Teratomas in Infancy and Childhood

A 54-Year Experience at the Children's Hospital Medical Center

DAVID TAPPER, M.D., ERNEST E. LACK, M.D.*

The clinical and pathologic features of 254 teratomas from 245 patients are reviewed. All patients were 21 years of age or younger and were treated at the Children's Hospital Medical Center from 1928 to 1982. Tumors arose in the following anatomic sites: sacrococcygeal (102), ovary (94), head and neck (14), retroperitoneum (12), mediastinum (11), testes (eight), central nervous system (nine), liver (two), abdominal wall, and back (one each). One hundred twenty-four tumors (49%) were detected in the newborn period. Teratomas characteristically contained elements derived from all three embryonic germ layers. Tumors with any recognizable component of embryonal carcinoma or other malignant germ cell elements at the time of initial surgery were excluded. Immature teratomas were significantly larger than mature tumors in nearly all sites where statistical analysis was possible. The single most important factor affecting prognosis was whether the tumor could be resected successfully at initial surgery. No patient who did not undergo surgery, or in whom only partial resection was possible, survived the disease—regardless of other treatments used. Based upon the experience reported here the authors conclude: 1) complete surgical resection is the treatment of choice for all childhood teratomas; and 2) this is one of the few childhood tumors where decisions regarding adjuvant therapy must be individualized, particularly with regard to site of origin and age of the patient.

From the Departments of Surgery and Pathology, Children's Hospital Medical Center and Harvard Medical School, Boston, Massachusetts

TERATOMAS are neoplasms composed of tissue elements foreign to the organ or anatomic site of origin, and in childhood these tumors are notable for their diversity in anatomic location and biologic behavior. Etymologically the word teratoma is derived from the Greek "teratos" which literally means monster. As such, this clearly denotes the disturbed or malformed growth and appearance of these tumors. The earliest record of a sacrococcygeal teratoma was inscribed on a Babylonian cuneiform tablet dated approximately 600 B.C. In the modern era, Drs. Gross and Clatworthy described forty infants and children who presented with sacrococcygeal teratoma and made important suggestions regarding appropriate treatment.[1]

Teratomas display various degrees of differentiation, ranging from primitive somatic elements to highly organized axial and metameric structures meriting in one extreme the designation of fetus-in-fetu. They can affect individuals of all ages, but those occurring in childhood are of special interest since biologic behavior is strongly related to age at diagnosis and anatomic site of origin.

Histologically, teratomas typically contain tissue elements of tridermal lineage, *i.e.*, ectoderm, endoderm, and mesoderm; but in recent decades, this definition has become less stringent with the acceptance of examples that are composed of only bidermal ingredients. In the classification of ovarian teratomas, there are even highly specialized variants that are considered to be monodermal, *i.e.*, ovarian carcinoid tumors.[2] The issue of histogenesis remains complex and unsettled, particularly for extra-ovarian tumors. Popular theories of histogenesis include origin from primordial germ cells and primitive somatic cells that have escaped influence of organizers and inducers. In recent decades, there have been a number of clinical and pathologic studies of teratomas arising in specific organs or sites such as ovary,[3] testes,[4] sacrococcygeal region,[5] mediastinum,[6] and retroperitoneum.[7] There have been relatively few accounts of a large series detailing the cumulative experience from a single institution devoted to pediatric care.[6,8] Some pre-

* Presently Chief of Surgical Pathology, National Cancer Institute, National Institutes of Health, Bethesda, Maryland.

Presented at the Annual Meeting of the American Surgical Association, May 12–14, 1983, Boca Raton, Florida.

Reprint requests: David Tapper, M.D., 4800 Sand Point Way, Seattle, Washington 98105.

Submitted for publication: May 16, 1983.

