The addition of radiotherapy as routine established two important points. Firstly, however radical the surgery, microscopic residual disease existed in the abdomen in a significant population of patients, which ultimately, via local recurrence or distant metastases, caused their death. Secondly, control of this local disease was possible with radiotherapy, and survival doubled.

The price of improved survival figures after radiotherapy has been failure of bone growth with spinal column shortening, or scoliosis if only one half of the spine has been irradiated. Less often seen is toxicity to the liver or gonads coupled with necrosis of the femoral head.

Just as the quality of surgery was improved, so have radiotherapy techniques been refined and dosages determined. Restriction of liver dosage to less than 3000 cGy will prevent clinical hepatic toxicity [9]. Clinical trials, particularly those conducted by the NWTS, have shown that, with favourable histology, major reductions in radiotherapy dosage are possible – down to 1000 cGy – and in many instances radiotherapy has been replaced by chemotherapy.

What has become clearer over the years is that, in many cases, recurrent abdominal disease can be prevented by either radiotherpay or chemotherapy with equal effectiveness, and those who benefit from both forms of treatment are few. Radiotherapy is less effective than chemotherapy in controlling secondary spread outside the abdominal cavity, and its role is becoming smaller but precisely defined. In general, it is used where residual disease is likely to be present, such as stage III cases, and in all those where high risk of recurrence is known, i.e. patients with unfavourable histology. It would also seem valuable adjunctive therapy in stage IV cases when pulmonary irradiation in conjunction with chemotherapy offers better survival than either therapy alone (see below). The risks of radiation pulmonary fibrosis and almost certain death can be averted by keeping pulmonary dosage below 1200 cGy [10].

Chemotherapy

The introduction of every new treatment for Wilms' tumour patients has met with considerable success and, like surgery and radiotherapy before it, the advent of chemotherapy added to clinical success with a further improvement on survival figures by 25%. The introduction of actinomycin D prevented recurrence of disease in the lung fields, but when used to treat established secondary deposits it was much less effective. The realisation quickly followed that patients who were given repeated doses of the drug fared better than those given only a single injection. The age of the oncologist was about to dawn: with other agents proving effective against Wilms' tumour, such as vincristine and then adriamycin (doxo-

rubicin), the surgical mind became bewildered, and patients drifted into the hands of those who seemed to understand the complex modes of administration of these new therapies. The evolution of chemotherapy protocols is a fine example of how fact, fancy, and fiction combined with a good deal of clinical experience and expertise can work to the good of patients, and the improved survival is there for all to see.

The conclusion to be drawn from 20 years of chemotherapy seems to be that chemotherapy is most effective in controlling micrometastases present at diagnosis or disseminated during removal of the tumour.

The usage of chemotherapy and radiotherapy may sometimes seem a little irrational to the busy surgeon, the dosage and spacing of chemotherapy seem to require divine guidance, and the administration and planning of treatment apparently a similar authority. But the refinement of therapy has been an immense triumph for the paediatric oncologist, who has rightly emerged to assume a major role in the management of patients.

It may be helpful to summarise some of the early trial results in simple form:

In Stage I disease:

NWTS I	AMD + DxR → fewer abdominal relapses
NWTS II	VCR + AMD = AMD + DxR
MRC I	VCR more effective than AMD
MRC II	VCR short course = VCR long course
	Surgery + VCR = Surgery + VCR/AMD
	Surgery + VCR = Surgery + VCR/DxR

(VCR: vincristine; AMD: actinomycin D; Do: doxorubicin (adriamycin); DxR: radiotherapy)

In stage II/III disease:

NWTS studies established that disease-free survival at 2 years was:

77% with three drugs (VCR, AMD, Do)
62% with two drugs (VCR, AMD)

and that lymph node status affected the disease-free survival considerably. Disease-free survival overall at 2 years was:

56% when lymph nodes involved
80% when lymph nodes not involved

It was these figures which led to a structuring of staging, bringing lymph node-positive cases into stage III for more intensive treatment.

Broaching the subject of the design of clinical trials can be likened to disturbing a hive of bees. The buzzing and activity induced often leave the culprit weakened and in pain, with a firm resolve that such behaviour should not be repeated: the lure of the honey may be strong, but its collection is best left to those wearing protective clothing. Currently, it seems that whatever strategy is employed, each group collects honey of similar quality!

The SIOP has long held the view that tumour rupture during removal gives an adverse prognosis, and its early trials showed that pre-treatment with radiotherapy followed by chemotherapy were effective in preventing this complication. There has been continued stress on this approach in all subsequent trials conducted by that group, but the overall results obtained in the three main interest groups UKCCSG, NWTS and SIOP seem comparable, and the current treatment plans and thoughts on post-operative therapy will now be described.

Treatments and Results

Stage I, Favourable Histology

It is now evident that patients in this category require little in the way of post-operative treatment, and provisional results from NWTS III suggest that 10-week therapy with vincristine and actinomycin D is as effective as 6-month therapy with regard to relapse-free survival. The UKCCSG trial coordinators will be proposing that vincristine be used for single-agent therapy in these patients for 10 weeks only. Radiotherapy confers no additional benefits and should not be given routinely. The results of this therapy should be excellent and as near 100% survival as is possible with any disease. The pattern of relapse most commonly expected would be relapse in the contralateral kidney, and the frequent use of ultrasound should contribute to the effectiveness of patient surveillance.

Stage II, Favourable Histology

Where the patient has been accurately pathologically staged, and the oncologist is certain from accurate gland sampling at surgery that nodal disease has been excluded, no benefit would seem to accrue from abdominal irradiation. The majority of historical evidence supports the use of chemotherapy alone in controlling local and potentially metastatic disease. It is also felt that 6 months of therapy with vincristine and actinomycin D is sufficient to induce long-term survival in more than 90% of cases, and further therapy brings only more complications without benefit.

Stage III, Favourable Histology

The basic clinical problem for this category is the high risk of microscopic residual abdominal tumour, and routine use of radiotherapy in this group of patients seems sensible. Simultaneous reductions in both chemotherapy and radiotherapy have led to an increased incidence of recurrent disease in some of the current studies, and the recommendation to use both treatment modalities is based on practical as well as theoretical grounds. Current therapy on the NWTS protocol has shown that radiation dosage above 1000 cGy confers no additional benefit to the patient, yet some centres continue to give 2000 cGy and concentrate on reduction in chemo-

therapy duration. Triple-drug therapy is usual with vincristine, actinomycin D, and doxorubicin, and the UKCCSG are proposing a reduction in therapy to a total of 6 months only, after which survival rates of 85% or more should be expected.

Stage III, Inoperable

I have never seen any figures to suggest that patients in the SIOP trials have an incidence of inoperability after pre-treatment, but the overall incidence of inoperability at initial laporotomy is just under 10%. Such patients as these are excluded from NWTS reports and it is difficult to know how best to treat them. The results of the UKCCSG study confirm that survival in this group is 50% only, which agrees with data from my own institution. More intensive therapy, as for stage IV disease, might be applicable. My local figures show that in patients with initial inoperability who subsequently had lymph node involvement, mortality was 100%. An operation to remove a Wilms' tumour is therefore not lightly to be foregone.

Stage IV

Historically, the survival of this group has been poor and only 10 years ago was less than 30%. The small number of patients with such advanced disease makes numerical comparisons difficult. Additional drug therapy, such as adding cyclophosphamide to the AMD/VCR/Do schedule, confers no increase in survival, only in toxic effects, and is not recommended. Radiotherapy to lung fields in NWTS studies has given a 2-year survival of 80% when used in conjunction with surgery and triple-drug chemotherapy, but the current figure for the United Kingdom where radiotherapy has not been given to lung fields is only 50%. Where pulmonary irradiation is used, the incidence of pulmonary fibrosis is 10% at 1400 cGy, but this can be reduced to zero by limiting dosage to 1200 cGy. Chemotherapy usually continues for 12 months.

Unfavourable Histology

Eleven per cent of patients in Wilms' tumour studies have an unfavourable histology, and treatment schedules for them are more intensive. If disease recurs in this group, three out of every four patients will die. Again, it seems that cyclophosphamide adds nothing to survival figures, and that current triple-drug therapy is the best available. Only stage I patients might escape radiotherapy, the remainder receiving 3000 cGy to the tumour area. Survival in this group of patients is about 50%, and without a breakthrough in chemotherapy, seems likely to remain at this level.

Tribulation

If one accepts the morbidity of major abdominal surgery, the hair loss, nausea, and infection associated with chemotherapy, and the growth failure from radiotherapy, then the treatment of Wilms' tumour is indeed a success story. We quantify mortality much more readily than morbidity.

Why then as parents would our hearts grow cold if we were faced with this diagnosis in one of our own dear children? It is because we know that the treatment still failes, the "promised magic" never materialises. It is worth looking at the causes and rate of death in Wilms' tumour:

Surgical complications	1.5% of all patients
Medical complications	2%
Recurrent disease	10%
Treatment complication during relapse	0.75%

The treatment peaks in each stage of this disease may have been scaled, and most patients are now at risk from too rapid descent, too early cessation of chemotherapy or still further dosage reduction in radiotherapy. But the treatment is toxic, does kill, and needs skilful handling and modification.

It must also be remembered that the results reported are from major centres with significant experience in the management of children with this disease. Not every child yet receives that benefit – maybe our efforts ought to be directed towards achieving a more universal acceptance of the principles and practice that govern the treatments reported above.

Summary

Surgery, radiotherapy and chemotherapy are currently the basis of multimodal treatment of Wilms' tumor. Surgery plays the central role in the management of this tumour and will cure 25% of patients if employed alone. Surgical mortality has been reduced to 1.5% at major centres and the most dangerous intra-operative complication is a venacaval tumour embolising into the pulmonary artery. Patients found to be initially inoperable who then have local and systemic therapy, followed by successful secondary surgery, have a reduced survival rate. Definite statements on bilateral tumours are difficult to make. The most fundamental determinants of survival are the histological characteristics of the tumour and the stage of the disease at presentation. Just as the quality of surgery has improved, so have radiotherapy techniques been refined. However, radiotherapy has been replaced by chemotherapy in many instances. The advent of chemotherapy has added to clinical success with a further improvement of survival figures by 25%. Chemotherapy is most effective in controlling micrometastases. However, it must be remembered that the treatment is toxic and needs skilful handling and modification.

Résumé

Exérèse chirurgicale, irradiation et chimiothérapie constituent actuellement l'orientation thérapeutique généralement acceptée pour la tumeur de Wilms. L'exérèse chirurgicale en est l'élément central et, employée seule, elle permet d'obtenir 25% de survives. La mortalité due à l'intervention chirurgicale n'est plus que de 1.5% dans les centres très importants et al complication la plus grave reste la tumeur de la veine cave provoquant une embolie de l'artère pulmonaire. Dans les cas initialement inopérables, quand la mise en place d'un traitement local et systémique est suivie d'une exérèse chirurgicale secondaire, le taux de survie augmente. Il est difficile de pronostiquer clairement l'avenir des tumeurs bilatérales.

La survie dépend essentiellement des caractères histologiques de la tumeur initiale et du stade lors de la première manifestation. De même que les techniques chirurgicales ont fait des progrès, l'irradiation a elle aussi évolué. Toutefois, dans de nombreux cas, l'irradiation a été remplacée par une chimiothérapie.

La chimiothérapie a permis d'obtenir 25% de survies en plus. La chimiothérapie est extrêmement efficace en ce qui concerne le contrôle des micrométastases. Il ne faut pourtant pas oublier que ce traitement est toxique et exige beaucoup de doigté et de souplesse.

Zusammenfassung

Die augenblickliche Behandlung des Wilms-Tumors ist eine kombinierte Behandlung, bestehend aus Chirurgie, Radiotherapie und Chemotherapie. Die Chirurgie hat den Hauptanteil bei dieser Behandlung und ermöglicht eine Heilung bei 25% der Patienten, wenn sie alleine verwendet wird. Die Sterblichkeitsrate bei der Operation wurde auf 1,5% gesenkt in den großen Behandlungszentren. Die gefährlichste Komplikation während der Operation ist eine pulmonale Tumorembolie aus der vena cava.

Bei Patienten mit einem ursprünglich inoperablem Tumor und die einer lokalen und systemischen Behandlung gefolgt von einem gelungenen Sekundäreingriff unterzogen wurden, wurde die Überlebensrate beträchtlich verbessert. Es ist nach wie vor schwierig, Prognosen über bilateralen Tumoren aufzustellen. Von herausragender Bedeutung, was die Überlebenschancen anbetrifft, sind die histologischen Kriterien und das Stadium des Tumors bei der ersten Untersuchung. Die Chirurgie hat Fortschritte gemacht, und die Technik der Radiotherapie ist auch verfeinert worden. Dennoch wird öfters die Radiotherapie durch eine Chemotherapie ersetzt. Die Einführung der Chemotherapie hat dazu beigetragen, die Überlebensrate um weitere 25% zu verbessern. Die Chemotherapie hat sich bei der Kontrolle von Mikrometastasen bestens bewährt. Man darf jedoch nicht vergessen, daß die Behandlung toxisch ist und viel Feingefühl und Anpassungsfähigkeit verlangt.

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The Place of Surgery in the Management of Germ Cell Tumours in Childhood

A. Barrett

Tumours of germ cell origin are very rare. In the Manchester Children's Registry from 1954–1978 141 cases were recorded. There appears, however, to be a continuing trend to increasing incidence, first noticed in 1973, so that the annual incidence is now four per million person years, compared with one in 1954. The factors responsible for this increase have not been clearly defined. Malformations, particularly of the central nervous and genito-urinary systems, may be found in association with benign teratomas or yolk sac tumours [1].

Discussion of the management of these tumours is made more difficult because of the variety of histological subtypes to be considered and the multiplicity of sites of origin. A comparison of the British Testicular Tumour panel and the World Health Organisation (WHO) classifications [2] is shown in Table 1. Yolk sac tumours comprise the entities formerly described as endodermal sinus tumours, orchioblastoma, infantile adenocarcinoma and Teilum's tumour. Dysgerminoma of the ovary in childhood is analogous to seminoma in the adult. Their probable histogenesis from the primitive germ cell is shown in simplified form in Fig. 1.

Tumours may arise in any site where there is arrest of germ cells during embryological development. Cells from the yolk sac endoderm (the germinal ridge on the posterior wall of the embryo) migrate round the primitive hind gut where the

Table 1. Comparison of classifications of germ cell tumours by the British Testicular Tumour Panel (BTTP) and the World Health Organisation (WHO)

BTTP	WHO
Teratoma	
Differentiated	Mature teratoma
Malignant undifferentiated	Embryonal carcinoma
Malignant intermediate	Immature teratoma
Malignant trophoblastic	Choriocarcinoma
Yolk sac tumours	Yolk sac tumour
(endodermal sinus tumours, orchioblastoma, Teilum's tumour, infantile adenocarcinoma)	
Dysgerminoma (seminoma)	Germinoma

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Progress in Pediatric Surgery, Vol. 22
Ed. by L. Spitz et al.

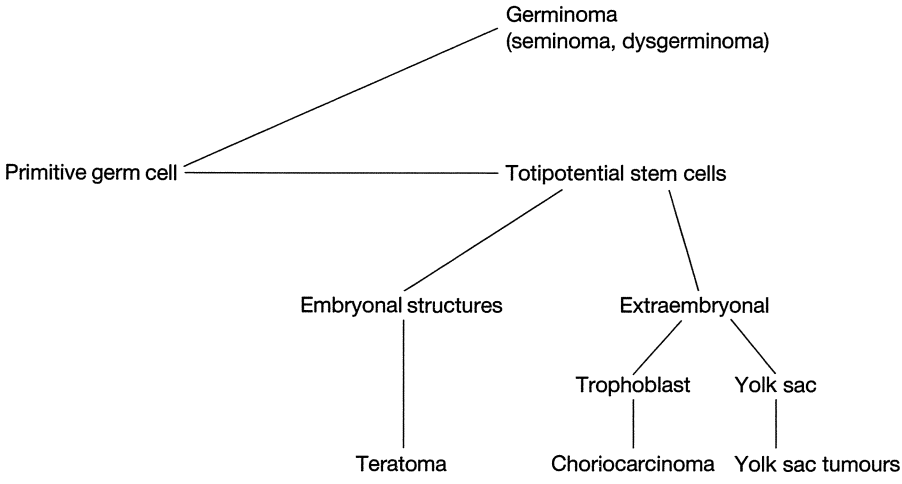

Fig. 1. Histogenesis of germ cell tumours

gonad develops and subsequently descends to its final position in the pelvis or scrotum.

Aberrant patterns of migration may carry cells to the pineal region or mediastinum or occasionally to other sites such as the eye, orbit, liver, vagina or sacrococcygeal region, and malignant transformation may then lead to tumour development in any of these sites.

A major contribution to the management of these tumours was made with the development of radio-immunoassays for serum α-fetoprotein (AFP) and β-human chorionic gonadotrophin (βHCG). Tumours of yolk sac origin may produce AFP and those of trophoblast βHCG which can be used to monitor response to treatment. Blood for these assays should be taken before any surgical excision and then serially post-operatively. Initially elevated values which return to normal within the expected half-life (for AFP 4–7 days and for βHCG 24 h) indicate complete removal of tumour, rendering further treatment unnecessary. Persistently elevated levels should fall in response to effective therapy. Complete remission can only be confirmed when all clinical parameters *and* serum marker levels are normal. Investigation of a placental alkaline phosphatase suggests it may be a useful marker for some dysgerminomas [3].

The management and prognosis of malignant germ cell tumours has been radically changed by the advent of effective chemotherapy. From 1970, combinations of vincristine, doxorubicin (adriamycin) or actinomycin and cyclophosphamide have been used and have proved curative in many patients with ovarian or testicular lesions, especially yolk sac tumours [4]. The response of mediastinal and sacrococcygeal tumours to these agents has been less favourable. Primary pineal tumours have conventionally been treated with radiotherapy to the brain and craniospinal axis, with good results in the radiosensitive types such as germinomas.

The development by Einhorn and Donohue [5] of a regimen consisting of vinblastine, bleomycin and platinum for the treatment of testicular teratomas in adults has proved equally effective in the management of germ cell tumours in childhood and has improved the control rate of lesions which previously had a poor prognosis [6–9]. Addition of other drugs may increase response rates [10], and substitution of etoposide for vinblastine has reduced the toxicity [11]. Courses of treatment are given at 3-weekly intervals until serum markers return to normal values or maximal tumour regression is obtained. The toxicity is considerable, often with severe vomiting, weight loss and electrolyte disturbances, and extra hospital admissions for treatment of septicaemia are frequent. In spite of this toxicity, chemotherapy of this type is probably the optimal primary treatment for all tumours other than those confined to the ovary or testis, and it is in the light of this that the role of surgery must be considered.

Surgery for Diagnosis

In most instances surgery will be required to obtain a histological diagnosis, although problems may arise from sampling a tumour which may be very heterogeneous. Immunofluorescent staining for AFP and βHCG may be helpful in determining the tumour type. If complete surgical excision is not possible without functional or cosmetic impairment it should not be attempted and an incisional biopsy is adequate. In rare circumstances even biopsy may not be indicated. For example, a child over the age of 1 year presenting with superior vena-caval obstruction from an anterior mediastinal mass, and in whom elevated serum levels of AFP are found, has a germ-cell tumour, and chemotherapy may be started forthwith – avoiding the hazards of biopsy and delay in treatment.

Biopsy of pineal lesions has in the past been considered very hazardous, but with modern techniques of anaesthesia and stereotactic surgery it has become safer and should be attempted whenever possible, since knowledge of the histological subtype may be important. Germinomas may be very radiosensitive, where teratomas are not, and definitive diagnosis will enable one to avoid potentially toxic brain irradiation where it is unlikely to be effective [12].

Surgery for Cure

Removal of primary tumours may be elective or performed as an emergency for torsion of an ovary or testis.

Surgery alone is the treatment of choice for stage 1 ovarian or testicular tumours [13]. If serum AFP or βHCG levels were raised pre-operatively they must be measured sequentially to confirm return to normal within the expected half-life. No further treatment is then necessary, regardless of histology. Failure of a marker to return to normal is an indication for chemotherapy. It must be remembered that physiologically high levels persist in infants under 1 year.

For testicular tumours, the testis should be removed through an inguinal excision, with high ligation of the cord. Scrotal incisions or aspiration of a hydrocele should be avoided where malignancy is suspected.

For ovarian tumours, the occasion of laparotomy should be used to rule out intra-abdominal spread or to determine its exact extent, since investigations such as CT scanning of the abdomen are often unhelpful. The peritoneum, particularly over the inferior surface of the diaphragm and the liver, the broad ligament, the uterus and the other ovary, should be examined and any ascites studied histologically, with measurement of markers. For tumours localised to one ovary, unilateral salpingo-oophorectomy with preservation of the uterus and other ovary is adequate. If more extensive disease is found, chemotherapy is indicated in the first instance. Careful follow up with post-lymphography abdominal radiography, CT scanning and markers is necessary, since chemotherapy may still be curative for relapses occurring after surgery alone.

Surgery is also the treatment of choice for benign teratoma in accessible sites. Sacrococcygeal lesions occurring at or soon after birth should be excised radically as early as possible, since delay in removal predisposes to malignant change [14]. Excision should include complete removal of the coccyx and tumour en bloc with any local extensions. This reduces the local recurrence rate from 8–37% (when the coccyx is not removed) to a negligible incidence [15, 16].

Node Dissection

The place of retroperitoneal node dissection in the management of testicular and, to a lesser extent, ovarian tumours has been much disputed. Lymph node involvement in up to 13% of cases has been reported from centres which have routinely undertaken this procedure, with significant complications in a proportion of patients.

In a review of all reported testicular yolk sac tumours, a comparison of disease-free survival of children after orchidectomy alone with those undergoing orchidectomy and unilateral or bilateral retroperitoneal node dissection showed no significant difference [17]. Its value is, therefore, purely in the diagnosis of microscopic disease, since enlarged nodes can be demonstrated by scanning or lymphography. Many tumours, particularly those of yolk sac derivation, spread haematogenously and lung metastases will occur simultaneously with node metastases, so that chemotherapy will in any case be necessary. The role of surgical removal of nodes after chemotherapy will be discussed below.

Surgery for Residual Disease

Residual masses in sites of initially bulky disease may persist after chemotherapy. If all distant metastases have been cleared, surgery may then be advisable, although its role is not yet clearly defined. Residual masses may consist of fibrous

tissue only, or mature teratoma, but even for these excision may be necessary, since reactivation of benign teratoma after many years has been observed. Removal of abdominal nodes or a localised mass may reveal persistent tumour at the centre of a necrotic or fibrotic lesion, and surgery with or without further chemotherapy may then convert partial remission to cure. This approach may be required particularly for sacrococcygeal tumours, which are often very large at presentation: it seems prudent to remove any residual mass and the coccyx, as for benign lesions in the infants. Complete remission of mediastinal tumours is often difficult to achieve by chemotherapy alone because of their bulk. Surgery should be attempted after maximum shrinkage has been obtained, but is often difficult because of the close association of the tumour with the great vessels and heart. In adults with testicular tumours, surgery for residual disease appears to have a therapeutic as well as a diagnostic role. Subsequent relapse is more likely where there has been a previous incomplete or difficult excision [18].

Prophylactic Surgery

Prophylactic surgical removal of gonads may be indicated to prevent the development of malignancy in two situations. Maldescent of the testis is associated with a 20-fold increase in malignant change. There is also an increased risk of development of a tumour in the contralateral testis [11]. Patients with gonadal dysgenesis have a 25% risk of developing a germ cell tumour, either a germinoma or a gonadoblastoma. Gonadoblastoma, which usually occurs before the age of 20, behaves benignly but may be associated with a malignant tumour in the opposite gonad. Surgical removal of both gonads may be recommended [19].

Summary

Because of their rarity and the availability of effective, if toxic, treatment, germ cell tumours should be managed by a team familiar with their behaviour and response to therapy. Treatment decisions from the time of presentation onwards should be made by surgeon and oncologist together, and, where the diagnosis is made unexpectedly after emergency surgery, early consultation is necessary to establish the best approach to treatment for that individual patient. Mutual recognition of the possibilities and problems of each modality of treatment will lead to their use together in the most effective way.

Résumé

Les tumeurs des cellules germinales sont très rares mais il existe un traitement, toxique mais efficace et qui ne devrait être confié qu'à des équipes parfaitement rodées à l'évolution et la réponse de ces tumeurs au traitement. Les décisions

thérapeutiques doivent être prises, dès l'apparation de ces tumeurs, en un commun accord avec le chirurgien et le cancérologue et, dans le cas d'un diagnostic fortuit (découverte chirurgicale, par exemple), cette décision doit être prise avec le consultant afin de correspondre au plus près aux besoins individuels du patient.

Si chacun est prêt à reconnaitre le bien fondé et les problèmes des différentes modalités du traitement, l'efficacité pourra être assurée.

Zusammenfassung

Da Keimzelltumoren sehr selten sind und ihre Behandlung toxisch ist, sollte diese Behandlung ausschließlich den Teams vorbehalten bleiben, die mit der Entwicklung und dem Ansprechen dieser Tumoren auf die Behandlung vertraut sind. Von der ersten Untersuchung an sollte die Behandlung zwischen dem Chirurgen und dem Onkologen abgesprochen werden. Wird die Diagnose zufällig gestellt, z. B. im Laufe eines chirurgischen Eingriffes, ist eine sofortige Konsultation unerläßlich, um die bestmögliche Behandlung für den Patienten festzulegen. Gegenseitige Anerkennung der Möglichkeiten und Probleme wird die Zusammenarbeit fördern und die Erfolgschancen verbessern.

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Second Primary Tumours in Children

J. E. Kingston

Introduction

The quality of life and late morbidity following treatment for cancer in childhood are matters of increasing concern to clinicians, because approximately 50% of children newly diagnosed with cancer will be alive at 5 years from diagnosis and a large proportion of these will survive to adulthood. With the experience gained from long-term follow-up of these patients, the considerable optimism engendered by the improvements in survival has been tempered by a growing awareness that children who have been successfully treated for one cancer appear to be at risk of developing a second malignancy [1, 2, 3]. The problem of second malignancies is most pertinent to those children who have a relatively good prognosis, for example, children with retinoblastoma, Wilms' tumour and Hodgkin's disease. However, following the introduction of effective therapy for children with malignancies which until recently were associated with a poor prognosis, for example, leukaemia and non-Hodgkin's lymphoma, increasing numbers of second tumours are now being observed in children with these diagnoses. Unfortunately, no tumour type appears to be immune to the problem of second malignancy.

Incidence of Second Tumours

Two major epidemiological studies, one an international study by the Late Effects Study Group (LESG), initiated in the United States, and the other a British population-based study carried out by the Childhood Cancer Research Group (CCRG) in Oxford, have been set up to monitor the incidence of second tumours and to establish the magnitude of the problem. In an analysis of the LESG data [3], Mike et al. reported that children with one malignancy have a ten-fold increased risk of developing a second cancer compared to age-matched population controls, with a cumulative risk of 12% by 20 years from diagnosis of the first tumour. Results from the British study suggest a somewhat lower incidence with a relative risk of approximately 6 times at 10 years from diagnosis of the first tumour [4]. However, it appears that the incidence of second tumours is increasing, and in the British

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Progress in Pediatric Surgery, Vol. 22
Ed. by L. Spitz et al.

Table 1. Number of double tumour cases by year of diagnosis of first tumour (source: British study by Kingston et al. [5])

Diagnosis of first tumour	Year of diagnosis of first tumour					All years
	1940–1949	1950–1959	1960–1969	1970–1979	1980–1982	
CNS tumour	6	15	10	9	5	45
Retinoblastoma	11	8	14	4	–	37
Acute leukaemia	–	–	–	14	2	16
Lymphoma (HD/NHL)	–	1	3	10	3	17
Wilms' tumour	1	5	4	3	–	13
Neuroblastoma	–	1	3	1	–	5
Rhabdomyosarcoma	–	1	–	3	1	5
Carcinoma	–	1	1	4	–	6
Osteosarcoma/Ewing's sarcoma	–	1	3	2	–	6
Other	2	4	5	–	–	11
Total	20	37	43	50	11	161

HD/NHL: Hodgkin's disease/non-Hodgkin's lymphoma

study [5] more multiple primary tumour cases have already been identified for the decade 1970–1979 than for the previous decade (Table 1), even though the period of risk for patients diagnosed during the 1970s is shorter.

Children with the genetic form of retinoblastoma appear to be at greatest risk of developing a second neoplasm. Abramson et al. [6] have assessed the incidence of second tumours in retinoblastoma patients as ranging from 20% after 10 years 90% after 30 years. However, studies by Draper et al. [7] indicate a much smaller risk with an actuarially calculated cumulative risk of 8.4% after 18 years.

Patterns of Double Tumours

Bone sarcomas are the most frequently observed second neoplasms following treatment for cancer during childhood. Acute leukaemia, tumours of the central nervous system (CNS), carcinomas and soft tissue sarcomas are also commonly encountered (Table 2). A frequently observed association of tumours is that of retinoblastoma with either osteosarcoma or soft tissue sarcoma, accounting for about 16% of all cases in the British study. Recently several children with leukaemia or lymphoma and a tumour of the CNS have been described, and it has been suggested that such cases may represent a new genetic syndrome [8]. The development of acute non-lymphocytic leukaemia (ANLL) after treatment for Hodgkin's disease in adults is well documented [9, 10], with an incidence as high as 6% at 10 years in patients receiving a combination of chemotherapy and radio-

Table 2. Patterns of double tumour cases (source: British study of Kingston et al. [5])

Diagnosis of first tumour	Diagnosis of second tumour								All
	Osteo-sarcoma	CNS	Skin	Leukaemia	Soft-tissue sarcoma	Carcinoma	Lymphoma	Other	
CNS tumour	2	12	7	5	6	9	1	3	45
Retinoblastoma	21	5	3	1	4	3	–	–	37
Acute leukaemia	1	7	–	3	–	1	3[a]	1	16
Wilms' tumour	2	–	1	1	4	5[b]	–	–	13
Hodgkin's disease	2	1	3	2	1	–	1	–	10
Non-Hodgkin's lymphoma	1	1	–	4	1	–	–	–	7
Neuroblastoma	–	–	1	1	–	1	–	2	5
Rhabdomyosarcoma	1	1	1	–	–	1	–	1	5
Ewing's sarcoma	1	–	1	1	–	–	–	1	4
Osteosarcoma	–	–	–	1	–	1	–	–	2
Carcinoma	2	1	–	–	1	1	–	1	6
Adrenal cortical tumour	1	1	–	–	–	–	–	1	3
Other	1	2	2	–	1	2	–	–	8
Total	35	31	19	19	18	24	5	10	161

[a] Includes two children with Hodgkin's disease
[b] Includes three patients with carcinoma of the colon

therapy [9]. Following the introduction of intensive combination chemotherapy into treatment programmes for childhood Hodgkin's disease, the development of ANLL also appears to be an increasing problem in children. The latent interval to the development of a second neoplasm is variable and second malignancies have been described at intervals ranging from less than 1 month to more than 40 years, with a peak incidence between 5 and 15 years following the diagnosis of the first tumour.

Aetiological Factors

Although the occurrence of multiple primary tumours in an individual may reflect an inherent predisposition to cancer, it seems likely that the therapies given to eradicate the first tumour are significant factors in the pathogenesis of many second tumours. Most children with cancer are treated with either radiation or cytotoxic agents and many receive a combination of these two modalities of treatment.

Table 3. Factors predisposing to the development of the second tumour (source: British study by Kingston et al. [5])

Diagnosis of second tumour	Within/ edge of radiation field	Chemo-therapy	Hormone therapy	Genetic factor
Osteosarcoma	17	14	2	22
CNS tumour	22	10	2	7
Skin tumour	14	–	4	5
Leukaemia	16	13	2	2
Soft-tissue sarcoma	8	6	2	10
Carcinoma	11	3	2	6
HD/NHL	1	3	–	–
Other	2	1	1	1
Total	91	50	15	53

However, "simultaneous" double tumours, i.e. tumours developing within a few months of each other, are unlikely to be related to therapy and occur more frequently in children with conditions predisposing to cancer, suggesting a genetic influence.

Radiation

The carcinogenic potential of ionising radiation is well recognised. In 1977, Li [11], reporting a series of 36 second tumours in children, stated that 28 of the total could be attributed to prior radiation. The basis for this assumption was that the second tumour developed within tissue that had been irradiated. In a recent analysis of the LESG data [12], 208 (67%) of 308 second tumours were classified as radiation-associated. In the British study [5], 61% of the second tumours were considered to be radiation-associated (Table 3). In 52 children, the second tumour was situated within tissue that had been irradiated, while in 23 the tumour developed on the edge of the radiation field. A further 16 children who had been irradiated developed acute leukaemia as their second tumour. The finding that a significant proportion of radiation-associated second tumours develop on the edge of a radiation field has been noted by other workers [8].

Chemotherapy

Animal studies with cyclophosphamide have shown that the main target organs for oncogenesis are the haemopoietic system, bladder and nervous tissue. The

problem of the carcinogenic activity of antineoplastic drugs in humans is complex. In patients treated with a combination of drugs it is often difficult to identify the specific carcinogenic agent, and assessment is frequently complicated by the fact that many patients treated with cytotoxic drugs have also received radiation at some stage during their illness. In a review of the double tumour cases reported in the literature, where chemotherapy was considered to have been an aetiological factor in the induction of the second malignancy, Schmähl et al. [13] found that an alkylating agent was implicated in the majority of cases. Cyclophosphamide, chlorambucil and melphalan were the drugs most frequently cited. In the recent analysis of the LESG data [12], 49 children developing second malignancies had been treated with chemotherapy alone and all but two of these had been treated with at least one alkylating agent. In the British study, 50 children (33%) had received single or multiple agent chemotherapy either as the sole mode of treatment or in combination with radiotherapy. An alkylating agent had been used in 38 of the 50 children. Thirty-two children had received cyclophosphamide, and the remaining six either mustine or procarbazine.

Genetic Factors

Recently, clinicians have become aware that second tumours occur more frequently in children with known cancer-predisposing diseases. A number of genetically determined conditions such as von Recklinghausen's disease, tuberose sclerosis and basal cell naevus or Gorlin's syndrome are frequently associated with the development of multiple primary neoplasms [14]. In the report by Meadows et al. [12] of the LESG data, 73 (25%) of a total of 292 patients had a known cancer-predisposing condition, a much higher percentage than in the overall population of children who develop cancer. In the British study, a possible genetic influence was identified in 53 (33%) of the total of 161 patients. The genetic diseases included familial retinoblastoma, von Recklinghausen's disease, Gorlin's syndrome, tuberose sclerosis, Sipple syndrome, Turcot's syndrome and the Klippel-Trenaunay-Weber syndrome. A family history of malignancy in at least one first-degree relative was identified in a further eight cases with no known genetic disease, although four of these families had features of the Li-Fraumeni syndrome. Three children had a sibling with cancer and in two the tumours were concordant.

Hormone Therapy

In the British study, 15 patients had received hormone replacement therapy. Two of the three patients treated with oestrogen replacement therapy for ovarian dysfunction developed malignant tumours of the uterus: a leiomyosarcoma in one and an adenocarcinoma in the other. One child with a pituitary adenoma, treated with injections of growth hormone for growth failure secondary to pituitary irradiation, subsequently developed an osteosarcoma of the femur.

Discussion

It is evident that the number of children developing second primary tumours is increasing. This is partly explained by the increased number of survivors at risk but probably reflects the likelihood that intensification of treatment programmes is contributing to the induction of second tumours. Patterns of second tumours also appear to be changing. Prior to 1970, the two tumour types most frequently associated with the development of a second tumour were familial retinoblastoma and CNS tumours. Since 1970, children with leukaemia and lymphoma have been the major group to develop second tumours (see Table 1).

In previously reported series of second tumours following treatment for childhood cancer, radiation was considered to be an important aetiological factor in the induction of the majority of the second tumours [2, 8]. There is a paucity of data available on the effect of chemotherapy in relation to second malignancies but at least one recent report has commented on the excess of secondary leukaemia following the use of alkylating agents [15]. It appears that children with an underlying genetic disorder may be more susceptible to the carcinogenic influence of ionising radiation and certain cytotoxic drugs, in particular the alkylating agents.

One of the more interesting childhood tumours to study with regard to second tumours is retinoblastoma. Retinoblastoma is genetic in approximately 40% of cases and it appears that the increased risk of second tumours in retinoblastoma is confined to children with the genetic form of the disease [7]. The most commonly observed second tumour in children with retinoblastoma is osteosarcoma and the risk of developing osteosarcoma appears to be many hundred times greater in these children than in the general population. The retinoblastoma gene has been mapped to band 14 on the long arm of chromosome 13; of considerable interest, therefore, is a recent report that the genes for osteogenic sarcoma and retinoblastoma may have a common chromosomal origin [16]. During the past decade it has been recognised that some patients with Wilms' tumour carry a genetic predisposition, and a specific deletion of band 13 on the short arm of chromosome 11 has been described in a small proportion of patients. In the LESG series [12], 30% of the children with Wilms' tumour who developed a second tumour had characteristics compatible with the genetic form of the disease, e.g. bilaterality, positive family history and/or specific congenital anomalies.

Summary

The problem of second primary tumours is likely to increase in magnitude as the number of long-term survivors of childhood cancer grows and treatment protocols are intensified. Children with an underlying genetic disease appear to be at particular risk of developing a second tumour. While most cases of second malignancy appear to be associated with either radiotherapy or chemotherapy, a small proportion of patients have no identifiable risk factor. In these children, unrecognised predisposition or, indeed, chance may play a role. It would seem to be im-

portant to identify factors such as genetic susceptibility and specific modalities of therapy, including ionising radiation and alkylating agents, which may contribute to the development of second tumours, because awareness of the risk factors may make it possible to modify treatment programmes and thereby minimise the risk of second neoplasms. Long-term surveillance of patients treated for cancer during childhood is recommended so that the problem of second malignancies can be monitored.

Résumé

Le risque de voir apparaître une seconde tumeur primaire augmente en fonction du nombre croissant de survies dans les cas de cancers de l'enfance et en fonction de l'amélioration des orientations thérapeutiques. Les enfants présentant une affection génétique sous-jacente courent un risque accru de voir se manifester une seconde tumeur. Dans la plupart des cas, une seconde tumeur maligne semble liée à l'irradiation ou à la chimiothérapie mais, dans le cas d'un certain nombre de patients, aucun facteur de risque n'est identifiable. Dans le cas de ces enfants, il semble qu'une prédisposition non identifiée ou tout simplement le hasard, soit à mettre en cause. Il semblerait donc utile d'identifier les facteurs de risque tels que susceptibilité de nature génétique et modalités spécifiques de traitement pour minimiser le risque d'un second néoplasme malin. Il est donc utile de suivre à long terme les patients traités pour une affection cancéreuse durant leur enfance pour contrôler le problème des secondes tumeurs malignes.

Zusammenfassung

Das Problem eines zweiten Primärtumors wird sich vermutlich immer häufiger stellen, denn die Anzahl der Kinder, die eine Krebserkrankung in der Kindheit überlebt haben, wird immer größer und die Behandlungsmethoden werden immer intensiver. Es sieht so aus, als ob Kinder mit einer genetischen Grunderkrankung dem Risiko eines zweiten Tumors besonders ausgesetzt wären. In vielen Fällen eines zweiten Malignoms scheint es einen Zusammenhang zu geben zwischen dieser Erkrankung und der Durchführung einer Radiotherapie oder Chemotherapie, aber bei einem kleinen Prozentsatz der Patienten läßt sich kein eindeutiger Risikofaktor ermitteln. Bei diesen Kindern spielt vermutlich eine unerkannte Veranlagung oder auch nur der Zufall eine Rolle. Es wäre also von Bedeutung, Faktoren wie genetisch bedingte Anfälligkeit oder bestimmte Modalitäten der Therapie zu erkennen, um das Risiko eines zweiten Tumors einzugrenzen. Kinder, die wegen einer Krebserkrankung behandelt wurden, müssen sehr langfristig Kontrolluntersuchungen durchführen lassen, um das Problem einer zweiten bösartigen Erkrankung in den Griff zu bekommen.