0003-4932/83/0900/0398 $01.40

TABLE 1. *Comparison of Teratomas by Site of Origin Age at Diagnosis and Sex Distribution*

Anatomic Site	No. (%)	Age at Diagnosis	Sex Distribution	Mean Tumor Diameter (cm)	
				Mature	Immature
Sacrococcygeal	102 (40)	newborn	13M, 89F	7.5	11.6
Ovary	94 (37)	13 yrs. (mean)	all female	8.7	17.9
Head and neck	14 (5.5)	newborn	6M, 8F	6.2	6.6
Retroperitoneum	12 (5)	5 mos. (median)	3M, 9F	8.2	12.1
Mediastinum	11 (4)	8 mos. (median)	5M, 6F	7.4	9.8
Brain/spinal cord	9 (3.5)	2½ yrs. (median)	4M, 5F	4.4	6.7
Testis	8 (3)	3½ yrs. (mean)	all male	2.6	3.5
Liver	2 (1)	newborn	1M, 1F	6.0	—
Abdominal wall, paraumbilical	1	newborn	M	4.5	—
Scapula (back)	1	1 yr.	F	3.0	
Total	254				

vious studies have included patients with frankly malignant germ cell elements (*e.g.*, embryonal carcinoma), thereby making comparison with the results from studies with only pure teratomas difficult.[9]

It is our purpose to review the clinical and pathologic features of 245 patients with teratomas, both mature and immature at initial presentation, who were treated at Children's Hospital Medical Center, and identify those factors which influence therapy and prognosis.

Materials and Methods

A systematic search of the pathology files of the Children's Hospital Medical Center disclosed 245 patients, 21 years of age or younger, who had received either primary or referral care for a teratoma. Including those teratomas that were bilateral or multicentric, there was a total of 254 tumors (Table 1). These teratomas were diagnosed and treated during the 54-year period from 1928 through 1982.

The term teratoma as used herein refers to a neoplasma containing at least two germ layer derivatives typically foreign to the anatomic site of origin which, on initial resection or biopsy, contained no frankly malignant elements such as embryonal carcinoma. Routinely stained histologic sections were reviewed in each case, and, where necessary, additional sections were prepared from paraffin-embedded tissues. Clinical records were analyzed and up-to-date follow-up was obtained in 215 of 245 patients. All patients with mature teratomas that were successfully resected survived. Therefore, we focused our attention on the treatment strategies and outcome in patients with immature teratomas. The extent of disease or clinical stage was assessed by review of operative findings and/or consultation with the attending surgeon. The FIGO staging system was used for ovarian tumors,[10] and sacrococcygeal teratomas were typed or grouped according to criteria established by the Surgical Section of the American Academy of Pediatrics in 1972.[5] Exclusive of testes, staging criteria for teratomas in other anatomic sites are not well defined and specification of extent of disease remains more or less descriptive.

Histologically, the degree of immaturity was assessed in each case using criteria established for ovarian teratomas.[11,12] Briefly, the histologic grade of the primary or metastatic tumor was based upon the degree of immaturity of the tissue elements present and the amount of primitive neuroepithelial components. By convention, mature teratomas are composed of well-differentiated tissue elements and were assigned a grade of 0. Increasing grades of immaturity from I to III were assigned when immature tissues (predominantly neuroepithelial) became progressively more prevalent in representative tissue section as outlined by Norris et al.[12] Assignment of a meaningful and reproducible histologic grade depends to a large extent upon an adequate sampling of the resected primary tumor. Once again, it should be emphasized that tumors containing any recognizable component of embryonal carcinoma at the time of initial therapy were excluded.

Results

Clinical Features

The most common clinical manifestation of teratomas as a group is a mass lesion with signs or symptoms ascribable to specific location and consequent impingement upon or compression of adjacent organs or tissues (Fig. 1). The age at diagnosis and anatomic location of the tumor together establish many of the clinical and pathologic correlates and ultimately the prognosis. The clinical features of some of the more commonly occurring teratomas are considered separately.