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Fibrous Tissue Tumours

Y. Hayashi, L. Spitz, E. Kiely, J. Pritchard, and J. R. Pincott

Tumours of fibrous tissue origin are typically composed of a mixture of fibroblasts and their biosynthetic product, collagen. The group includes a range of pathological conditions from the fibromatoses to malignant fibrosarcomas. Most show a greater or lesser propensity for focal infiltration and, if incompletely resected, will recur. Metastases rarely occur, however, even from fibrosarcomas. The classification of these tumours has undergone little modification since it was originally documented by Stout in 1951 and 1954 [1, 2].

Treatment consists primarily of local excision. Radiotherapy and/or chemotherapy have recently been employed with varying degrees of success as adjunctive therapy.

In this paper we describe an analysis of 33 patients admitted to The Hospital for Sick Children, Great Ormond Street, London, over a 15-year period.

Clinical Material

From 1970 to 1984, 33 infants and children with newly diagnosed fibrous tissue tumours were admitted to the Hospital for Sick Children: 15 male and 18 female. The age distribution of the patients is shown in Fig. 1. Seven infants had one or

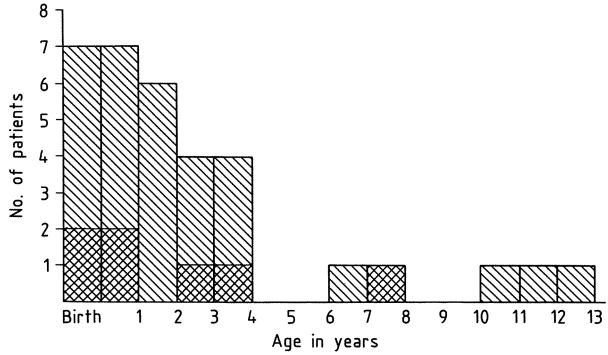

Fig. 1. Age distribution of the patients. The darker hatched areas indicate cases of fibrosarcoma

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Progress in Pediatric Surgery, Vol. 22
Ed. by L. Spitz et al.

Table 1. Anatomical distribution of the fibrous tissue tumours. Figures in parentheses indicate fibrosarcoma

Site	No. of cases
Head and neck	10 (1)
Upper extremity	6 (1)
Hand	4
Upper arm	1 (1)
Shoulder	1
Lower extremity	5 (2)
Foot	3 (1)
Thigh	1
Buttocks	1 (1)
Trunk	6
Chest wall	1
Abdominal wall	2
Axilla	2
Perineum	1
Thoracic cavity	2 (1)
Heart	1
Post. mediastinum	1 (1)
Abdomen/GIT	4 (2)
Pelvis	1
Bladder	1 (1)
Small bowel mesentery	1
Anal canal	1 (1)
Total	33 (7)

GIT, Gastrointestinal tract

more lesions recognised at birth, and in a total of 14 infants (42%) the lesions were noted during the 1st year of life. The mean age at presentation was 3.3 years.

The anatomical distribution of the lesions is shown in Table 1. The sarcomatous cases involved the upper arm, foot, buttocks, nasal cavity, posterior mediastinum, urinary bladder and anal canal. There were three infants with multiple primary tumours (Table 2).

The individual tumours ranged in size from 0.5 cm to 19 cm in diameter, with an average diameter of 5 cm. The histopathological classification of the lesions is listed in Table 3. Five of the seven cases of fibrosarcoma were classified as the infantile variety, while the remaining two were designated low-grade fibrosarcoma and myxomatous fibrosarcoma.

Where technically feasible, complete excision of the tumour was carried out. This was accomplished primarily in 22 patients and in a further six following an

Table 2. Patients with multiple primary lesions

Age at diagnosis	Sex	Anatomical sites	Histological diagnosis
3 months	F	All fingers of left hand	Infantile digital fibromatosis
2 years	F	Scalp, face, back, chin and hand	Juvenile hyaline fibromatosis
At birth	F	Both elbows	Infantile fibrosarcoma

Table 3. Histopathological classification of the lesions

	No. of cases
Fibrosarcoma	7
Infantile fibromatosis	7
Infantile digital fibromatosis	5
Musculo-aponeurotic fibromatosis	2
Fibrous hamartoma of infancy	2
Congenital keloid	2
Generalised congenital fibromatosis	1
Fibromatosis colli	1
Palmar fibromatosis	1
Juvenile hyaline fibromatosis	1
Gardner's syndrome	1
Cardiac fibroma	1
Mesenteric fibromatosis	1
Nasopharyngeal fibroma	1
Total	33

initial biopsy. In two of these patients excision was delayed until after a course of radiotherapy and multi-agent chemotherapy, and in one after a course of radiotherapy alone had been administered. Only partial resection of the tumour was possible in three patients, one of whom received a course of postoperative radiotherapy. One infant with a large pelvic tumour died after biopsy only of an unresectable mass. A 3-year-old girl has shown a good response to chemotherapy (vincristine and actinomycin D) for a huge unresectable primary tumour of the neck and is disease-free 6 months after therapy.

There were two deaths in this series. The femal infant referred to above died at the age of 20 days with an unresectable pelvic tumour. The second death occurred in a 6-year-old boy who died during attempted resection of a fibroma of the left ventricle of the heart.

Recurrence of the tumour was recognised in 14 of 29 children. Two cases are excluded, one for insufficient follow-up data and the other being too recent for

assessment. The recurrence rate was therefore 48.2%. Nine patients (31%) experienced multiple recurrences of their tumours, ranging from once to eleven times. The time interval between excision and appearance of the recurrence ranged from 1 month to 4 years, with an average time interval of 13.8 months. The recurrence rate for the sarcomatous tumours was similar to the tumours with a more benign appearance on histopathological examination.

Illustrative Cases

Case 1

A 3-week-old female infant underwent amputation of a perianal polyp (Fig. 2) which on histological examination was shown to be an infantile fibrosarcoma with

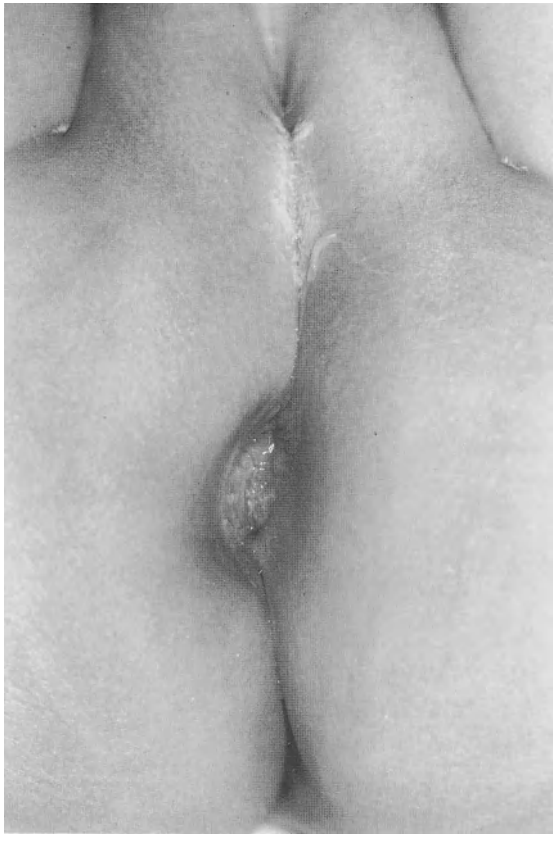
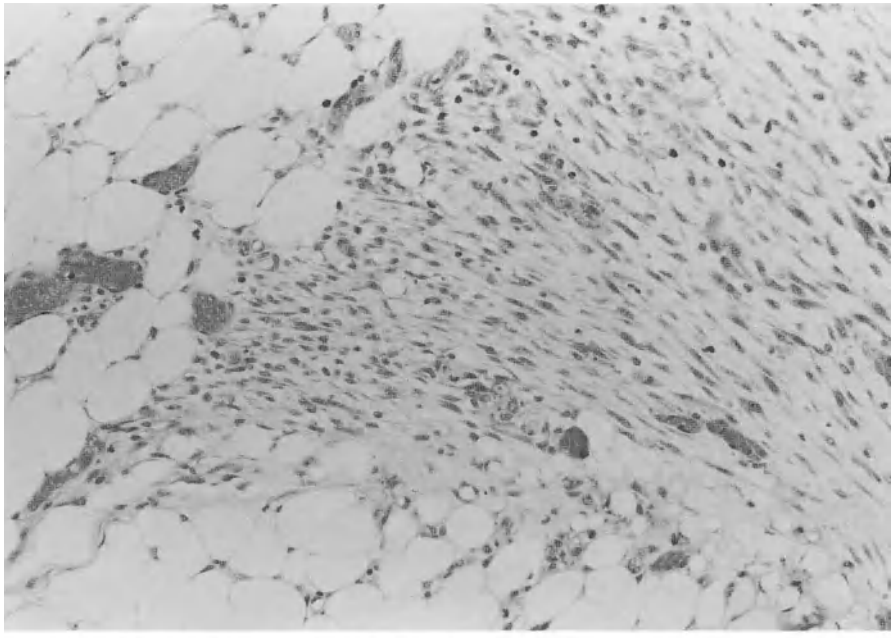


Fig. 2. Case 1, fibrosarcoma involving the right side of the anal canal in a 3-week-old female infant



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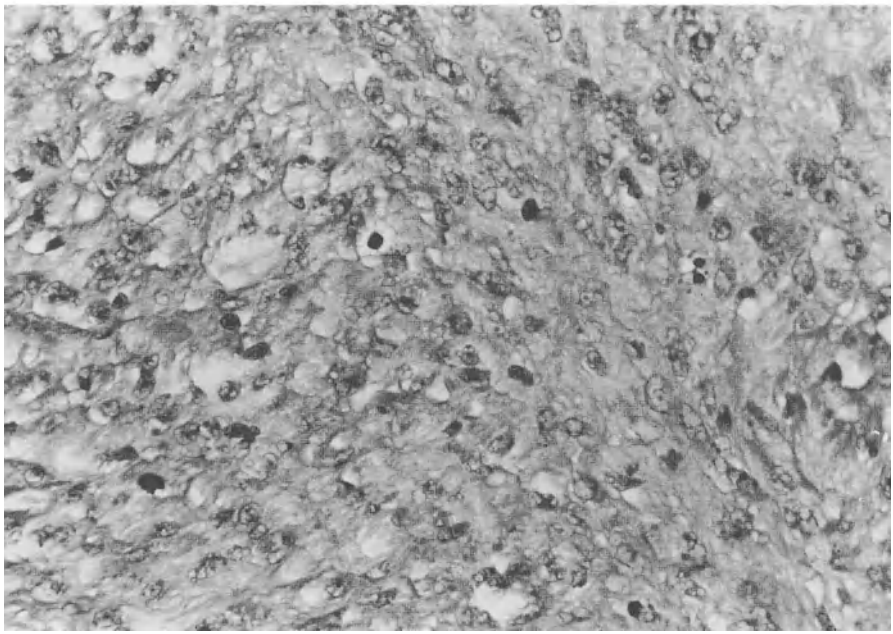

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Fig. 3. Case 1, infantile fibrosarcoma. Fasciculi of plump fibroblasts infiltrate deeply into perianal adipose tissue. Haematoxylin and eosin × 200

Fig. 4. Case 1, infantile fibrosarcoma. The tumour comprises interwoven fasciculi of plump, though only mildly pleomorphic fibroblasts, with occasional mitotic figures. Masson's trichrome stain × 500

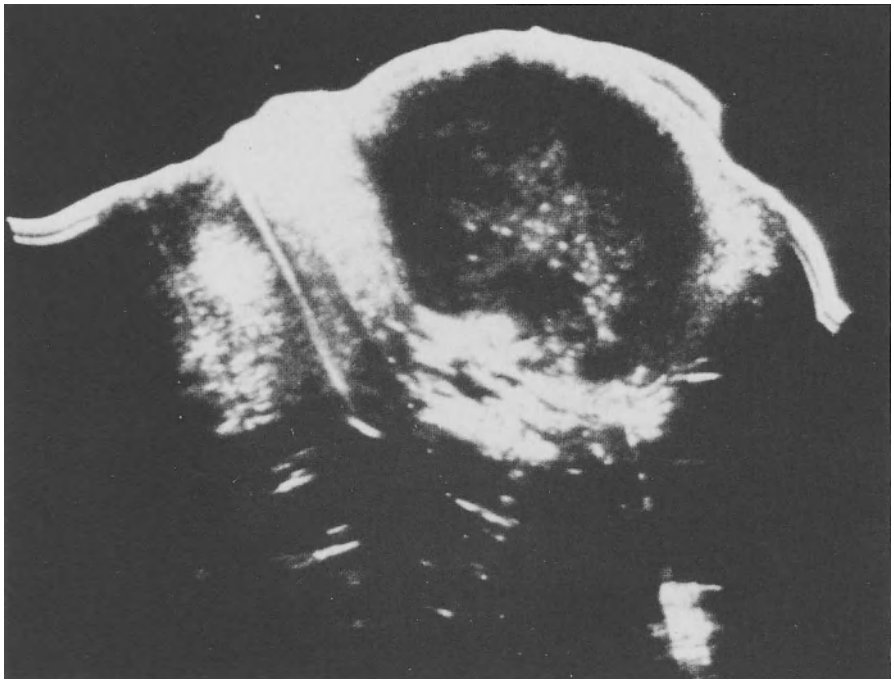

Fig. 5. Case 2. Untrasound scan showing a large solid tumour in the abdomen in the patient

invasion of the base (Fig. 3). She was transferred to this hospital where three further local excisions and the establishment of a temporary defunctioning sigmoid colostomy were performed before histologically clear margins were achieved (Fig. 4). The perianal wound healed by secondary intention and 1 year later, local recurrence and metastatic disease having been excluded, the colostomy was closed.

Addendum 1988: Two years later the tumour recurred locally. A further biopsy reevaluation of the original histopathology was undertaken. The diagnosis changed to that of a rhabdomyosarcoma.

Case 2

A 2-year-old girl was admitted with a large firm central abdominal mass. The lesion was shown to be solid on ultrasound scan (Fig. 5) and separate from the kidneys. Investigations for neuroblastoma were negative. At laparotomy a solid tumour $11 \times 8 \times 6$ cm was found within the small bowel mesentery (Fig. 6). A 95% resection only was possible as complete excision would have severely compromised the vascular supply to the small intestine. Follow-up 3 years later revealed no evidence of recurrence.

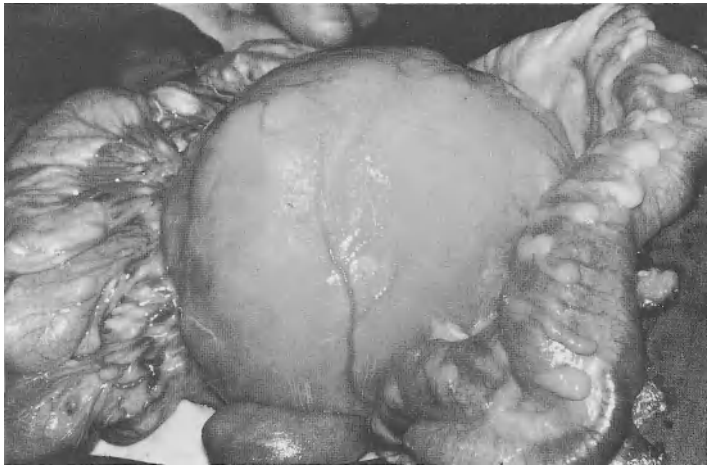

Fig. 6. Case 2, fibromatosis of small intestinal mesentery

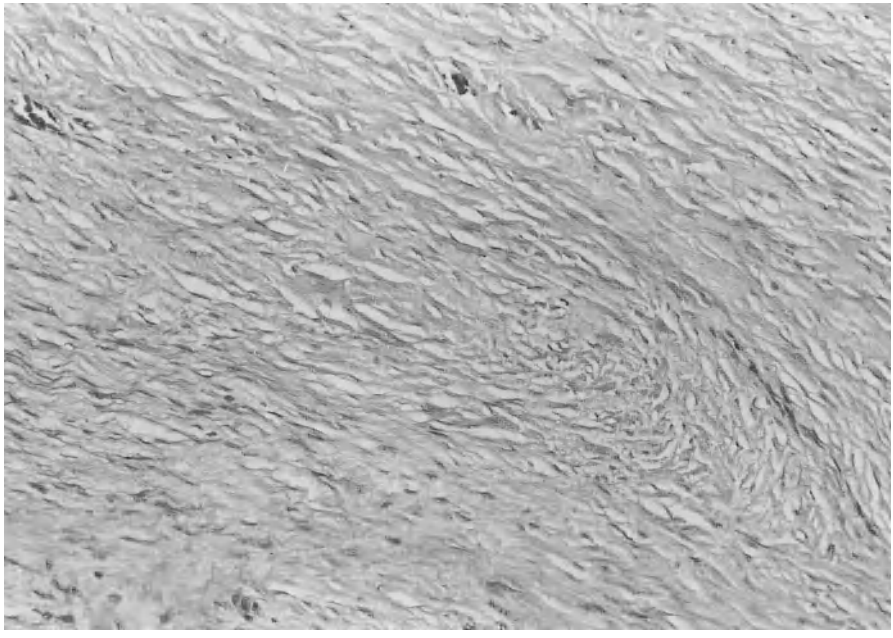

Fig. 7. Case 3, infiltrative fibromatosis. The tumour is mainly collagenous, though the fibroblasts appear plump; no mitotic figures are seen. There is, however, a discernible fascicular pattern. Haemotoxylin and eosin × 200

Case 3

A 3-year-old boy presented with a solid mass in his right thigh extending into the buttocks. Local excision of an infiltrative fibromatosis (Fig. 7) occurred on eleven further occasions, requiring resections of tumours measuring on average $5 \times 4 \times 3$ cm, before a final cure was achieved by the age of 15 years.

Case 4

An 11-month-old male infant was referred with a large lower abdominal mass. Biopsy revealed an infantile fibrosarcoma. The tumour was considered unresectable and the infant received 3500 rads local irradiation followed by chemotherapy (vincristine, cyclophosphamide, actinomycin D and adriamycin). At the age of 19 months local excision of the tumour, which was arising from the urinary bladder, was performed. There has been no recurrence.

Case 5

A 6-year-old girl was admitted with multiple cutaneous swellings. The lesions were first noted in the scalp at the age of two years. Later other lesions appeared

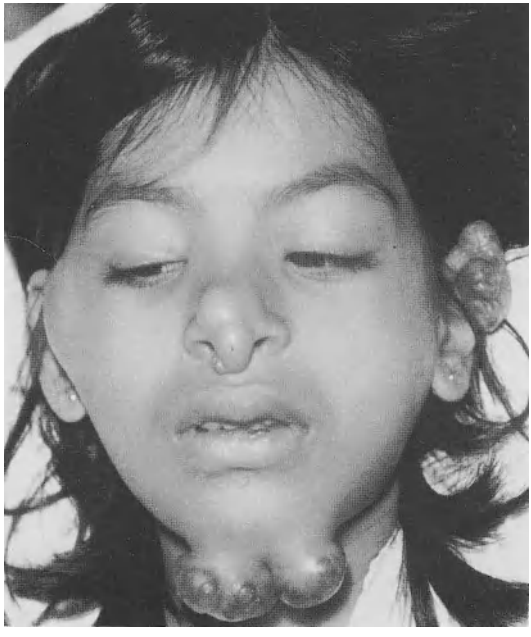

Fig. 8. Case 5, showing lesions of the nose, chin and left ear

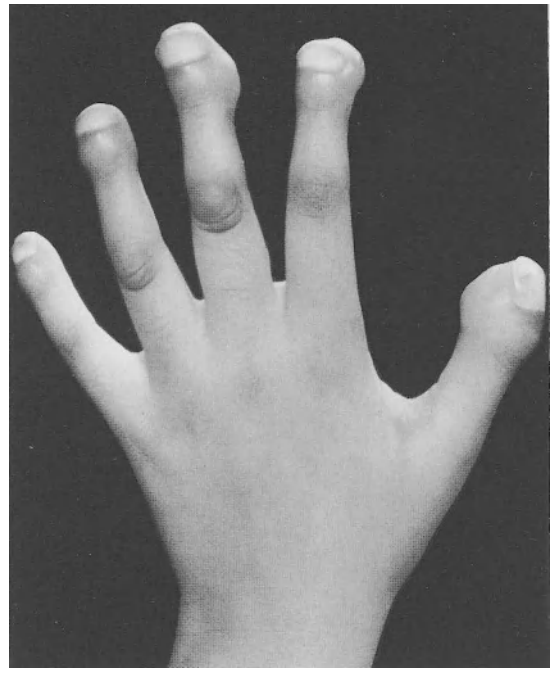

Fig. 9. Case 5, showing lesions of the fingers of the left hand

on the face, particularly involving the nose, ears and chin, hands and feet, and back (Figs. 8, 9). She also exostoses of the left ulna and right fibula. There was also involvement of the gingival mucosa, requiring multiple extractions, and of the rectal mucosa, causing recurrent episodes of rectal bleeding. In spite of numerous local excisions of the lesions, she remains with multiple lesions on the face and extremities. This patient is one of two children in this series with Gardner's syndrome.