Sacrococcygeal teratomas. These tumors accounted for 40% of all teratomas in the first two decades of life

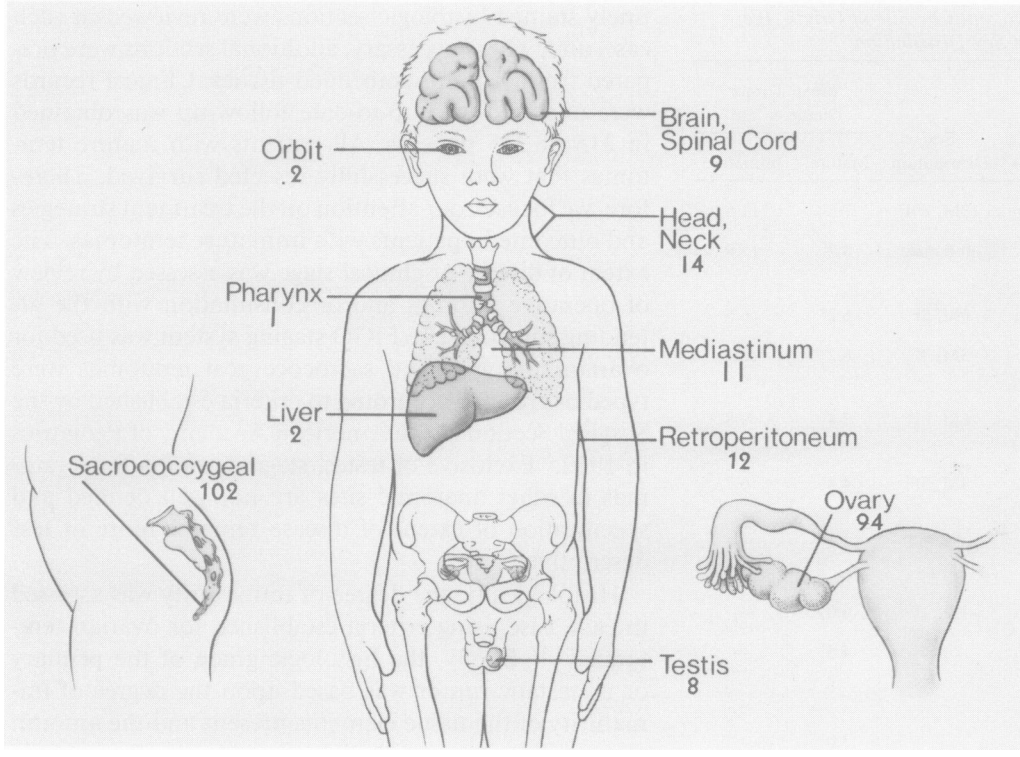

FIG. 1. Anatomic site of origin of the teratomas. The most common site was sacrococcygeal area, followed by ovary, head and neck, retroperitoneum, mediastinum, testes, and central nervous system.