Discussion

Congenital generalized fibromatosis occurs in one of two forms. Type I, which carries a favourable prognosis, involves skin, subcutaneous tissue or muscle. Type II includes visceral lesions in addition to skin and skeletal involvement and carries a poor prognosis. One of the two deaths in this series occurred in a 3-week-old infant with an unresectable pelvic tumour of type II.

Fibrous hamartoma of infancy is a lesion with unique morphology. It occurs only in the first 2 years of life and histologically consists of an organoid growth of tissues indigenous to the area but differing in quantity, arrangement and differentiation from the adjacent tissues [4]. The histological features include a well-defined fibrous trabeculation, immature loose-textured cellular areas and mature

fat. The most common situations for these lesions are in the subcutaneous tissues of the axilla and upper arm and shoulder region. The prognosis is good provided complete excision is achieved. The one example of this tumour in this series occurred in a 20-month-old male infant with a lesion in the left axilla. There has been no recurrence following excision.

Infantile digital fibromas, also known as recurring digital fibromas of childhood, are lesions confined to the fingers and toes of young children, have a high recurrence rate and intracytoplasmic inclusions [5]. Most of the lesions are multiple and fingers are involved more frequently than toes (3:1). Treatment consists of local excision which occasionally involves amputation of the affected digit. There have been no recurrences beyond the digit and metastases have not been reported. There were five examples of this tumour in children (one male, four females) ranging in age from 3 months to 10 years. The fingers were involved in three cases and the toes in two. Recurrences were documented in four of the five patients.

The most malignant variety of the fibrous tissue tumours are the fibrosarcomas (also known as aggressive fibromatoses). Microscopically, the tumour comprises a dense cellular network which actively invades the adjacent tissues. The cells are characteristically spindle-shaped and pleomorphic and are arranged in a herringbone pattern [6]. By 1978, only 14 cases of metastasizing fibrosarcomas in childhood had been reported [6, 7]. We were able to identify seven patients (four male, three female) with fibrosarcoma. Their clinical presentation (age, anatomical site, tumour size) and course did not differ from those of patients with other fibrous tissue tumours, which confirms previous experience [3]. Complete excision of the tumour was achieved in six of the seven cases, two after initial radiotherapy and chemotherapy and one after radiotherapy alone. The anal fibrosarcoma in the infant appears to be the first of its type in this particular site. Three repeat resections and the establishment of a temporary defunctioning sigmoid colostomy were required before disease-free margins were attained.

Treatment of all the fibrous tissue tumours consists of excision of the lesion. The objective is to obtain disease-free margins, but radical resections sacrificing vital structures are not recommended. The addition of radiotherapy [8, 9] and/or chemotherapy [10] may be of benefit in reducing the size of the primary lesion, making excision feasible, or in treating inoperable tumours. The likelihood of recurrence is 43% while there is a 7.3% risk of mortality from the primary lesion or metastatic spread [6].

Summary

Thirty-three patients, ranging in age from newborn to 12 years, with fibrous tissue tumours, were treated at the Hospital for Sick Children, Great Ormond Street, London, from 1970 to 1984. Seven infants presented with tumours at birth. In 42% of cases, the tumour was noted during the 1st year of life. The anatomical distribution of the lesions was: upper extremity 6, lower extremity 5, head and

neck 10, trunk 6, thoracic cavity 2 (heart 1), abdominal cavity 4 (pelvis, bladder, small bowel mesentery, anal canal). Three patients had multiple tumours. Seven of the tumours were classified as sarcomas. Complete excision was possible in 28 patients, following initial biopsy in six patients of whom three were treated preoperatively with radiotherapy and/or chemotherapy. There were two deaths, one in an infant with a huge resectable pelvic tumour and the other in a child with cardiac fibroma. Recurrences occurred in 14 patients (48%), in nine of whom the recurrences were multiple. The mean time interval to recurrence was 13.8 months.

Résumé

Notre expérience d'une quinzaine d'années, de 1970 à 1984, porte sur 33 patients, nouveaux-nés et enfants jusqu'a l'âge de 12 ans, présentant des tumeurs conjonctives et que nous avons traités au "Hospital for Sick Children", Great Ormond Street, à Londres. Sept de ces enfants présentaient cette tumeur à la naissance. Dans 42% des cas, la tumeur s'était manifestée avant l'âge d'un an. Du point de vue anatomique, les tumeurs étaients réparties ainsi: extrémités supérieures: 6; extrémités inférieures: 5; tête et nuque: 10; tronc: 6; cavité thoracique: 2 (coeur: 1); cavité abdominale: 4 (pelvis, vessie, mésentère de l'intestin grêle, canal anal). Trois des patients présentaient des tumeurs multiples. Sept de ces tumeurs ont été identifiées comme des sarcomes. Une exérèse totale a pu être pratiquée dans 28 cas, dont six après biopsie initiale, trois d'entre eux ayant subi une irradiation préopératoire et/ou une chimiothérapie. Deux patients sont morts, un nourrisson présentant une volumineuse tumeur opérable du pelvis et un enfant présentant un fibrome cardiaque. Il y a eu une récidive dans 14 cas (soit 48%) dont neuf récidives multiples. Les récidives sont apparues en moyenne en l'espace de 13,8 mois.

Zusammenfassung

Zwischen 1970 und 1984 wurden am Hospital for Sick Children, Great Ormond Street, London, 33 Kinder (vom Säuglingsalter bis zum Alter von 12 Jahren) wegen Weichteiltumoren behandelt. In 7 Fällen handelte es sich um angeborene Tumoren, und in 42% der Fälle wurde der Tumor innerhalb des ersten Lebensjahres entdeckt. Die anatomische Verteilung sah wie folgt aus: obere Gliedmaßen: 6; untere Gliedmaßen: 5; Kopf und Hals: 10; Rumpf: 6; Brusthöhle: 2 (Herz: 1); Bauchhöhle: 4 (Becken, Harnblase, Mesenterium, Analkanal). In drei Fällen handelte es sich um multiple Tumore. Sieben Tumore wurden als Sarkome klassifiziert. Vollständige operative Entfernung war in 28 Fällen möglich, darunter war bei 6 Patienten zuerst eine Biopsie durchgeführt worden und in drei Fällen eine präoperative Radio- und/oder Chemotherapie. Es gab zwei Todesfälle: ein Kind mit einem riesigen operablen Beckentumor und ein anderes Kind mit Herzfibrom. Rezidive traten in 14 Fällen auf (48%), darunter 9 Mehrfachrezidive. Die Rezidive traten durchschnittlich innerhalb von 13,8 Monaten auf.

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Vascular Access

S. J. K. Holmes, E. M. Kiely, and L. Spitz

Introduction

As the treatment of malignancy in children becomes more complex, sophisticated techniques are needed to support the patient. Safe and reliable access to the vascular system circulation is an essential part of the overall management.

The Problem

Many of these patients are at an age when peripheral veins are small and fragile. Repeated venepuncture soon results in damage to the veins and extravasation of chemotherapeutic agents compounds the damage. As a result, the cooperation of the child with his attendants rapidly deteriorates.

Chemotherapy also inhibits division of stem cells in the intestinal mucosa. The malabsorption which results from mucosal damage exacerbates the nutritional problems associated with the anorexia and nausea which accompany malignant disease and its treatment. Parenteral nutrition is frequently required to support the patient during this period.

The myelodysplasia associated with chemotherapy results in depression of all blood cell lines. Serious and recurrent infections frequently neccessitate parenteral antimicrobial therapy. Blood products are often required to correct thrombocytopenia and anaemia, particularly when surgery is required.

All of these problems necessitate frequent monitoring of haematological parameters by repeated blood sampling. Vascular access by means of puncture of peripheral veins soon becomes impossible in the infant and even in the older child is difficult and distressing.

The experience of an 11-year-old boy with an abdominal lymphoma serves to illustrate these problems. The child presented with abdominal pain, malaise, anorexia and fever. Eleven courses of combination chemotherapy were parenterally administered. Each course was accompanied by anorexia and malaise. Nutrition was further impaired by vomiting and diarrhoea. In addition the child developed numerous episodes of sepsis.

In addition to administration of chemotherapy, vascular access was required for parenteral nutrition and transfusion of blood and blood products on 18 occa-

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Progress in Pediatric Surgery, Vol. 22
Ed. by L. Spitz et al.

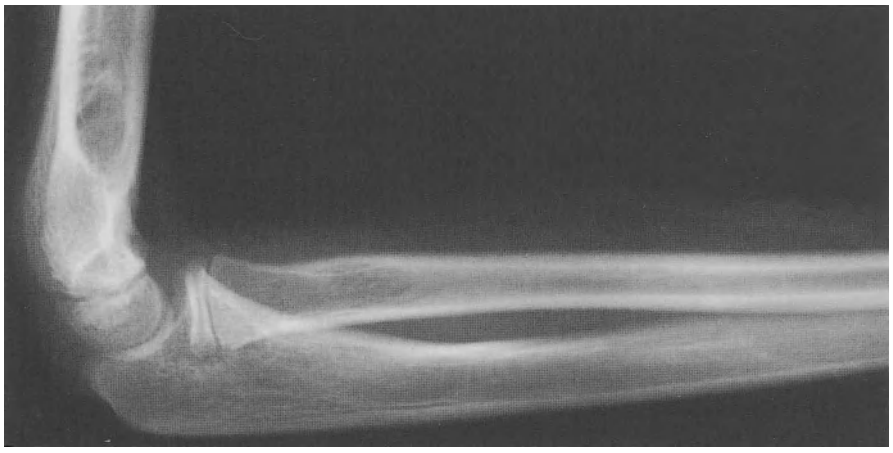

Fig. 1. X-ray of forearm showing calcification of veins in antecubital fossa as a result of thrombophlebitis

Table 1. Diagnosis of patients requiring vascular access, May 1984 to May 1985

18	Acute myeloid leukaemia
8	Neuroblastoma
8	Acute lymphatic leukaemia
4	B-cell lymphoma
3	Rhabdomyosarcoma
2	Aplastic anaemia
1	Hepatoblastoma
1	T-cell leukaemia
1	Abdominal sarcoma

sions. More than 200 blood samples were drawn and the child required numerous courses of parenteral antibiotics. A central venous catheter was inserted after peripheral veins had been used for some weeks. Episodes of thrombophlebitis in veins of the antecubital fossa produced the changes shown in Fig. 1.

Patients

In the 12-month period between May 1984 and May 1985, 46 patients suffering from malignant disease required central venous access. Their diagnoses are shown in Table 1. Nineteen of these patients received a bone marrow transplant. Most of the latter were patients with neuroblastoma or acute myeloid leukaemia. The patients with acute lymphatic leukaemia had relapsed after initial remission: long-term vascular access was rarely required for the initial treatment of this condition.

Table 2. Catheter data, May 1980 to May 1985

	Direct	Tunnel
Number of catheters	76	113
Mean lifespan (days)	20	77
Total lifespan (days)	1634	9302
Number removed for complications	55	44
Number removed for infection	25	36
Lifespan at removal (days)	20	65
Infections per catheter days	1/66	1/258

Results

A variety of techniques have been used to provide vascular access: (a) direct puncture, (b) subcutaneous tunnel, (c) subcutaneous portal, and (d) arteriovenous fistula. Our experience of catheters introduced by direct venous puncture and via a subcutaneous tunnel was compared.

Vascular access was provided on 250 occasions between May 1980 and May 1985. Catheters were inserted directly into the vein on 100 occasions; the remaining 150 were introduced via a subcutaneous tunnel. Seventy five per cent of the catheters inserted directly were removed prematurely because of complications, compared with 40% of those inserted via a tunnel. The mean lifespan of catheters was 20 days for those inserted directly and 77 days for those via a tunnel. One-third of all catheters were removed because of infection. This information is summarised in Table 2.

As a result of this experience, long-term venous access is provided entirely by means of Bròviac [2] and Hickman [6] catheters (Evermed, Kirkland, Washington, USA).

Methods

Insertion of the catheter is an elective procedure. This allows a crucial period of preparation for the child and his or her family to adjust to life with a catheter. The preparation involves a nursing sister, employed specifically to manage patients with venous catheters, and a play leader. Both work closely with the medical staff. Toys and practice catheters are used to explain the system before the new family are introduced to another family who have been living with a similar situation for some time.

The catheter is inserted in conditions of strict asepsis under general anaesthesia. Radiological facilities are available to ensure accurate positioning of the catheter tip in the right atrium. The right internal jugular vein is the most direct

and preferred route, although any large central vein or tributary is acceptable. In order to minimise risk of contamination, the catheter should not be handled.

When using the jugular vein, the patient's neck is extended by placing a radiolucent roll under the shoulders and turning the head to the opposite side. The operative field, including the neck and upper chest wall, is prepared with an aqueous solution of 10% povidone-iodine (Betadine, Napp laboratories, Cambridge, UK). Sterile drapes are applied and the field protected with an adhesive film (Op-Site, Smith and Nephew, Hull, UK).

A 2-cm skin crease incision is made over the distal third of the sternomastoid muscle. The jugular vein, which lies deep to the junction of the sternal and clavicular heads of the muscle, is approached by splitting the muscle fibres. The thin fascial sheath of the vein is cut and the vein ensnared by two slings to provide proximal and distal control. The catheter, filled with saline, is drawn up into the neck wound through a subcutaneous tunnel via a small incision in the right upper chest, avoiding the breast bud. The cuff of the catheter must be at least 2 cm inside the chest incision. The catheter is laid over its estimated intravascular course and the tip cut with a bevel at the surface marking of the right atrium near the right nipple.

The jugular vein is then lifted into the neck wound by traction on the slings which should be placed 2 cm apart. A small venotomy is made in the isolated segment of vein and the catheter passed down into the atrium. The venotomy is closed securely around the catheter with 6 O monofilament sutures (Prolene, Ethicon, Edinburgh, UK). The position of the catheter tip is checked radiologically and adjusted accordingly. A subcuticular suture of polyglycolic acid (Dexon, Davies and Geck, Cyanamid GB, Gosport, UK) is used to close the neck incision. That on the chest is closed with a monofilament mattress suture which is also used to tie around the catheter. Heparinised saline, 10 units per millilitre (Hepsal, CP Pharmaceuticals, Wrexham, UK) is used to fill the catheter and the screw cap fitted. The entry point is covered with a sterile gauze dressing held in place by a silicone adhesive and tape (Medical Adhesive B, Dow Corning, Brussels, Belgium).

Once the catheter is in place, all handling, which is kept to a minimum, is supervised by the nursing sister. Full aseptic precautions are used and, after the 1st week, dressings at the entry site are changed every 2nd day. Patients and their families are encouraged to perform this care themselves and in most cases are both willing and able to comply. Catheters not in regular use are flushed and left full with heparinised saline (Hepsal) every 2nd day.

Discussion

Vascular access via Broviac and Hickman catheters greatly facilitates the management of childhood malignancy. Current knowledge of the effects of chemotherapy and natural history of the treated disease allows accurate prediction of the need for this access in each patient.

Use of these catheters is not without risk: complications may arise in association with catheter insertion; venous thrombosis and sepsis. Furthermore, catheters may be rendered unusuable as a result of fracture or obstruction by thrombous. However, these complications may be minimised by attention to detail.

We have always inserted catheters by direct exposure of the vein and have not encountered complications. Direct puncture has not been employed because of the type of catheter available and because of concern about reported insertion complications [1, 10]. The favourable report from Dudrick et al. [3] and the development of more sophisticated techniques for direct percutaneous insertion of cuffed catheters may however justify reappraisal of this method.

Major venous thrombosis has not been a problem in our patients, which may reflect placement of the catheter tip in the right atrium as originally recommended by Broviac [2]. Venous thrombosis rates around 5% are typical in reports of catheters placed in the vena cava [3, 4, 11]. Reports of cardiac complications resulting from atrial placement [5, 8] did not involve Broviac or Hickman catheters but are a cause for concern.

Infection led to the premature removal of 32% of the catheters. This high infection rate reflects the frequent and severe episodes of sepsis which afflicted the immunologically compromised patients. One catheter infection occurred per 258 catheter days, which compares with 1/289 and 1/490 in two reports of chemotherapy in adult patients [9, 10].

The management of infection in these children is difficult. Investigations need to include microbiological examination of blood drawn from the catheter and directly from the vascular system. All infections are vigorously treated with appropriate antibiotics and every attempt is made to preserve the catheter. Catheters are removed when all other sources of sepsis have been excluded and the infection is damaging the health of the patient. We have not used prophylactic antibiotics, although there is some evidence for the efficacy of sulphonamide and trimethoprim in this respect [9]. Although our survey did not address the question, we share the belief of Keohan et al. [7] that management of patients and catheters by a specially appointed nursing sister reduces the incidence of sepsis.

Catheter occlusion by thrombus should be prevented by correct maintenance; when it occurs, patency may be restored by injections of streptokinase. Catheter fracture is not common and again largely preventable. Repair may be effected using a special kit if undertaken promptly and in conditions of strict asepsis (repair kit for Broviac and Hickman catheters, Evermed).

Summary

In a retrospective survey of vascular access by means of central venous catheters, those inserted via a tunnel lasted four times longer than those inserted directly into a vein. The latter were four times more likely to become infected. The general health of patients receiving chemotherapy resulted in frequent episodes of sepsis and one-third of all catheters were removed because of presumed infection.

There were no complications relating to insertion, which was by direct exposure of a central vein, preferably the right internal jugular. Long-term atrial catheters were not associated with major venous thrombosis or cardiac complications.

Safe vascular access is an important contribution to the management of children with malignant disease, notwithstanding the high infection rate. A specially trained nurse, working closely with experienced play leaders and social workers, minimises the technical and psychological problems associated with long-term central venous catheters.

Résumé

Une étude rétrospective de l'exploration vasculaire au moyen d'un cathéter central par voie veineuse a montré que ceux qui étaient mis en place par tunélisation avaient une durée de vie quatre fois supérieure à celle de ceux qui sonst introduits directement dans une veine. Ces derniers tendent aussi quatre fois plus à s'infecter. L'état général des patients subissant une chimiothérapie est souvent altéré par des septicémies et un tiers des cathéters a été enlevé du fait de ce risque.

La pose n'a donné lieu à aucune complication. Elle se fait par exposition directe d' une veine centrale, de préférence la veine jugulaire interne. Les cathéters de l'atrium, mis en place pour assez longtemps, n'ont apparemment pas causé de thrombose veineuse grave ni de complications cardiaques. Une mise en place de cathéters veineux en toute sécurité est indispensable lors du traitement d'enfants atteints de tumeurs malignes, malgré un risque d'infection qui est considérable. Une infirmière ayant bénéficié d'une formation adéquate, peut, en étroite coopération avec des assistantes sociales et des thérapeutes occupant et faisant jouer les enfants, réduire au minimum les problèmes de nature technique ou psychologique inhérents à un cathéter central veineux, mis en place pour longtemps.

Zusammenfassung

Eine retrospektive Untersuchung über Zentralvenenkatheter zeigte, daß Katheter, die durch einen Tunnel eingeführt werden, die vierfache Lebenszeit von denjenigen haben, die direkt in die Vene eingeführt werden. Der Allgemeinzustand von Patienten während einer Chemotherapie wird oft durch Sepsis beeinträchtigt, und ein Drittel aller Katheter muß wegen Infektionsgefahr entfernt werden. Die Einführung des Katheters ist relativ unkompliziert und geschieht durch Freilegung einer zentralen Vene, meistens der rechten Jugularis interna. Vorhoflangzeitkatheter verursachten weder Venenthrombosen noch Herzkomplikationen.

Der sichere Zugang zu den Blutgefäßen ist von besonderer Bedeutung bei der Behandlung von Kindern mit bösartigen Erkrankungen, und die hohe Infektionsrate muß dabei eine untergeordnete Rolle spielen. Ein Team von besonders ausgebildeten Krankenschwestern, erfahrene Beschäftigungstherapeuten und Sozial-

arbeitern kann die technischen und psychologischen Probleme, die von einem Langzeitzentralkatheter verursacht werden können, auf ein Minimum reduzieren.

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Surgery for Neuroblastoma

E. M. Kiely

Introduction

Complete excision of disease is regarded as optimal treatment for stage I and II neuroblastoma [1]. Management of stage III and stage IV disease, however, is more controversial. Surgery can reduce tumour bulk but may not influence survival. In particular, surgical clearance of the primary tumour after chemotherapy is widely practised, but without firm evidence as to its effectiveness. Furthermore, this surgery is frequently difficult and hazardous. This account details the author's experience with surgery for neuroblastoma.

Patients and Methods

Between May 1983 and February 1986, 31 patients with neuroblastoma presented for surgery. Seventeen of the total were females. Six were aged less than 12 months and one was more than 5 years of age. Table 1 shows the sites of primary disease. Table 2 shows disease classification by the Evans staging method [2].

Diagnosis was confirmed by urinary catecholamine excretion, histology or the presence of neuroblastoma cells in bone marrow aspirate or trephines. The presence of a mass with a raised VMA was considered diagnostic, as was histological confirmation of tumour in bone or bone marrow. Negative results of urinary catecholamine tests and bone marrow examination necessitated confirmation of the diagnosis by biopsy.

Table 1. Site of primary disease

Site	No.
Suprarenal	18
Pelvic	1
Other intraabdominal	7
Thoracic	4
Cervical	1

Table 2. Stage of disease (Evans' classification)

	No.
Stage I	1
Stage II	6
Stage III	1
Stage IV	23

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One patient who had had a cervical primary tumour excised at another centre had a normal lymph node excised. He was the only patient in the series with stage I disease. Four of those with stage II disease had chemotherapy prior to surgery. Twenty-two of the 23 patients with stage IV disease had chemotherapy prior to surgery as well. The solitary patient with stage III disease did not have pre-operative chemotherapy. Chemotherapy at present consists of courses of vincristine, cyclophosphamide, cisplatinum and teniposide (VM26), given at 3- or 4-weekly intervals.

All patients had pre-operative staging investigations which included 24-h urinary catecholamine tests, bone marrow and trephine examinations, isotope bone scans, abdominal or chest ultrasound examinations and CT scans. The pre-operative investigation and treatment of these patients was undertaken by the oncology team. The timing of surgery was arranged after discussion with the author.

Surgery

All operations were performed under intubated general anaesthesia. In two children where bulk disease was not anticipated only a peripheral intravenous cannula was sited; all the others had at least one central venous cannula inserted for pressure measurement and rapid volume replacement. Heart rate and blood pressure were monitored continuously by ECG and by a radial artery cannula respectively. All patients had a nasogastric tube and bladder catheter inserted prior to surgery.

Thoracic tumours were approached through the bed of an appropriate rib. Complete macroscopic clearance was not possible in the majority of these patients as the tumours which had been pre-treated were very ill-defined and all passed posteriorly through one or more intercostal spaces.

The majority of laparotomies were performed through transverse upper abdominal muscle-cutting incisions. All the tumours were retroperitoneal and were exposed by reflecting the colon medially on one or both sides. In all cases the dissection was commenced distally at a level where the major blood vessel was visible. If neither the inferior vena cava nor the aorta was visible, the dissection was commenced along the common or external iliac vessels. Using sharp dissection, the relevant blood vessel was dissected free and could then be lifted up on a sling. The dissection was then advanced proximally using sharp dissection and keeping close to the vessel well. Although many tumours were densely adherent to the vessels, penetration of a vessel wall had occurred in only one case. In this child the right hepatic vein and part of the adjacent inferior vena cava were penetrated by tumour which could not be completely excised at that point. The correct plane of dissection was more easily found when dealing with major arteries than with veins, where the distinction between vein wall and tumour was not always apparent. As the dissection advanced proximally it was usually possible to preserve lumbar arteries but not always to preserve lumbar veins. The renal, superior mesenteric and coeliac arteries were readily identified and preserved, as were the

corresponding veins. Proximal control of the aorta was obtained as soon as possible but unfortunately this was usually towards the end of the procedure. Proximal caval control was not usually sought.

In general, right-side tumours tended to displace the vena cava and not completely encase it. The vein could then be dissected out of a groove on the tumour surface. Left-side tumours more often than not surrounded the aorta and its branches and the dissection was, therefore, more prolonged.

Once the vascular phase of the operation was complete, the tumours could then be excised with adherent portions of diaphragm or posterior abdominal wall. In most patients the margins of the tumours were indistinct and the extent of resection required unclear. As much tumour was removed as seemed possible without unduly increasing the risk to the patient or to vital structures. Kidneys were preserved unless directly invaded by tumour. Renal vessels were commonly surrounded by tumour and in all these cases the kidneys were preserved. Difficulty was sometimes encountered when right-side tumours were adherent to the retrohepatic inferior vena cava. Rotation of the liver to the left considerably eased dissection under these circumstances.

Haemostasis was not a problem in any case once the tumours had been removed. All abdomens were closed without drainage using a mass closure technique. Interrupted 4/0 Dexon sutures (Davis and Geck, Cyanamid GB, Gosport, UK) were used in the majority. The skin was closed using subcuticular Dexon, and no tension sutures were used. All wounds were nursed exposed.

Vascular monitoring was maintained for at least 24 h after operation. When all measurements were stable, monitoring was discontinued and the bladder catheter was removed. Oral feeding was commenced when the nasogastric aspirate had diminished in volume and was no longer bile-stained. This usually occurred on the 2nd or 3rd post-operative day. Chemotherapy was recommenced when necessary after 5 or 6 days.

Early Results

Operations lasted between 2 and 10 h with a mean time of about 4 h. No significant vascular injuries occurred. Two kidneys were removed en bloc because of direct tumour invasion.

The single patient with stage I disease has been mentioned above. Of the six patients with stage II disease, one had no residual tumour after chemotherapy. A second had about two-thirds excision of a diffuse fibrous plaque in the chest, and two further children had more than 90% excision of tumour and local lymph nodes. The remaining two had complete macroscopic and microscopic excision of their tumours.

The only patient with stage III disease had complete macroscopic excision but tumour extended to the resection margins on microscopy.

One of the patients with stage IV disease had no residual tumour at laparotomy. Two had more than 80% and six others more than 90% of primary tumour mass

Table 3. Survival related to disease stage at presentation

	No. of cases	No. alive
Stage I	1	1
Stage II	6	6
Stage III	1	1
Stage IV	23	13

excised. Twelve had complete macroscopic clearance but in nine of these tumour extended to the edge of the specimen on microscopic examination. The remaining two had inoperable disease. In one the aorta and inferior vena cava were encased in tumour from the pelvis to the diaphragm. The second had direct invasion of the portal triad by a fresh growth of tumour.

There was a single operative death. A 4-year-old male child with stage IV disease had a large upper abdominal primary tumour which had not responded to chemotherapy. His metastases had disappeared. Complete excision was performed and this entailed division of the left hepatic artery. He suffered an infarct of the lateral segment of the left hepatic lobe. Twenty-four hours after operation he collapsed with severe hypoglycaemia despite dextrose infusion and sustained irreversible cerebral damage. Death ensued 5 days later. At post-mortem no residual tumour was present in the abdomen although microscopic extension to the edge of the resected specimen was present.

There were no post-operative wound infections, disruptions or incisional hernias. Two children subsequently developed adhesion obstruction requiring surgery.

Intermediate Results

Twenty-one of these children are still alive; fifteen of these are thought to be disease-free. The survival related to the stage at presentation is shown in Table 3.

Of the 23 who presented with stage IV disease, six are alive and thought to be disease-free at least 2 years after surgery. Most of the other stage IV survivors are still undergoing chemotherapy. Five of the ten who have died were known to have local recurrence of disease. Complete macroscopic clearance had been achieved in each of the five. In one, massive local recurrence was apparent less than 4 weeks after operation.

Discussion

Textbooks of operative technique give little guidance on how best to excise neuroblastomas. The problems involved are not the usual difficulties of isolating

the blood supply prior to excision of a viscus. Widespread tissue invasion and vascular attachment require a different approach. There are no planes of separation and blunt dissection has limited application. Knife dissection on the other hand is safe and effective and allows cmplete or near complete excision of even the most adherent tumour. The safest plane of dissection is beside the vessel wall. Only one case of vascular penetration was encountered and arterial invasion was not seen. Proximal arterial control was not achieved in these cases before the aorta was dissected. It may be safer, however, to open the diaphragm in some cases. The tumours were excised en bloc with involved lymph nodes in almost all cases, although this is not regarded as essential. Two kidneys were excised because of direct tumour invasion. Invasion of the renal pedicle was not a reason for nephrectomy and it was possible to clear the vessels of tumour in all cases where this had occurred.

The preponderance of cases in this series had stage IV disease. In almost all the cases the primary tumour had shrunk and the edges of the tumours were ill defined. Frequently the main tumour mass merged into fibrous tissue at the margins and despite wide excision microscopic disease was present at the edges in nine of the 12 cases where complete clearance had been achieved.

Pre-operative hypertension was not a feature of any of these cases and no patient was receiving hypotensive agents at the time of surgery. There were no problems with catecholamine secretion during or after operation.

When pre-operative chemotherapy was utilised most had six courses. If the tumour was still large but responsive, up to eight courses were utilised. All but a few of the primary tumours shrank to a remarkable degree and surgery then became a practical proposition. In addition, the tumours became more fibrous, less vascular and more easily handled. There is a limit to what is technically possible but better clearance was obtained in the later cases, because of increased operator experience.

The use of vascular monitoring has eased peri-operative and post-operative fluid management. Some of these patients had twice or three times their blood volumes replaced during the course of lengthy operations. Accurate assessment of needs was more readily estimated by continuous pressure monitoring. Most also needed plasma in the post-operative period to replace losses from the operative field. In this regard peripheral skin temperature monitoring proved most sensitive in estimating requirements.

Prior to the death of the patient described above, it was not our practice to routinely monitor blood glucose levels in older infants and children after major surgery. Now, however, we monitor all children of whatever age using reagent strips. Estimations are done 2- to 4-hourly initially and monitoring is continued for about 48 h. We have not seen any further episodes of hypoglycaemia.

No imaging technique could accurately predict tumour resectability. Ultrasonography and CT scanning were helpful in assessing the response to chemotherapy and in planning the operation; of the two, the CT scans were more helpful. The site and extent of the tumour as seen on the scan allowed the surgeon to prepare for likely difficulties, but unlike others [3], we did not find that either

mode of imaging could give any precise information on the possibilities for resection.

Although the technical aspects of surgery have been emphasised in this article, the exact place of surgery in the management of neuroblastomas is unclear. Complete removal of tumour is likely to be curative in stage I and II disease. However, it remains to be seen if surgery has anything to contribute in the management of stage III and IV disease, with or without chemotherapy.

Summary

Over a 33-month period, 31 infants and children had surgery for neuroblastoma. Twenty-three of the total had stage IV disease at the time of presentation and all but five had an abdominal primary tumour. In only two children was the tumour considered unresectable. The operative mortality was 3%. Neither ultrasound nor CT scanning could accurately predict resectability.

Résumé

Au cours de 33 mois, 31 nourissons et enfants atteints d'un neuroblastome ont été opérés. 23 d'entre eux présentaient un neuroblastome de stade IV à la première consultation et dans tous les cas, sauf cinq, il s'agissait d'une tumeur abdominale primaire. Dans deux cas seulement, la tumeur était jugée inopérable. Le taux de mortalité lors de l'intervention fut de 3%. Ni l'échographie ni la scintigraphie n'ont permis de prévoir fiablement si la tumeur était opérable ou non.

Zusammenfassung

Während eines Zeitraumes von 33 Monaten wurde bei 31 Säuglingen und Kindern ein Neuroblastom operativ entfernt. In 23 Fällen handelte es sich bei der ersten Untersuchung um ein Neuroblastom Stadium IV und in allen Fällen bis auf fünf um einen primären Abdominaltumor. In nur zwei Fällen wurde der Tumor als inoperabel angesehen. Die Sterblichkeitsrate bei der Operation betrug 3%. Weder durch Ultraschalldiagnostik noch durch Computertomographie konnte zuverlässig ermittelt werden, ob der Tumor operabel war oder nicht.

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Implantation of a Silastic Balloon for Reduction of Radiation Injuries of the Bowel in Two Children with Neuroblastoma

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Introduction

The curability of malignant disease by radiation not only depends on tumour type and mass, as well as surgical and chemotherapeutic procedures, but also on the anatomical site of the tumour. Radiation dosage is limited by the critical organs surrounding the tumour. Doses necessary for tumour destruction often cannot be administered without a significant risk of severe side effects. This is particularly true for pelvic tumours where the small bowel is the limiting factor. Two children with stage IV neuroblastoma who underwent chemotherapy and irradiation following surgical partial tumour excision died from severe bowel reaction. This led us to an attempt to push the bowel out of the radiation field (Table 1). Several surgical techniques can be used for solution of this problem:

1. *The omental plug* (Fig. 1). In tumours of the rectum or the urogenital tract, the small bowel can be elevated out of the pelvis above the sacral promontory by means of the major omentum. According to Russ et al. [1], further advantages of this technique are that the surgical defect is peritonized, any anastomotic leakages are sealed, and a barrier is formed against tumour spreading into the peritoneal cavity.

2. *The absorbable mesh* (Fig. 2). An absorbable mesh (Polyglycolacid) can be used as an artificial diaphragm to remove the small bowel from the pelvis. The tolerance of the material is excellent and the absorption is complete after 4 months, when the small bowel moves back in its normal position.

3. *The silastic sac.* Without doubt, the best, most flexible method is to implant an inflatable silastic sac. The sac is connected with a small chamber (like the Port-a-cath) (Pharmacia, Freiburg, FRG) which, implanted subcutaneously, allows inflation and deflation of the sac. As is known from breast reconstruction, this material is extraordinarily well tolerated. The advantages of this method are that:

a) Organ displacement can exactly be confined to the duration of irradiation.
b) The volume of the balloon is exactly adaptable to the technical requirements of irradiation.

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Progress in Pediatric Surgery, Vol. 22
Ed. by L. Spitz et al.

Table 1. Review of operative procedures in stage III and IV neuroblastomas with and without balloon implantation, 1981–1986

Case/stage	Primary op.	Second look	3rd op.	4th op.
Stage IV, K.J., no. 22628	Biopsy	Tumour excision & nephrectomy; balloon		
Stage IV B.Ch., no. 22102		Delayed primary op., tumour excision & nephrectomy		
Stage IV M.B.	Biopsy	Tumour excision & nephrectomy		
Stage IV H.P., no. 21999		Delayed primary op., tumour excision, liver metastases		
Stage IV U.K., no. 28645		Delayed primary op., tumour excision & nephrectomy; balloon		
Stage III B.S., no. 7557	Biopsy	Tumour excision	Tumour excision & nephrectomy	Suspected recurrence
Stage III F.K., no. 20137	Biopsy	Tumour excision	Tumour excision & nephrectomy	

c) Since the balloon consists of material foreign to the body, the volume dose to normal tissues can considerably be reduced. This is of great importance, since both immediate tolerance and late damage, such as inflammation, fibrosis and secondary tumours, largely depend on the volume of irradiated tissue (Fig. 3).
d) Neither computed calculation of dose distribution nor effective dose distribution is influenced, since the radio-opacity of the materials is similar to that of tissue. CT scanning is not disturbed either.
e) The sac can be placed anywhere. Placement into the thoracic cavity for lung protection may be envisaged.
f) Unlike the omental plug, the sac has no dose tolerance threshold. The only disadvantage of the inflatable sac is that it must be withdrawn surgically. However, this drawback can be turned to advantage if the occasion of surgical removal is used for inspection of tumour and surgical field at the same time. Organ displacement prevents adhesion between bowel and surgical field, thus yielding an excellent approach to the latter after the silastic sac has been withdrawn [3].

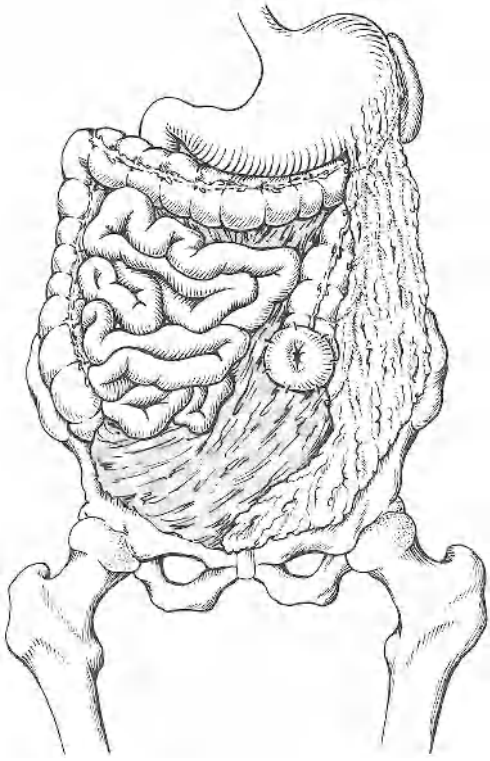

Fig. 1. The omental transposition flap, based on the left gastroepiploic vessels, is rotated into the pelvis along the left pericolic gutter. The small intestine is elevated out of the pelvis above the sacral promontory

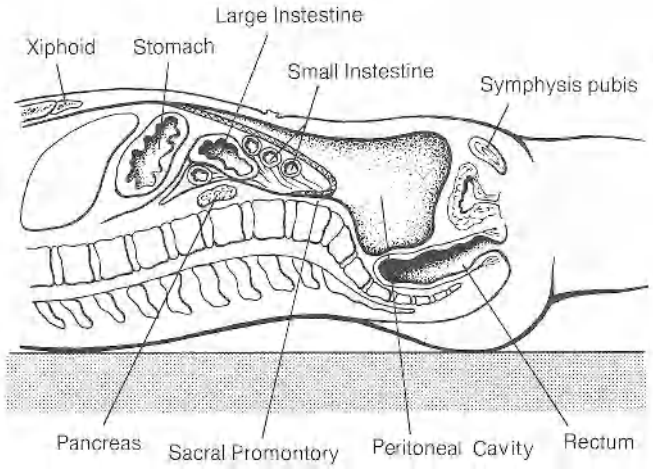

Fig. 2. The synthetic absorbable mesh acts as a sling to exclude the small bowel from the pelvis

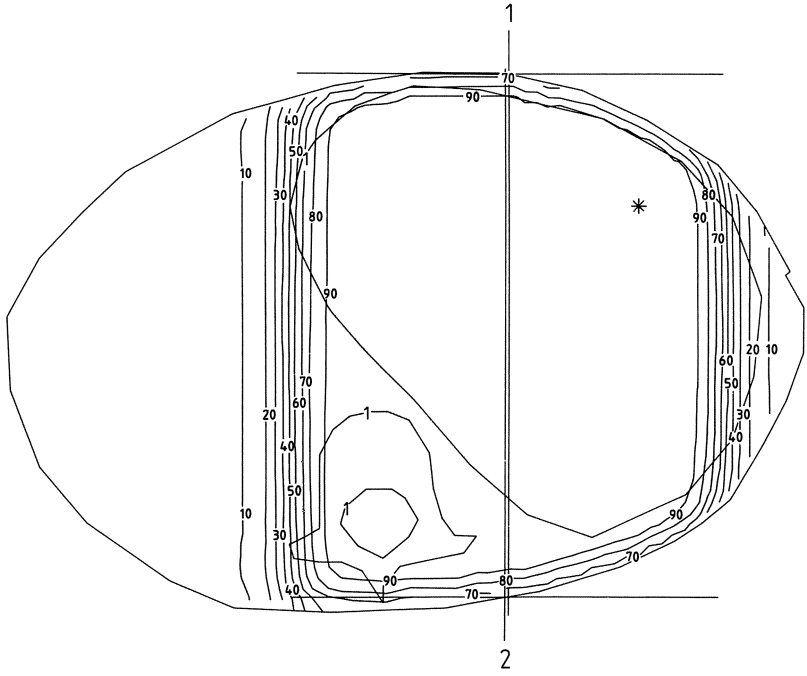

Fig. 3. Computer diagram of dose distribution calculated according to CT scan for 6-MeV photons in an excised paravertebral neuroblastoma. Volume dose is reduced by the balloon by more than two-thirds

Technical Procedure

During a second look laparotomy an inflatable silastic balloon (How Medica) is implanted retroperitoneally into the tumour bed following tumour excision and fixed by sutures. The filling chamber is inserted subcutaneously, allowing the sac to be filled by single puncture at any time. It is useful to pre-fill the sac with 500 ml liquid immediately after implantation and to inflate up to 1000 ml before irradiation. Ringer's lactate is used as the filling solution.