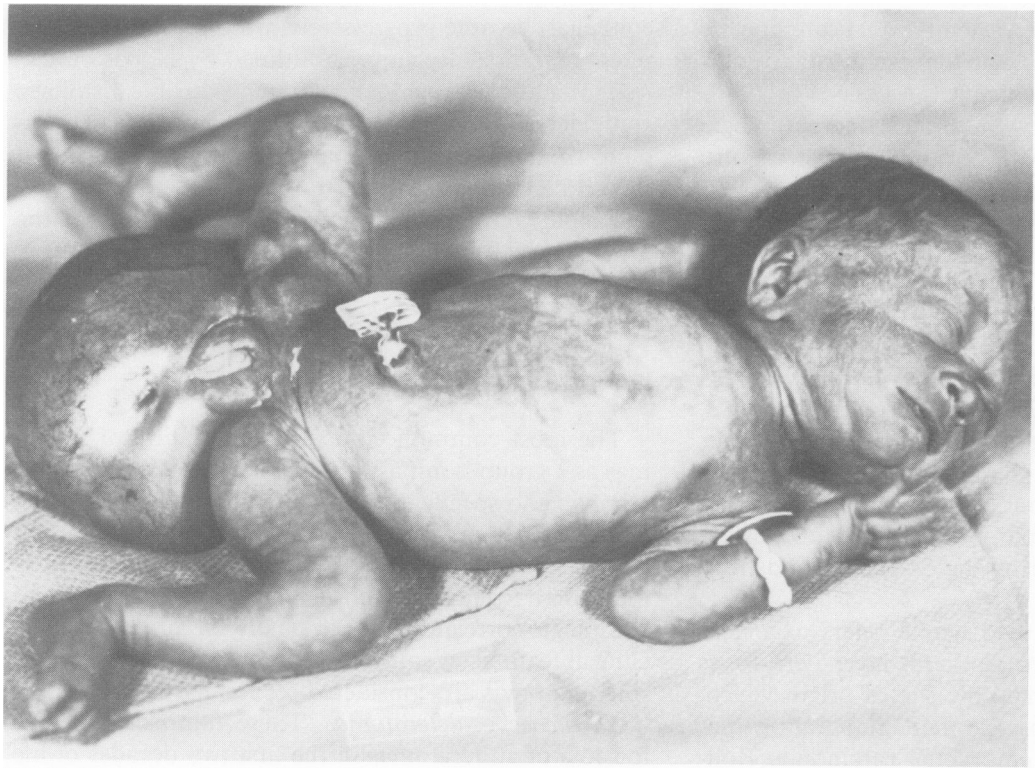

FIG. 2. Large exophytic (AAP type I) sacrococcygeal teratoma. The lesion is midaxial in location, seemingly suspended from the coccyx.

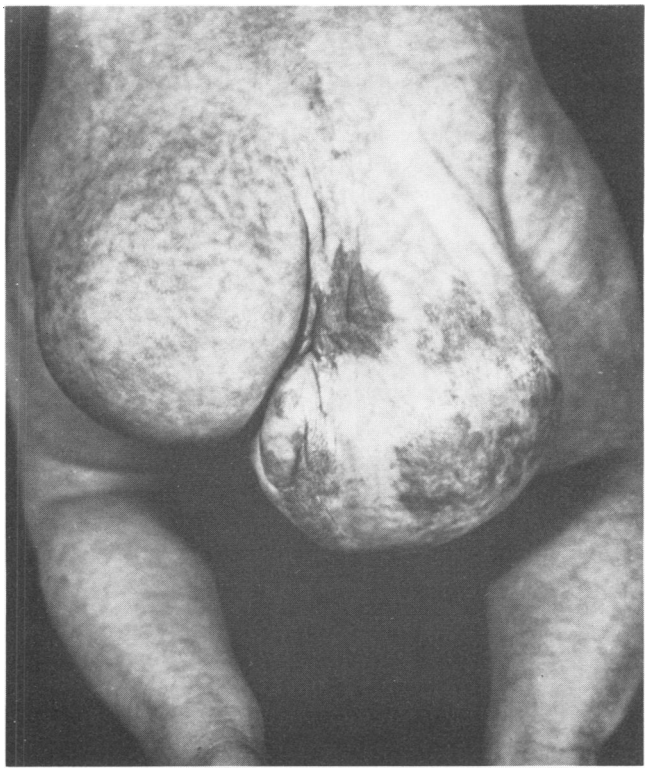

FIG. 3. Sacrococcygeal tumor which presented primarily in the right buttock area. Note the vascular stain of the overlying skin, suggesting a hemangioma.

and were overwhelmingly the most common type in early childhood (Table 1). In our experience, they rank as the most common type of congenital neoplasm and typically present in the newborn era as an exophytic mass (AAP types I and II) which is usually midaxial in location (Fig. 2). Some tumors display para-axial growth away from the midline. Rare tumors of large size cause birth dystocia, and in two cases, there was evidence of high output heart failure presumably due to vascular shunting through the tumor. Changes in overlying skin such as redundancy or patchy, dark discoloration can simulate a hemangioma or lymphangioma (Fig. 3). There was a decided predilection for females in a ratio of 7:1. There were no significant differences in age or AAP type of tumor for children with mature *versus* immature teratomas. Immature teratomas were significantly larger than the mature ones (11.6 cm *versus* 7.5 cm) (Table 2).

Ovarian teratomas. The ovary is second only to the sacrococcygeal area as the most common site for the appearance of teratomas in childhood (Table 1). Ovarian teratomas (Table 3) are quite rare within the first 24 months of life and seldom appear before 6 years of age. The mean age at diagnosis was 13 years and was similar for patients with immature and mature teratomas. Patients typically presented with symptoms or signs ascribable to an intraabdominal adnexal mass, and a palpable tumor was usually apparent on physical examination. Five patients had bilateral mature tumors (7%). The immature teratomas of the ovary were significantly larger than the mature ones (17.9 cm *versus* 8.7 cm) (Table 3).

Retroperitoneal teratomas. These tumors posed a significant problem in the differential diagnosis of an intraabdominal mass due to the young age of the patients (mean age, 5 months) and the consequent confusion with Wilms' tumor, neuroblastoma, and other intraabdominal masses (Table 4). As with teratomas in other sites, the presence of calcification or bony structures on plain radiographs was a useful diagnostic aid, but was apparent only in a minority of cases.

Teratomas of the head and neck region (Table 5). Each of these tumors was diagnosed in the immediate newborn period and they were similar to those arising in the sacrococcygeal region. The most common site of origin was the anterior or lateral neck, followed by the face, oro- or nasopharynx, and orbit. Sex distribution was roughly equal. Clinically, some of the tumors simulated a lymphangioma or cyst hygroma, particularly those that were cervical in location. The solid, nonfluctuant nature of the tumor, coupled with the occasional calcification evident by radiography, provided valuable aid in resolving the differential diagnosis.

Mediastinal teratomas. The mean age at diagnosis was 8 months and the affected children usually manifested a combination of symptoms such as dyspnea, cough, fever, or chest pain. Chest radiography demonstrated a mediastinal mass in most cases with localization in the anterior/superior mediastinum. In one patient, the tumor was located in the posterior mediastinum (case 9) (Table 6). A small but important subset of teratomas was situated within the pericardial sac near the base of the heart (cases 5 and 10) (Table 6). Both of these newborns presented with signs and symptoms mimicking congenital heart disease or idiopathic cardiomegaly.

Testicular teratomas. Testicular teratomas, like the ovarian group, were present more commonly outside the newborn period (Table 7). The mean age at presentation was 3½ years. Younger children commonly have testicular teratomas, whereas the adolescent more commonly has a germ-cell neoplasm.

Teratomas in other sites (Table 1). Teratomas arising in other sites follow similar patterns. Those in the central nervous system, liver, abdominal wall, and soft tissue

TABLE 2. *Immature Sacrococcygeal Teratomas*

Case	Age at Initial Surgery	Tumor Diameter (cm)	Histologic Grade	AAP Type	Treatment	Follow-up
1) P.M.	Newborn	6.5	I at initial surgery	II	Surgical resection	Recurrence 10 months later—embryonal carcinoma DOD—3 months later with metastases
2) B.R.	Newborn	6.0	I	II	Surgical resection	Post-op death No metastases
3) J.G.	Newborn	6.0	I	II	Surgical resection	NED—9 months
4) S.R.	Newborn	12.0	I	II	Surgical resection	NED—4 9/12 months
5) S.M.	Newborn	11.0	I	I	Surgical resection	NED—5 years
6) B.W.	Newborn	—	II	III	None	Death due to immaturity and RDS
7) M.C.	Newborn	8.0	II at initial surgery	II	Surgical resection	Recurrence 20 months later—embryonal carcinoma DOD—7 months later with metastases
8) E.S.	Newborn	18.5	II	III	Surgical resection	NED—8 years
9) S.G.	Newborn	9.0	II	III	Surgical resection	NED—9 years
10) D.G.	Newborn	18.0	II	II	Surgical resection	NED—9 years
11) M.B.	Newborn	18.0	II	II	Surgical resection	NED—10 years
12) P.B.	Newborn	10.0	III	II	Surgical resection	Post-op death No metastases
13) K.A.	Newborn	17.0	III	II	Surgical resection	NED—8 months
14) K.T.	7 Years	4.0	III at initial surgery	I	Surgical resection	DOD—2 years with embryonal carcinoma metastatic to lung
15) J.H.	Newborn	9.0	III	III	Surgical resection	NED—5 1/2 years
16) A.D.	Newborn	7.0	III	III	Surgical resection	Massive intrapelvic recurrence 3 years later; treated with surgery, Rtx & Ctx NED—7 years
17) B.D.	Newborn	12.0	III	I	Surgical resection	—
18) B.T.	Newborn	8.0	II	I	Surgical resection	NED—3 years
19) M.C.	Newborn	16.0	II	I	Surgical resection	NED—4 1/2 years
20) B.H.	Newborn	13.0	III	I	Surgical resection	Post-op death 5-cm tumor in right lobe of liver with identical histology