Case Reports

Case 1: K.J., 1½-year-old girl, no. 22628

Diagnosis of a stage IV neuroblastoma with bone marrow, skin and ovarian metastases was made when the child was 13 months old. Following tumour biopsy and bilateral ovarectomy, chemotherapy was undertaken for 5 months (Fig. 4). Subtotal tumour excision and left nephrectomy were carried out during second look

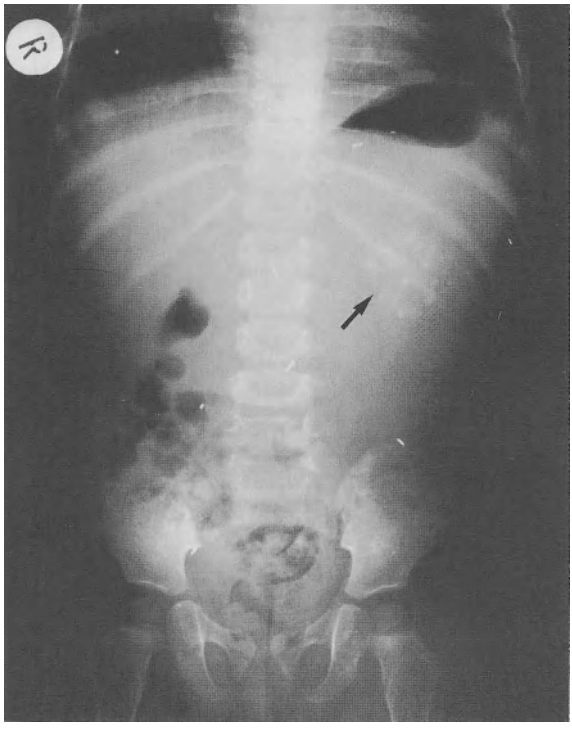

Fig. 4. Case 1, plain abdominal radiograph. Status after primary operation (bilateral ovarectomy, biopsy and tumour marking by metal clips); typical stage IV neuroblastoma with calcifications in the upper left abdominal quadrant *(arrow)*

laparotomy, followed by implantation of the balloon into the tumour bed (Fig. 5). Increased lymphatic secretion occurred postoperatively, although it remained unclear whether or not this was due to the implanted balloon. The balloon was completely filled before irradiation. No complications occured during or after irradiation. After this initially uneventful course, tumour recurred para-aortically on the right-hand side with damage to the right kidney, finally leading to death of the girl.

Case 2: U. K., 3½-year-old girl, no. 28645

After prolonged, uncharacteristic anamnesis, diagnosis was made in September 1985 of a stage IV neuroblastoma with bone marrow, bone and orbital metastases (Fig. 6). Subtotal tumour excision was carried out in January 1986 after systemic chemotherapy. A silastic sac was implanted into the tumour bed and inflated to 600 ml. After continued chemotherapy and autologous bone marrow transplantation and before irradiation, the balloon was completely filled and its position corrected. When irradiation was finished, the sac contents were reduced by half (Fig. 7).

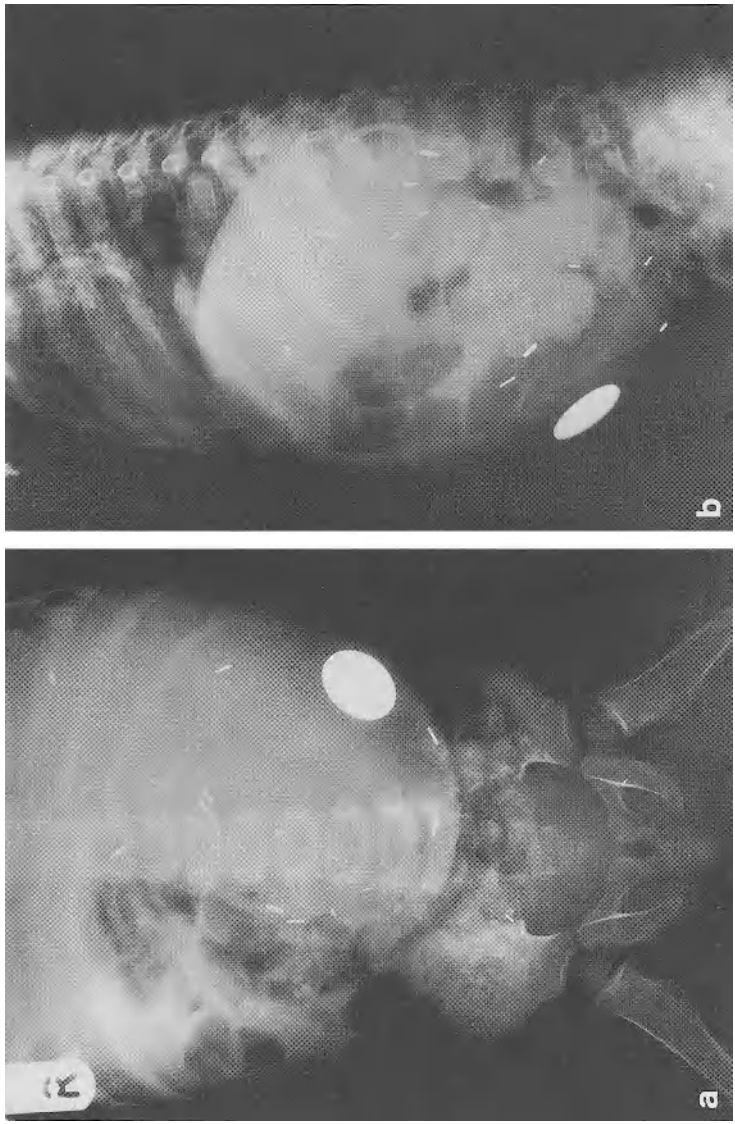

Fig. 5a, b. Case 1, **a** anteroposterior and **b** lateral plain abdominal radiographs. Status after subtotal tumour excision and left nephrectomy; the contours of the balloon are visible. The metal disk in the left middle abdomen is the filling chamber

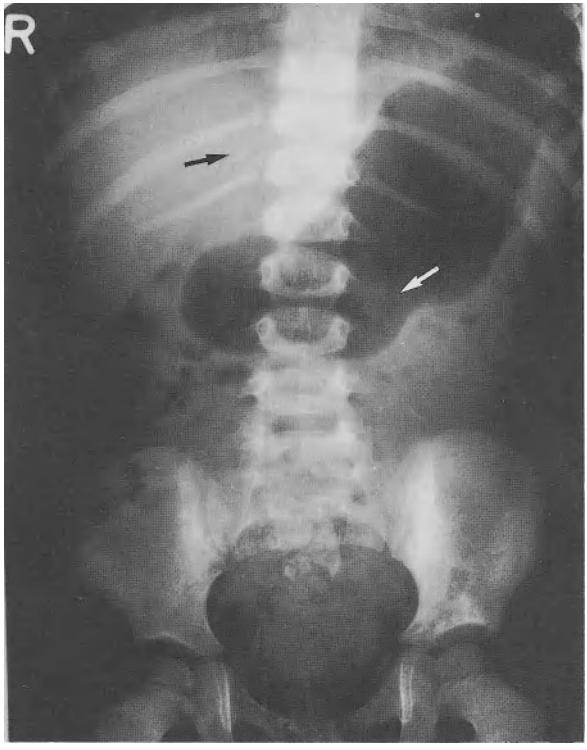

Fig. 6. Case 2, preoperative plain abdominal radiograph. Typical stage IV neuroblastoma with clearly visible left and right paravertebral calcifications. Delayed primary operation because of progressive metastases *(arrows)*

The tolerance of radiation was excellent even after bone marrow transplantation combined with 12 Gy total body irradiation.

Discussion

Assuming that the bowel damage in the first two cases was irradiation-induced, extensive protection of the surrounding organs would be of great advantage. Our two cases, however, should be considered preliminary, since no further similar cases have been reported. The complications encountered (increased lymph secretion and dislocation of the sac) were minor and easily correctable (lymph secretion stopped spontaneously), giving no cause for negative conclusions. The excellent tolerance of a high dose of radiation without any reaction at the bowel, as seen in other cases, seems positive. Furthermore, the balloon could be filled and emptied when required without disturbing the child. Removal of the balloon presented no difficulties, and the necessary second look operation was easier. All in all, this method can be recommended for local bowel protection against radiation damage in the retroperitoneal field.

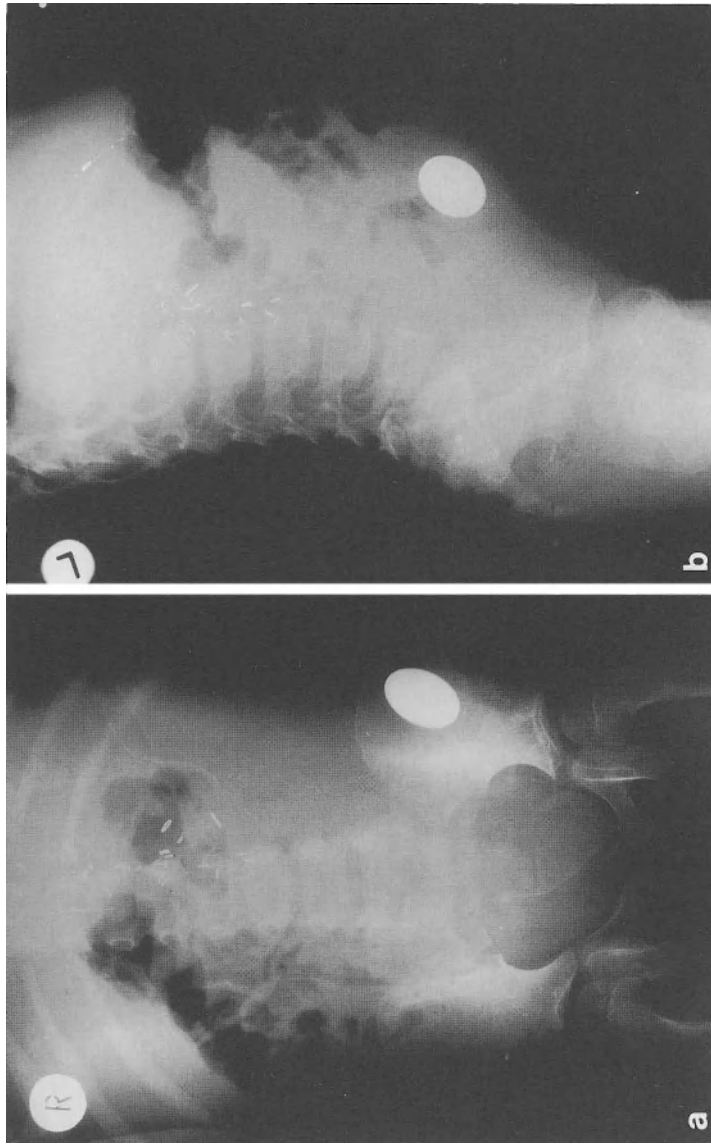

Fig. 7a, b. Case 2, **a** anteroposterior and **b** lateral pain abdominal radiographs. By means of a puncture the balloon contents were reduced by half following irradiation. The radiographs show the contours of the emptied balloon and the metal filling chamber

Summary

Two children with stage IV neuroblastoma died from severe reactions of the bowel due to radio-chemotherapy. This led to the suggestion of protecting the bowel by implantation of a silastic balloon to push the bowel away from the treatment volume. This procedure was tried in two children with stage IV neuroblastoma and resulted in excellent tolerance of the high-dose radiotherapy.

Résumé

Dans le cas de deux enfants atteints d'un neuroblastome de stade IV et subissant une radiothérapie, il s'est produit une lésion radiothérapique fatale de l'intestin. Cela a incité a concevoir l'implantation intra-abdominale d'un ballon de silastique pour pouvoir plus facilement soustraire l'intestion grêle au champ d'irradiation. Cela a été mis en pratique dans le cas de deux autres enfants atteints d'un neuroblastome de stade IV, dont l'un est mort entretemps des suites de la tumeur résiduelle.

Zusammenfassung

Bei zwei Kindern mit Neuroblastom Stadium IV war es im Rahmen der Radio-Chemotherapie zu schweren Schäden am Darm gekommen. Dies führte zu der Überlegung, durch die intraabdominelle Implantation einer Silastikprothese den Dünndarm leichter aus dem Bestrahlungsvolumen herauszuhalten. Dies wurde bei zwei Kindern mit Neuroblastom Stadium IV erprobt und eine ausgezeichnete Toleranz der hochdosierten Bestrahlung erreicht.

Surgical Aspects in the Treatment of Soft Tissue Sarcomas: A Preliminary Note

D. Bürger[1] and J. Treuner[2]

This analysis of surgical data collected in the Cooperative Soft-Tissue Sarcoma Study (CWS-81) of the Gesellschaft für pädiatrische Onkologie (Society of Paediatric Oncology) is based on the surgical records of 549 operations for soft-tissue sarcoma in a total of 323 patients. Histology, localization and treatment strategy varied. However, the results must be considered preliminary, since for 20% of the patients surgical records are still lacking. Following completion of data collection the final results will be published.

The Study protocol in use [1] includes the following procedures:

Primary Operations. If the tumour can be excised in toto, the excision should be performed in healthy tissue as far as possible and be combined with an examination of regional lymph nodes. Primary operations should preferably not involve mutilating procedures.

Second look Operations. Unless the patient presented with a primary stage I or IIa tumour or other specified conditions, residual tumour should be removed in a second look operation, performed after the second course of chemotherapy in the 16th post-operative week, if necessary, this may be a mutilating procedure.

Selected Results

Mutilating Operations

An important goal of the study was to use chemotherapy in order to avoid as far as possible, even in large tumours, the mutilating excisions often found necessary in the past. The study includes data on a total of 26 mutilating procedures, nine of which were performed as primary operations (Table 1), against the rules of the study protocol. In four patients, however, a primarily mutilating procedure was justifiable, among them two girls with uterine rhabdomyosarcoma, in whom a primary hysterectomy was carried out. It is well known that uterine rhabdomyosar-

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Progress in Pediatric Surgery, Vol. 22
Ed. by L. Spitz et al.

Table 1. 26 Mutilating operations; the numbers in brackets are of those which we would criticize

	Primary op.	Second-look op.	Non-responders
Enucleation of an eye	3 (3)	2	
Mutilating defect of the face	2 (1)	1	1
Amputation of an extremity	3 (2)	2	1
Artificial anus	1 (1)	1	
Hysterectomy	2		
Prostatectomy	2 (2)	3 (1)	1
Other mutilating surgery		1	

Table 2. Second look operations in 323 patients

No data		23
Second look performed		117
Second look not performed		
Reason:	stage I or IIa	73
	decision by centre	14
	inoperable	8
	localization	16
	no consent	3
	non-responder, local recurrence, metastases or dead	40
	no tumour detectable	29
		183

coma has an extremely poor prognosis so that the only chance of cure is radical surgery [2]. On the other hand, the radical bladder- and prostatectomy carried out in a boy for removal of a bladder wall tumour which had shown marked regression after 30 days' chemotherapy is to be criticized.

Second Look Operations

Second look operations were not performed in 183 patients, among them (in accordance with the study protocol) those with stage I or IIa disease (Table 2). Consent was refused three times by patients' parents: these three patients are still alive without recurrence. Second look operations were considered unnecessary in 29 patients, as diagnostic investigations did not reveal a residual tumour.

Table 3a, b. Event-free survival (EFS) rates after second look operation (calculated to Kaplan-Meier) according to time between beginning of therapy and date of second look

Week of op.	**a** All patients with second look operation			**b** Patients with less than complete response		
	n	EFS rate	SE	*n*	EFS rate	SE
−15	23	0.625	0.106	19	0.600	0.118
16–19	39	0.509	0.098	32	0.511	0.108
20–23	35	0.541	0.088	29	0.434	0.098
24–27	8	0.450	0.188	6	0.222	0.192
28–	11	0.227	0.136	10	0.133	0.120

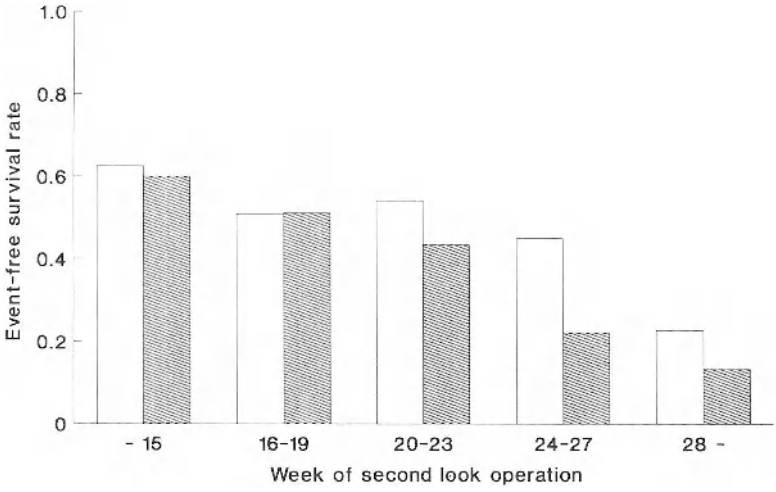

Fig. 1. Timing of second look operation. □ All patients given second look; ▨ patients with complete response excluded

Timing of Second Look Operations

As mentioned above second look operations are scheduled after the second course of chemotherapy, in the 16th week. Due to the preceeding chemotherapy, the operation is often actually carried out a little later. However, on the experience of individual cases we have long advised against postponing this operation for any greater length of time. A review of all patients who underwent a second look shows that an operation beyond the 28th week seems to be too late (Table 3, Fig. 1). When we exclude the patients who show complete regression of the tumour during the 7th–9th week following the first chemotherapy course (i.e. complete response), it becomes evident that the rate of recurrence-free survival de-

creases continuously with increasing delay of the second look operation (Table 3b, Fig. 1). The timing of the operation does not, however, seem to play a significant role in complete responders.