of the back frequently present as masses in the newborn period. Immature teratomas were significantly larger than the mature ones.

Gross Pathology

Teratomas vary considerably in size, depending upon site of origin and whether or not histologically immature elements were predominant. The largest tumors arose in the ovaries followed by retroperitoneum, sacrococcygeal region, and mediastinum (Table 1). The tumors had a similar gross appearance, regardless of site, and were well circumscribed with no direct invasion of adjacent soft tissue or bony structures. The tumors, regardless of site, typically had a variegate gross appearance on cross section, reflecting the diversity of tissue elements present and the presence or absence of immature elements. As a general rule, immature teratomas were more solid on section than the mature ones (Fig. 4). Necrosis and/or hemorrhage were unusual macroscopic features, even in immature teratomas of high grade. When present, these features were more often

TABLE 3. *Immature Ovarian Teratomas*

Case	Age (Yrs)	Tumor Diameter (cm)	Treatment	FIGO Stage	Histologic Grade	Follow-up
1) A.C.	14	15.0	S & O CTx- VCR, ADR, CTX	I	III	NED—Short term
2) L.C.	16	—	S & O 4 mos. later—widespread pelvic/peritoneal implants	I	II	DOD—8 months widespread pelvic/ peritoneal implants
3) M.C.	12	20.0	S & O	I	I	NED—5 years
4) S.M.	13	13.0	S & O 6 mos. later—pleuropulmonary metastases CTx- MTX, CTX, VCR, ActD RTx	I	III	DOD—2½ years peritoneal spread pulmonary metastases
5) R.S.	12½	15.0	S & O CTx- MTX, CTX, VCR RTx- 4000 R whole abdomen 250 R pelvis	III	II	DOD—1 year massive peritoneal spread with ascites
6) T.V.	18	—	S & O 1 yr. later—pelvic, peritoneal implants with ascites	I	III	DOD—15 months massive peritoneal spread; para lyno metastases
7) S.S.	13	30	BSO Partial omentectomy	III	III	—
8) V.G.	12 3/12	19	S & O Tumor spillage	II	III	NED—5 years
9) L.S.	12	15.0	S & O Omentectomy; 2nd look operation; 2nd look laparoscopy	III	I	NED—4 years
10) D.C.	11	23.0	BSO CTx- Vinblastine, Bleo, CisPlt.; changed to VCR, ADR, CTX	III "gliomatosis peritonei"	III	Alive at 18 months with presumptive pulmonary metastases
11) D.V.	16	21.0	BSO, TAH (patient gravid) Tx- Vinblastine, Bleo 2nd look operation—mature peritoneal implants recurrent tumor RTx- 5000 R spleen	III Implants Mature	II	NED—6 years
12) E.G.	17	15.0 4.0 ?bilateral ?implants opp ovary	BSO, Omentectomy CTx- MTX, High dose; later VCR, ADR, CTX; RTx	III Implants Immature	III	NED—6 years
13) S.S.	17	17.0	BSO, TAH 3 yrs later—peritoneal relapse CTx- ADR, VCR RTx- pelvis, abdomen	I	III	DOD—3½ years extensive peritoneal spread with ascites
14) I.B.	11	15.0	S & O	I	I	—
15) K.C.	4	15.0	S & O, Left	I	II	Developed EST Opposite ovary age 12½ years TAH; removal remaining adnexa. 21-cm tumor DOD—1 year 2° intraabdominal spread
16) P.P.	18	—	BSO CTx- ActD, MTX, VCR, & CTX Later P^{32} instillation Thoracic and peritoneal cavities; high dose MTX terminally	III	III	DOD—4 months extensive peritoneal seeding; ascites, metastases to mediastinum, lungs, pericardium, liver, spleen, adrenal glands; abdominal seeding required repeated centesis Tx