Scars Found at Second Look Operation

Analysis of the surgical data revealed that patients who later developed recurrence often showed no residual tumour during the second look. However, scar tissue was found in these patients remarkably often. Therefore, we went through the operative reports again and made the following classification into groups (Fig. 2, Table 4):

1. No residual tumour, no scars in the primary tumour bed: 10 patients, all alive without recurrence.
2. Minimal scars in the primary tumour bed which could be due to the preceding operation: 10 patients, all alive without recurrence.
3. No evidence of residual tumour, but more extended scars in the primary tumour bed: 30 patients. The criteria for assignment to this group were interpreted liberally in order to avoid subjective influences in the judgement of scarring. In 20 of these 30 patients, no evidence of residual tumour was found histologically in the scar tissue, residual tumours were found 7 times, and for three patients histology was not available. Only 10 out of 30 patients were alive recurrence-free at the time of data evaluation, two of whom were lost to follow-up immediately after surgery. In only two patients were the operations performed more than 1 year ago, which explains the low rate of recurrence-free survival calculated according to Kaplan-Meier. If the histological finding is included in the assessment of the patients with scar tissue, only 7 out of 20

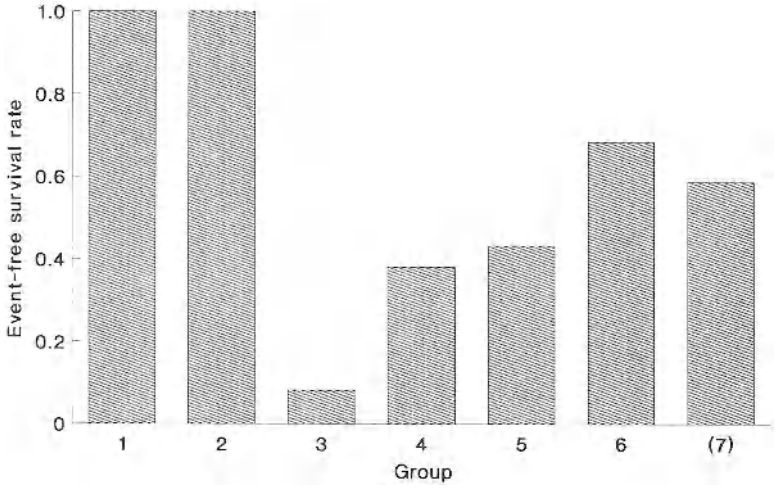

Fig. 2. Event-free survival rate after second look operation related to second-look surgical findings at site of primary tumour (for definition of groups, see Table 4)

Table 4. Surgical findings during second look operation and event-free survival (EFS) rates according to Kaplan-Meier

Group	Findings	*n*	EFS rate	SE	Days after second look op.
1	No scars	10	1.000	0.000	1829
2	Minimal scars	10	1.000	0.000	1736
3	Scars	30	0.082	0.075	1338
4	Scars & tumour	7	0.381	0.199	1484
5	Tumour	38	0.432	0.087	2072
6	Unknown	13	0.684	0.131	1806
7	No second look, no tumour left	29	0.588	0.105	1819[a]

[a] Days after beginning of therapy

Table 5. Treatment of scars at second look operation

Surgical procedure	*n*	Kind of event	
		Local recurr.	Metastases
Left in situ	2		1
Biopsy or partial resection	18	10	4
Complete resection	10	2	4

patients without histological evidence of a residual tumour are recurrence-free, and this includes not one of the 7 patients where a residual tumour was found in the scar tissue.

4. Macroscopic residual tumour and scars in the primary tumour bed: 7 patients.
5. More or less extensive tumour found at second look operation: 38 patients.
6. No classification possible, since surgical reports were incomplete or missing: 13 patients.
7. Second look operations not done due to normal CT findings: 29 patients.

Scars were left in situ in 2 patients, partial excisions or biopsies of the scars were carried out in 18 patients, and an extended scar excision in the remaining 10 patients (Table 5). Despite the low number of cases, it is noticeable that patients who had a biopsy or incomplete excision of the scars only developed local recurrences more often than metastases, whereas metastases predominated in patients with extensive scar excision.

Conclusions

The results presented urgently demand that the study committee proceed to verification of the suspicion that development of scarring is of major prognostic sig-

nificance. For this reason, we are at present calling for further surgical reports and histological findings. If the suspicion can be verified, regimens for treatment of this group of patients must be discussed in the committees responsible. It is mandatory for physicians – surgeons, oncologists and radiologists – who deal with soft-tissue sarcomas in children (a) to carry out a second look operation whenever possible, (b) to perform this second look during the 16th–19th week, according to the protocol, and not to wait for possible further tumour regression by chemotherapy or radiation therapy, (c) to document the local findings at second look as exactly as possible, and (d) to take particular care of patients with scars, in order not to be lulled into false security by the fact that no residual tumour was histologically proven at second look.

Summary

This preliminary analysis of surgical data is based on the evaluation of 323 patients operated on for soft-tissue sarcoma of varying histology. Data were collected for the Cooperative Soft-Tissue Sarcoma Study of the Gesellschaft für Pädiatrische Onkologie (Societyy of Paediatric Oncology).

The following preliminary results are presented:

1. The number of mutilating operations, formerly undertaken with great frequency, can be reduced by chemotherapy, except where very aggressive tumours necessitate radical tumours excision.
2. According to the protocol in use, second look operations were performed in 117 patients, usually following the second course of chemotherapy. It is concluded that second look operations should be performed between the 16th and 19th post-operative week. Patients with scars in the former tumour bed must be assessed particularly critically, since residual tumour nodes may be masked by the scars.

Résumé

Il s'agit d'une analyse provisoire des données obtenues sur la base de 323 cas d'opérations de sarcomes alvéolaires des parties molles d'histogénèse variée. Ces données ont été recueillies dans le cadre d'une "Etude Collective du Sarcome des Parties Molles" entreprise à l'initiative de la Société de Cancérologie Pédiatrique en RFA". Les résultats provisoires en sont les suivants:

- le nombre des interventions mutilantes, pratiquées autrefois sans hésitation, peut être réduit grâce à la chimiothérapie, sauf dans les cas ou des tumeurs particulièrement agressives exigent une exérèse radicale.
- en fonction du protocole thérapeutique utilisé, 117 patients ont subi des interventions de contrôle, dites "second look", en règle générale à l'issue du second cycle de chimiothérapie. Il en ressort que les interventions de contrôle doivent

être pratqiuées entre la 16ème et la 19ème semaine suivant la première intervention. Les patients présentant des cicatrices des tissus sous-jacents de la tumeur reséquée doivent étre examinés avec la plus grande attention car ces cicatrices peuvent dissimuler des tissus tumoraux résiduels.

Zusammenfassung

Die vorläufige Analyse chrirugischer Daten basiert auf der Auswertung von 323 Patienten, die wegen eines Weichteil-Sarkoms verschiedener Histologie operiert worden waren. Diese Daten wurden gesammelt im Rahmen der "Cooperativen Weichteil-Sarkom-Studie" der Gesellschaft für Pädiatrische Onkologie. Folgende vorläufige Ergebnisse werden präsentiert:

- verstümmelnde Operationen, früher häufig angewendet, können durch den Einsatz der Chemotherapie reduziert werden,
- nach dem verwendeten Schema wurden bei 117 Patienten Second-look Operationen gewöhnlich nach dem zweiten Chemotherapie-Cyclus durchgeführt. Second-look Operationen sollten zwischen der 16. und 19. postoperativen Woche vorgenommen werden. Patienten mit Narbenbildungen im ehemaligen Tumorbett müssen besonders kritisch beurteilt werden, da durch die Narben Tumorrestgewebe überdeckt werden kann.

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New Aspects in the Treatment of Childhood Rhabdomyosarcoma: Results of the German Cooperative Soft-Tissue Sarcoma Study (CWS-81)

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Introduction

Prior to the introduction of chemotherapy only 10–20% of children suffering from rhabdomyosarcomas (RMS) were successfully treated by surgery alone [1–4]. The introduction of combined multi-agent cytostatic therapy in the last 15 years has led to a dramatic improvement in the cure rate obtained in RMS patients [5–8]. Effective chemotherapy has not only increased the disease-free survival rate but has by and large also made it possible to avoid the mutilations inevitably associated with extensive surgery: for example, cystectomy, amputation or orbital resection.

In spite of such therapeutic successes in the treatment of RMS today, many questions remain open. Some of the most important of these concern the scale on which primary surgical intervention is required, the optimal time for second look surgery, the value of radiotherapy in combination with chemotherapy, the identification of prognostic factors which would help in tailoring therapy more closely to primary risk group (e.g. tumour extent, histological subtype) and, in the case of primarily inoperable tumours, ascertainment of the optimal time for presurgical chemotherapy before the risk of developing drug resistance increases, which would then diminish the chances of cure.

Both radiation and chemotherapy should be used for local tumour control before radical surgical intervention at the price of mutilation becomes unavoidable.

These matters are taken up in this report of the results of the cooperative soft-tissue sarcoma study CWS-81. In 1981 the Gesellschaft für pädiatrische Onkologie (Society of Paediatric Oncology) initiated a multi-centre national study of the

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Progress in Pediatric Surgery, Vol. 22
Ed. by L. Spitz et al.

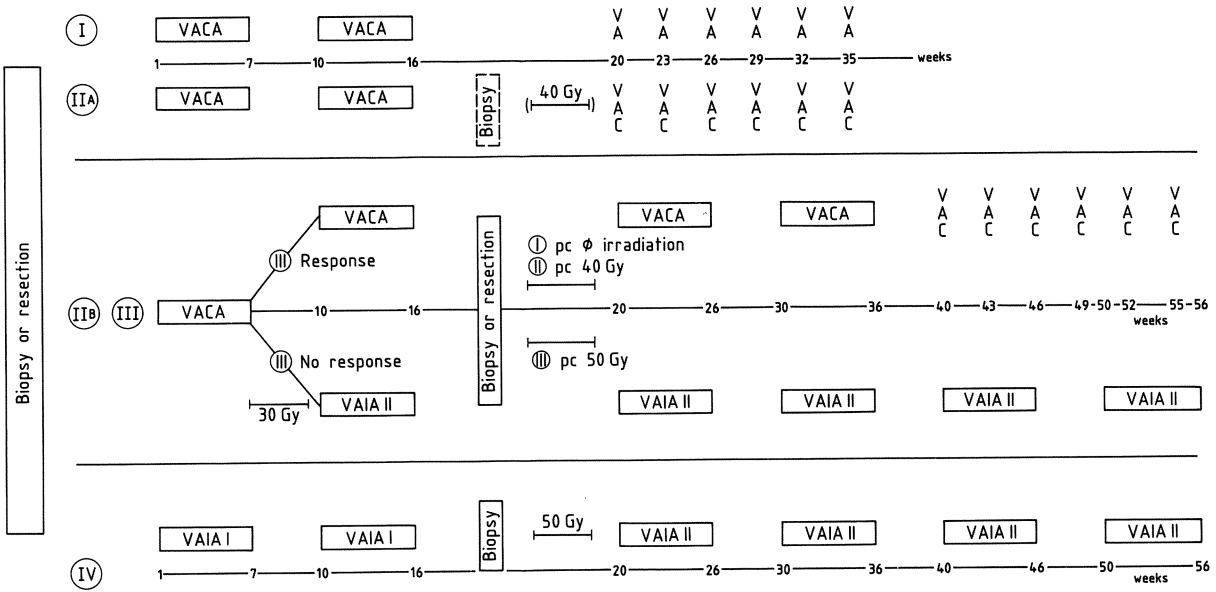

Fig. 1. Design of CWS-81 study: children were treated according to their disease stage after primary surgery. After 16 weeks of chemotherapy with the combination VACA (see Fig. 2), restaging was undertaken and radiotherapy adapted to the chemotherapeutic response manifested. Children without (histologically proved) tumour (Ipc) did not receive radiotherapy, children with microscopic residue received 40 Gy, and those with macroscopic tumours received 50 Gy after tumour resection. The length of chemotherapy was stage-dependent and varied from 36 weeks (stages I–IIA) to 56 weeks (stages IIB, III and IV)

treatment of soft-tissue sarcomas in children and teenagers. Between 1981 and 1985 374 patients were registered for this study from 50 clinics in West Germany. Of these 374 patients, 347 were available for evaluation and provided the data on which this report is based.

Study Design

Patients with soft-tissue sarcomas that are susceptible to chemotherapy – RMS, synovial sarcoma (Sy-Sa), extra-osseous Ewing's sarcoma (EES), undifferentiated soft-tissue sarcoma (US) (group A patients) – were treated in conformity with standardized protocol guidelines, whereas those with other kinds of soft-tissue sarcoma (group B patients) were not treated in accord with the guidelines. The therapeutic strategy is illustrated in Fig. 1. As far as the Intergroup Rhabdomyosarcoma Study (IRS) staging system is concerned, the patients were classified according to the primary post-surgical situation: stage I (microscopic complete tumour removal) and stage IIA (suspicion of microscopic tumour remains) are grouped together as a single risk group. Stage IIB (complete tumour removal with localized lymph node involvement) and stage III (residual tumour seen macroscopically or on biopsy only) formed a second risk group. Stage IV is defined as "disease disseminated at time of diagnosis." In all four stages, i.e. in all three risk groups, the initial chemotherapy combination consisting of vincristine, actino-

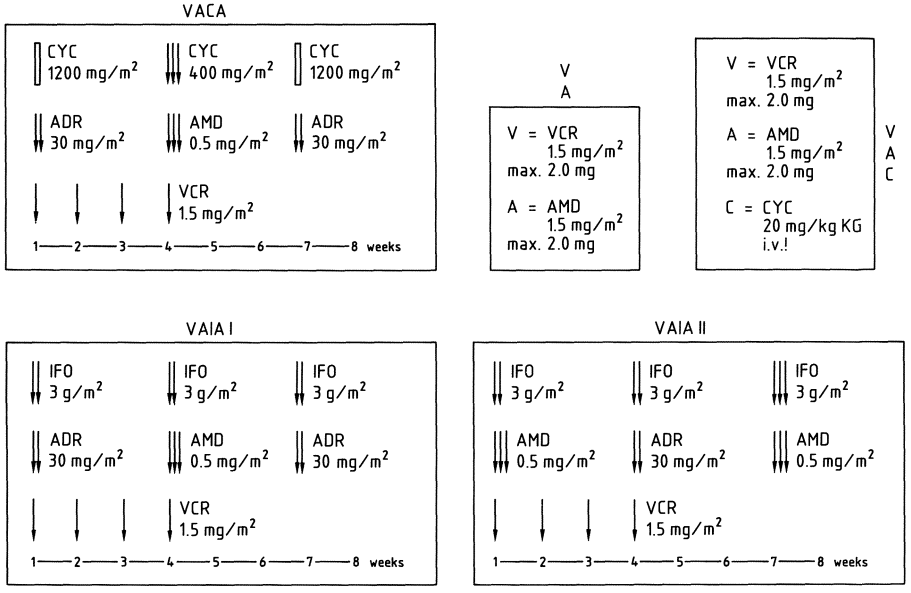

Fig. 2. Dosage and time scheduling of chemotherapeutic cycle. VCR, vincristine; ADR, adriamycin D; CYC, cyclophosphamide; IFO, ifosfamide

mycin D, cyclophosphamide and adriamycin (doxorubicin) (VACA) was administered over 7 weeks (dosage and scheduling are shown in Fig. 2). Chemotherapy was altered for patients in stage III and IV in the event of a less than one-third tumour reduction or a tumour progression (non-responders) and in stages I and II when renewed tumour growth was detected. For patients manifesting a response the same chemotherapy was continued up to week 16, then second look surgery was performed. Patients who were histologically tumour-free (Ipc) did not receive radiotherapy. Patients with microscopic residues (IIpc) received 40 Gy, while those with macroscopic tumours (IIIpc) received 50 Gy after resection. The chemotherapy was continued for all patients according to primary stage: stages I and IIA until week 36 and stages IIB, III and IV until week 56.

Patients and Methods

Of the 347 patients available, 225 (65%) were RMS cases, and of these 166 were able to be evaluated according to the protocol (protocol group patients), while 52 deviated from the protocol guidelines. The distribution of the 228 patients with RMS in terms of stage and location is illustrated in Tables 1 and 2. Each group of patients was analyzed with respect to survival and disease-free survival rate (DFS) using the statistical method developed by Kaplan and Meier [9]. The disease-free survival describes the following events: local relapse, metastasis, death through therapy-induced side effects and tumour progression in inoperable non-responders. To assess the significances involved the Wilcoxon rank test was used. The influence of prognostic factors was calculated by a multi-variable regression model. The regression coefficients show how strong the influence of the investigated regressor is.

The mean observation time for the study as a whole was 40 months (range 12–60 months).

Table 1. Patients with RMS registered in the CWS-81. Distribution by location

Location	*n*
Paratesticular	25
Genitourinary	31
Abdominal	24
Orbit	19
Head and neck	70
Extremity	39
Other sites	20
Total	228

Table 2. Patients with RMS registered in the CWS-81. Distribution by stage

Stage	*n*
I	39
II	27
III	123
IV	39
Total	228

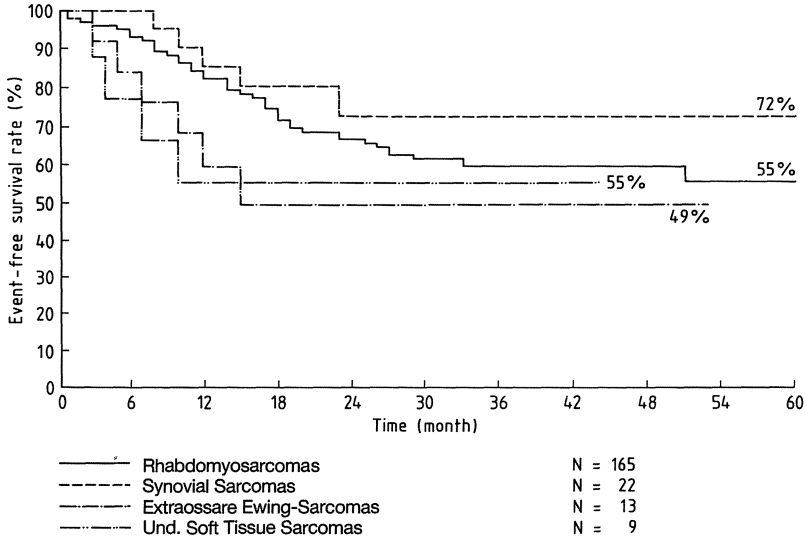

Fig. 3. Kaplan-Meier life-table analysis of disease-free survival according to histological subtype of soft-tissue sarcoma

Results

Before presenting the analysis of RMS patients, the DFS rate for group A patients according to their histological subtype will be considered in comparison with the rate for the whole group of RMS patients. Figure 3 illustrates the DFS rates for RMS, EES, US and Sy-Sa. EES and US patients relapse earlier than RMS patients, but over an extended observation time the final outcome was roughly similar: 55% DFS rate for RMS, 49% for EES, and 55% for US. Patients with Sy-Sa fare best of all with a 72% DFS rate; however, the divergence from the rate for RMS is not statistically significant.

Site and Prognosis

The relapse-free survival curves for the various locations of RMS are shown in Figs. 4 and 5. What stands out is the existence of three risk groups. The group with the most favourable results includes paratesticular RMS (93% DFS rate) and orbital RMS (71% DFS rate). Urogenital RMS (bladder, prostate, vagina), with a 59% DFS rate, and head and neck RMS (DFS rate 68%) all constitute an intermediate risk group. Patients suffering from RMS of the extremities have the most unfavourable results of all, with a DFS rate of 28%. RMS of the extremities is characterized by the histological alveolar subtype, a high frequency of primary metastasis formation and an increased risk of lymph node involvement. These three characteristics are in agreement with the data recorded in the literature [8].

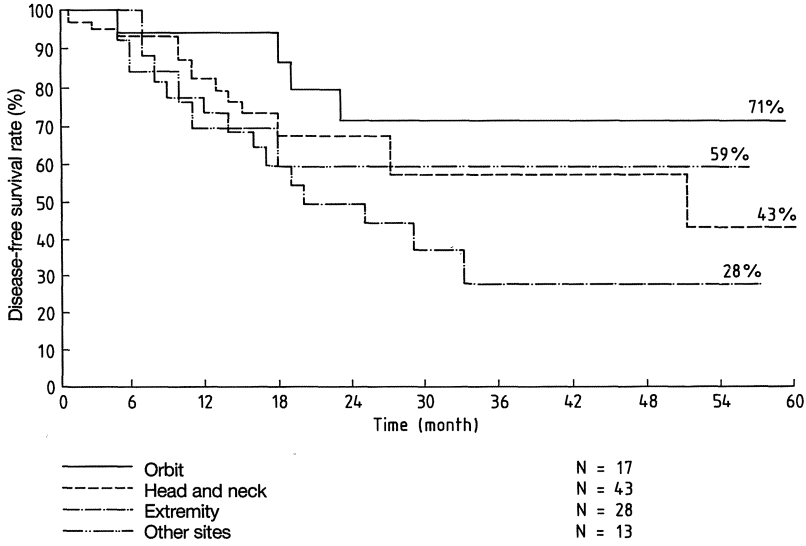

Fig. 4. Kaplan-Meier life-table analysis of disease-free survival for RMS patients according to tumour sites: orbit, head and neck, extremity, other sites

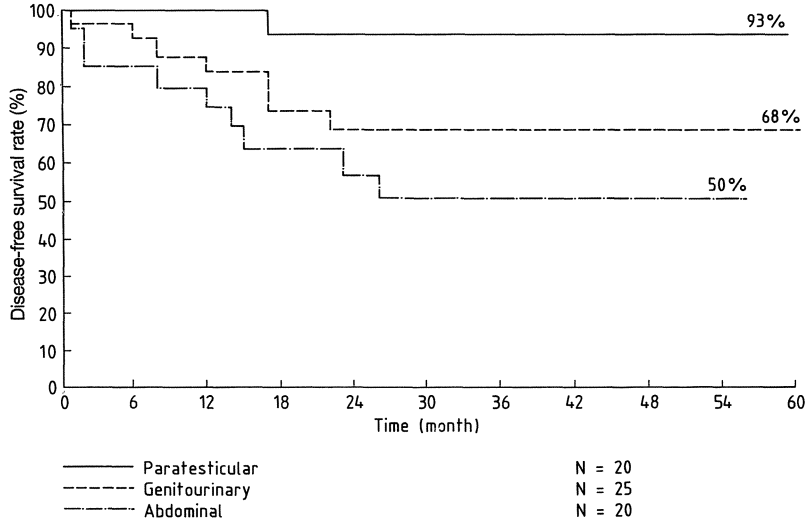

Fig. 5. Kaplan-Meier life-table analysis of disease-free survival for RMS patients according to tumour sites: paratesticular, genito-urinary tract, abdominal

In addition to these risk factors which affect RMS of the extremities, in the original study concept stage I and IIA patients were generally not to be irradiated. However, an increased local failure rate in this group of patients led to a revision of the study guideline bearing on this point. Following this readjustment to accommodate patients with stage I and IIA RMS of the extremities, local relapses were observed less frequently. If we compare the outcome of patients with RMS of the extremities (stages I–III) who received radiotherapy with the outcome of those who did not, there was a significant difference (60% versus 12% DFS).

Stage and Prognosis

The influence of surgical intervention in the treatment of RMS becomes manifest when the different stages after primary resection or biopsy are compared according to the chances of survival given by each. Figure 6 shows the influence of primary post-surgical stage on the prognosis. Patients with stage I disease achieved a relapse-free survival rate of 89% (including all patients with RMS of the extremities). Stage II patients (DFS rate 55%) have the same outcome as the patients with primary stage III (DFS rate 52%). Thus we can conclude that primary tumour resection does not improve the final results compared with patients with primary unresectable tumour. The assumption made at the beginning of the study that stage II comprises two separate risk groups, stage IIA and stage IIB, has not

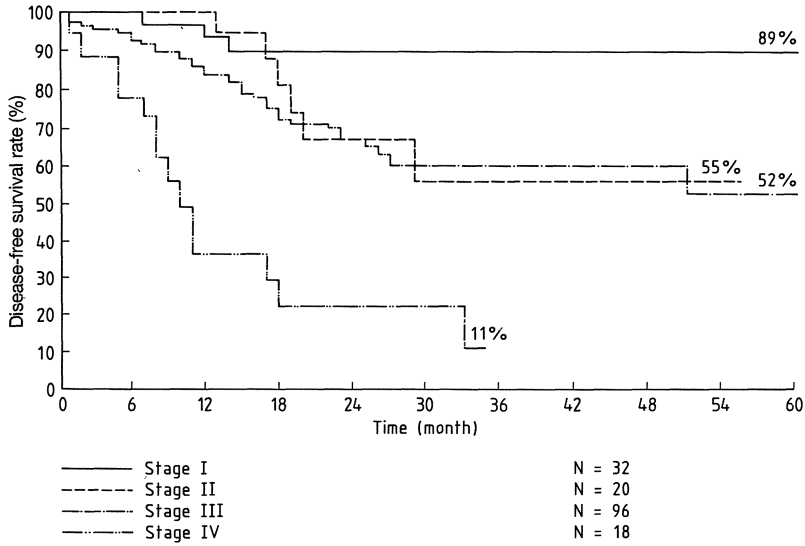

Fig. 6. Kaplan-Meier life-table analysis of disease-free survival for RMS patients according to primary post-surgical stage: I, without any tumour residue; IIA, with microscopic tumour residue; IIB, complete tumour removal with localized lymph node involvement; III, residual tumour seen macroscopically or on biopsy; IV, primary disseminated disease

been substantiated. It should be noted that stages I and II were negatively influenced by the cases of RMS of the extremities occurring in our study. If we exclude such cases, we find a 100% DFS rate for stage I and a 74% rate for stage II.

Cytostatic Time Response Factor

Ninety-six of the protocol group patients with RMS were classified as stage III, most of their tumours being located in the head and neck region (including orbital RMS) or the urogenital region (excluding paratesticular RMS), where primary complete surgical removal is only feasible at the cost of severe functional or cosmetic impairment. Hence the study design proposed for patients with stage III: a stratification of local tumour control depending exclusively on the results of the 16-week cytostatic treatment. At this point we take up the problem of pre-surgical chemotherapy in patients with primary unresectable tumours. In order to prevent the development of drug resistance, the question arises: How much tumour reduction is necessary? How long is pre-surgical chemotherapy of RMS permissible in order to be sure that the degree of response is sufficient? The sensitivity of tumours to cytostatic drugs ranges widely within the same histological type of tumour.

In the CWS-81 study, tumour reduction after VACA chemotherapy was clinically monitored by CT scan or ultrasonography for stage III patients. Of the 96 patients with stage III RMS, 14 (14.6%) were non-responders, showing either tumour regression of less than one-third of the original volume or else progression, while 82 (83.4%) responded with a tumour reduction of more than one-third within 7–9 weeks of chemotherapy. In 26 of the 96 stage III patients (27.1%) clinically complete tumour reduction was achieved during the first course of VACA therapy. In 24 (25%) a partial reduction of more than two-thirds of the tumour volume was achieved, while 25 patients (26%) registered a reduction of between one- and two-thirds. Of the 49 patients with partial response after the first course of VACA 11 (22.5% of the 96) went on to achieve complete remission during the second course. Thus, a total of 37 patients (38.6%) managed to attain complete remission after 16 weeks of chemotherapy.

The prognostic significance of the degree of tumour reduction per unit of time is shown in Fig. 7 by correlation between relapse-free survival and the response groups. Patients attaining a clinically complete response within 7–9 weeks have a DFS rate of 89%. The difference between the DFS rate of patients with more and less than two-thirds tumour reduction after the first VACA therapy course (44% and 23%) is insignificant, the deviation being due to a late relapse case which is unrepresentative. However, the relapse pattern does show a greater incidence of metastasis in the group with response less than two-thirds than in the group with greater than two-thirds tumour reduction. In the group with more than two-thirds, only local failure occurred. This difference of quality illustrates the effectiveness of chemotherapy for the prevention of metastasis, as well as the insufficient local tumour control in the half of the patients in the group with more than two-thirds tumour reduction.

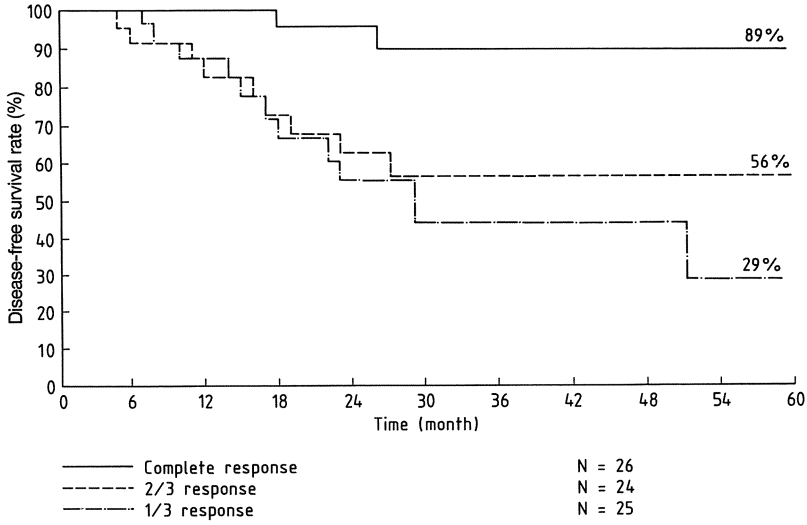

Fig. 7. Kaplan-Meier life-table analysis of disease-free survival for RMS patients according to degree of tumour reduction under initial chemotherapy up to week 7: complete response; > two-thirds tumour reduction; < two-thirds but > one-third tumour reduction

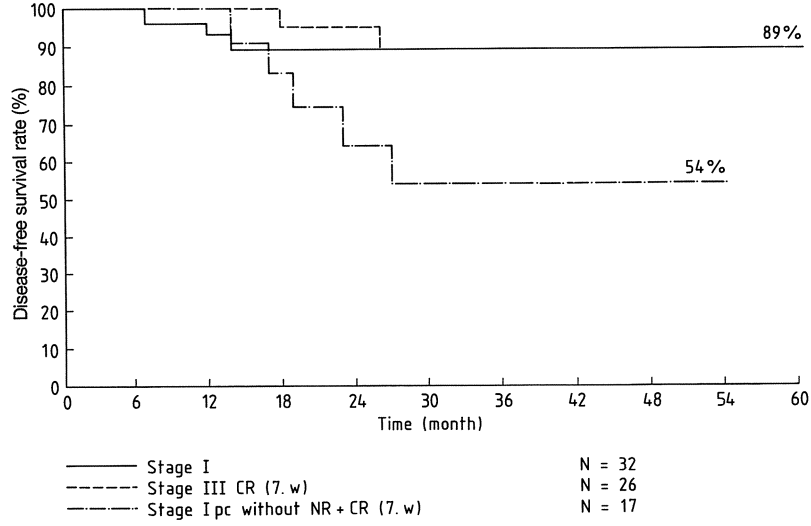

Fig. 8. Comparison of disease-free survival by Kaplan-Meier model for RMS patients: patients with primary stage I; patients who achieved clinical complete remission under chemotherapy by week 7 [*IIICR (7 w.)*]; patients with complete remission achieved up to week 16, excluding non-responder and complete responder at week 7 [*Ipc without NR + CR (7 w.)*]

If we compare the patients who achieved a complete response only later, by week 16 (partial responders at weeks 7–9), with the complete responders by weeks 7–9, we find clear differences: 89% DFS against 54% (Fig. 8). It may be concluded from these data that the time factor involved in tumour reduction under chemotherapy is of considerable importance; there is a qualitative difference between achieving complete remission early on and achieving the same result later.

By means of single and multi-variate analysis (Cox's regression model) it was possible to show that this cytostatic time response factor takes precedence over other well-known prognostic factors such as location, histological subtype, tumour size and age [10, 11]. The influence of these other risk factors on the cytostatic response was also investigated, and it is apparent that the tumour size had the greatest influence on the response behaviour [11].

Extent of Surgery and Local Tumour Control

In 52 (stages I and II) out of the 166 patients with RMS stages I–IV (31.2%) local tumour control proved possible by recourse to primary surgical intervention without mutilating consequences. Of the 96 children with stage III (primary unresectable) tumours, 37 (38.6%) achieved complete remission using chemotherapy alone; furthermore, only 5 local recurrences were observed in this group, and all of these were in a group of 17 patients who achieved remission between the 7th and 16th weeks. Twenty patients (21.8%) attained remission with microscopic residual tumours, while 6 of the 20 patients relapsed locally and only systemically. The last two groups together (57 out of 96 patients, or 59.3%) were treated without irreversible functional impairment or cosmetic disfigurement, while 11 local relapses in this group were observed, and the DFS rate of the 57 patients was 66%. Of the 24 children with macroscopic tumour after 16 weeks of chemotherapy, radical surgical intervention entailing mutilation was necessary for local tumour control in 12. In 6 of the 14 non-responsive cases involving radical surgical intervention, local tumour control was achieved, meaning that in 20 out of 96 primary unresectable tumours (20.8%) a loss of the patients' physical integrity had to be countenanced. The local failure rate for 82 responsive patients was 19.5%, in comparison to the non-responsive group where 42.8% of the children had local failure. Since there is no risk in pre-operative chemotherapy, the question that arises here is: Would it be possible to prevent more local recurrences by scheduling local treatment with radiotherapy or surgical intervention earlier than week 16?

Discussion

From our results the following conclusions can be drawn: in patients with primary stage III RMS, local tumour control by surgery or radiotherapy should be undertaken earlier than week 16 if complete remission has not been achieved by weeks

7–9. Patients undergoing complete remission or partial regression of more than two-thirds in this time should continue to be treated with the same combination of chemotherapy, while only the partial responders of both these groups need radiotherapy in addition. A more effective cytostatic combination should be instituted in those cases when there is only a moderate response (between one- and two-thirds), because of the high risk of metastasis. For local tumour control a higher dose of radiation can be tried before recourse is had to radical surgery. If there is no response, immediate surgery, even with mutilating consequences, must be considered.

Patients with tumours which are primarily resectable without mutilation have about a 90% chance of cure. The same chance of survival was found in our study for patients with primary unresectable tumours who achieve complete remission after 7–9 weeks of chemotherapy. However, the risk of local relapse is increased if complete remission is achieved later than this (see Fig. 8). The total results for patients in stage III (DFS rate 53%) are in line with the results obtained in other studies, especially in the IRS [12]. If we look at the results in detail, however, group III patients can be divided into various risk groups, depending on the degree of primary chemosensitivity. In this way, it will be possible in future to improve the chances of survival (including prevention in the widest possible sense) by altering the therapy modalities at an early time.

One task of surgery is to enable a primary decision to be made regarding possible primary removal of the tumour without mutilation or impairment. The other important task is to assess the quality of remission after chemotherapy or radiotherapy, by means of histological spot checks. If residual tumours are found after chemotherapy, surgical intervention will necessarily have to be of a radical nature.

Acknowledgements. The German Cooperative Soft-Tissue Study (CWS-81) is supported by the German Federal Ministry of Research and Technology, grant no. 01 ZP 0831. The authors wish to thank Sigrid Hönle for her help in preparing the manuscript.

Summary

The results of the German Co-operative Soft-Tissue Sarcoma Study (CWS-81) of the treatment of rhabdomyosarcoma are presented. Prior to the introduction of chemotherapy only 10%–20% of the children were successfully treated. Combined multi-agent cytostatic treatment improved the results dramatically. In patients with primary stage III rhabdomyosarcoma, local tumour control by surgery or radiotherapy should be undertaken earlier than week 16, if complete remission has not been achieved by 7–9 weeks. Patients with complete remission or partial tumour regression should be treated with the same combination of chemotherapy, while only partial responders need radiotherapy in addition. Patients with tumours which are primarily resectable without mutilation have a 90% chance of cure; this also applies to patients with primarily unresectable tumours who achieve complete remission after 7–9 weeks of chemotherapy. Total disease-free survival rate

for stage III rhabdomyosarcoma patients was 53%. The role of surgery includes primary removal of the tumour or assessment of remission by means of histological spot checks.

Résumé

Les auteurs présentent les résultats de l'étude collective en RFA sur le sarcome des parties molles (CWS-81) et le traitement du rhabdomyosarcome. Avant l'introduction de la chimiothérapie, 10% à 20% seulement des enfants étaient traités avec succès. La polychimiothérapie a permis d'améliorer considérablement les résultats. Dans le cas des patients présentant des rhabdomyosarcomes de stade III, il faut pratiquer une exérèse chirurgicale ou une irradiation avant la 16ème semaine si une rémission totale n'a pas été obtenue entre la 7ème et la 9ème semaine. Les patients présentant une rémission ou une régression partielle de la tumeur doivent être soumis à la même polychimiothérapie tandis que dans les cas où la réponse est partielle uniquement, il faudra ajouter une irradiation. Les patients dont la tumeur est opérable sans risque de mutilation ont une chance de survie de 90%. Cela est aussi le cas des patients ayant une tumeur inopérable à l'origine mais chez qui la chimiothérapie a donné une rémission complète après 7 à 9 semaines de traitement. Le taux de survie total dans le cas de patients présentant un rhabdomyosarcome de stade III est de 53%. L'intervention chirurgicale a pour but l'exérèse primaire de la tumeur ou la vérification histologique de la rémission au moyen des biopsies de contrôle.

Zusammenfassung

Vorgestellt werden die Ergebnisse der Kooperativen Weichteil-Sarkom-Studie über die Behandlung des Rhabdomyosarkoms. Vor der Einführung der Chemotherapie konnten nur 10%–20% der Kinder erfolgreich behandelt werden. Eine Polychemotherapie hat die Ergebnisse erheblich verbessert. Bei den Patienten mit einem Rhabdomyosarkom Stadium III sollte der Tumor operativ oder durch Radiotherapie vor der 16. Woche behandelt werden, wenn eine totale Remission nicht während der 7. bis 9. Woche erreicht wurde. Patienten mit einer vollständigen Remission oder partiellen Regression des Tumors, sollten die gleiche Polychemotherapie erhalten, während die Radiotherapie nur in den Fällen von partieller Regression angewendet werden sollte. Patienten mit einem Tumor, der ohne Verstümmelung operiert werden kann, haben eine 90%ige Heilungsrate. Dies gilt auch für Patienten mit einem ursprünglich inoperablen Tumor, bei denen jedoch nach der 7. bis 9. Woche Chemotherapie eine vollständige Remission erreicht wurde. Die gesamte krankheitsfreie Überlebensrate bei Rhabdomyosarkomen Stadium III betrug 53%. Aufgabe der Chirurgie sind die Primärentfernung und die Überprüfung der Remission durch Biopsien und deren histologische Untersuchung.

Appendix

Institutions Participating in the CWS-81 Study

Aachen	Universitäts-Kinderklinik
Augsburg	KZVA Kinderklinik
Bad Mergentheim	Caritas-Krankenhaus
Berlin	Universitäts-Kinderklinik
Bonn	Universitäts-Kinderklinik
Braunschweig	Städtische Kinderklinik
Bremen	Prof.-Hess-Kinderklinik
Celle	Allgemeines Krankenhaus, Kinderabteilung
Dortmund	Städtische Kinderklinik
Düsseldorf	Universitäts-Kinderklinik
Düsseldorf	Medizinische Univ.-Klinik
Duisburg	St. Johannes Hospital, Medizinische Klinik II
Erlangen	Universitäts-Kinderklinik
Essen	Universitäts-Kinderklinik
Frankfurt	Universitäts-Kinderklinik
Freiburg	Universitäts-Kinderklinik
Fulda	Städtische Kinderklinik
Gießen	Universitäts-Kinderklinik
Göttingen	Universitäts-Kinderklinik
Hamburg	Universitäts-Kinderklinik
Hamm	Kinderklinik St. Elisabeth
Hannover	Kinderklinik der medizinischen Hochschule Hannover
Heidelberg	Universitäts-Kinderklinik
Herdecke	Allgemeines Krankenhaus, Kinderklinik
Homburg/Saar	Universitäts-Kinderklinik
Karlsruhe	Städtische Kinderklinik
Karlsruhe	Medizinische Klinik I
Kassel	Städtische Kinderklinik
Kiel	Universitäts-Kinderklinik
Köln	Städtisches Kinderkrankenhaus
Köln	Universitäts-Kinderklinik
Köln	Medizinische Univ.-Klinik I
Krefeld	Städtische Krankenanstalten, Kinderklinik
Lübeck	Universitäts-Kinderklinik
Lüdenscheid	Krankenhaus des Märkischen Kreises, Urologische Abt.
Mainz	Universitäts-Kinderklinik
Mannheim	Städtische Kinderklinik
Marburg	Zentrum für Kinderheilkunde
München-Harlach	Städtisches Krankenhaus
München-Schwabing	Städtisches Krankenhaus
München	Haunersches Kinderspital

München 2	Univ.-Kinderpoliklinik
Münster	Universitäts-Kinderklinik
Nürnberg	Cnopf'sche Kinderklinik
Saarbrücken	Städtische Kinderklinik
Siegen	DRK-Kinderklinik
St. Augustin	Johanniter-Kinderklinik
Stuttgart	Olgahospital Kinderklinik
Trier	Krankenhaus Barmherzige Brüder
Tübingen	Universitäts-Kinderklinik
Ulm	Zentrum für Kinderheilkunde
Würzburg	Universitäts-Kinderklinik
Wuppertal	Klinikum Barmen, Kinderklinik

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