TABLE 4. *Retroperitoneal Tumors*

Case	Age	Site	Tumor Diameter (cm)	Histologic Grade	Treatment	Follow-up
1) B.E.	Newborn	Left upper quadrant; adjacent to pancreas and duodenum	8	III	Unresectable CTx- pulse VAC	DOD—2 months due to respiratory and hepatic failure
2) N.N.	3 months	Left upper quadrant; suprarenal	—	0	Surgical resection	NED—2 months
3) H.K.	4 years	Right upper quadrant; para-aortic	10.5	0	Surgical resection	NED—10 years
4) S.S.	4 years	Lower pole left kidney	4	0	Surgical resection	NED—5 years
5) K.S.	14 years	True and false pelvis	12	III	Incomplete resection	DOD—3 weeks due to intraabdominal bleeding & peritonitis, obstruction of rectum and writers by tumor
6) V.F.	4 months	Left upper quadrant; suprarenal	16	II	Surgical resection	NED—26 years
7) F.Z.	5 months	Right upper quadrant; adjacent to duodenum and pancreas	9	0	Surgical resection	NED—2 years
8) M.O.	Newborn	Upper quadrant; near kidney	11	0	Surgical resection	Recurrent tumor ("fetus-in-fetu") 15 years later surgical resected; NED—33 years
9) B.F.	Newborn	Upper abdomen	12	III	Incomplete resection	DOD—8 months at autopsy embryonal carcinoma metastatic to liver, spleen and peritoneum
10) C.M.	11 months	Left upper quadrant suprarenal	6.5	0	Surgical resection	NED—$3^{3}/_{12}$ years died at home, cause unknown; no autopsy
11) S.A.	5 months	Right upper quadrant	12.5	II	Surgical resection Right nephrectomy RTx- 2000 R (megavolts)	NED—34 years

TABLE 5. *Teratomas of the Head and Neck Region*

Case	Age	Site	Tumor Diameter (cm)	Histologic grade	Treatment	Follow-up
1) D.S.	Newborn	Right neck	6	II	Surgical resection	NED—3 years
2) B.B.	Newborn	Right neck	5.5	II	Surgical resection	NED—12 years
3) P.C.	Newborn	Right neck	7	II	Surgical resection	NED—9 years
4) T.J.	Newborn	Neck, midline	4.3	0	Surgical resection	NED—8 years
5) R.B.	Newborn	Right neck	5.0	I	Surgical resection	NED—8 years
6) B.F.	Newborn	Right neck	9.0	III	Surgical resection	NED—16 years
7) S.C.	Newborn	Parauricular right	7.5	0	Surgical resection	NED—1 year
8) B.P.	Newborn	Left face cheek	11	0	Surgical resection	NED—12 years
9) M.M.	Newborn	Right face near angle of mandible	3.4	0	Surgical resection	NED—12 years
10) E.G.	Newborn	Right face near angle of mandible	7	II	Unresectable	DOD—5 months due to local compression on airway and oropharynx; No evidence of metastases
11) S.C.	Newborn	Oropharynx	5	0	Unresectable	DOD—22 months with growth up through base of skull; lung and brain metastases
12) D.W.	Newborn	Nasopharynx	3.2	0	Surgical resection	NED—14 years
13) L.W.	Newborn	Orbit	3.0	0	Orbital exenteration	NED—24 years
14) B.M.	Newborn	Orbit	5.5	0	Enucleation of globe	NED—5 years

TABLE 6. *Mediastinal Teratomas*

Case	Age	Tumor Diameter (cm)	Histologic grade	Treatment	Follow-up
1) L.B.	3 months	7	II	Surgical resection	NED—7 years
2) J.F.	8 months	7	0	Surgical resection	NED—4 years
3) A.M.	16 years	8	0	Surgical resection	NED—5 years
4) A.C.	9 years	7	0	Surgical resection	NED—5 years
5) M.C.	Newborn	6	0	Surgical resection	NED—13 years
6) L.T.	7½ years	8.5	0	Surgical resection	NED—2 years
7) J.W.	9 months	8	0	Surgical resection	NED—5 years
8) J.A.	2 months	7	0	Surgical resection	NED—1 year
9) M.S.	6 months	9.5	0	None	Death due to congenital malformations and tumor compression of adjacent vital structures; at autopsy tumor was located in posterior mediastinum
10) R.F.	Newborn	6	0	None	Dead in 4 weeks due to compression of great vessels and heart
11) J.A.	1½ years	12.5	I	Surgical resection	NED—5 years

seen in the larger neoplasms, arising in the ovary, retroperitoneum, or sacrococcygeal region.

Microscopic Pathology

Two or more embryonic germ layer derivatives were apparent in each of the tumors, and all three were well represented in 90% or more of the cases (Fig. 5). The expression of tissue types and their arrangement and degree of differentiation varied from case to case and even within areas of the same tumor, depending upon extent and adequacy of sampling. The average number of tissue sections examined in each case was nine, but ranged from one to over 20 in selected cases. Endodermal sinus-tumor (yolk sac tumor, Teilum tumor), a form of embryonal carcinoma, subsequently appeared in six patients following biopsy or surgical removal of their primary tumor—case 1, 7, and 14 (Table 2), case 15 (Table 3), case 9 (Table 4), and case 11 (Table 5). These tumors had distinctive histologic features with reticular pattern and loose arrangement of cells forming clefts and irregular papillary structures (Fig. 6). A characteristic feature was the presence of intra- and extracellular hyaline globules which were PAS-positive and resistant to diastase digestion.

TABLE 7. *Testicular Teratomas*

Case	Age	Tumor Diameter (cm)	Histologic grade	Treatment	Follow-up
1) C.K.	1 year	1.8	0	Orchiectomy	NED
2) M.K.	10 months	3	0	Orchiectomy	NED
3) R.A.	1½ years	2	0	Orchiectomy	NED
4) R.D.	5½ years	3	0	Orchiectomy	NED
5) E.D.	5 years	4.5	0	Orchiectomy	NED
6) M.R.	13½ years	2	0	Orchiectomy	NED
7) J.L.	6 months	4	II	Orchiectomy	NED
8) J.C.	1½ years	3	II	Orchiectomy	NED

Treatment and Follow-up

Complete surgical resection remains the prime goal in each case, but anatomic localization of tumor proved to be the most significant extenuating factor in optimal management and clinical outcome. Optimal treatment of sacrococcygeal teratomas was en block removal of the tumor along with the coccyx. Significant presacral extension (AAP types III and IV) presented some technical difficulties. While mature and immature teratomas were deemed equally resectable, children with immature tumors experienced significantly greater blood loss during surgery. The tumors that were least amenable to complete resection were those arising in the retroperitoneum and central nervous system (Tables 5 and 8). Complete removal was hampered by extensive local growth or close relation with adjacent vital structures. Intrapericardial teratomas present difficulties in management as well as diagnosis due to close relation with the great vessels at the base of the heart.

In this series, there were 21 tumor-related deaths (9%). When this mortality was analyzed according to anatomic location, children with central nervous system tumors experienced the highest fatality rate (66%), regardless of whether the tumor was histologically mature or immature. This was a reflection of technical difficulties in complete surgical resection that was possible in only two cases (Table 8). Patients with immature ovarian teratomas ranked second in terms of fatal out-

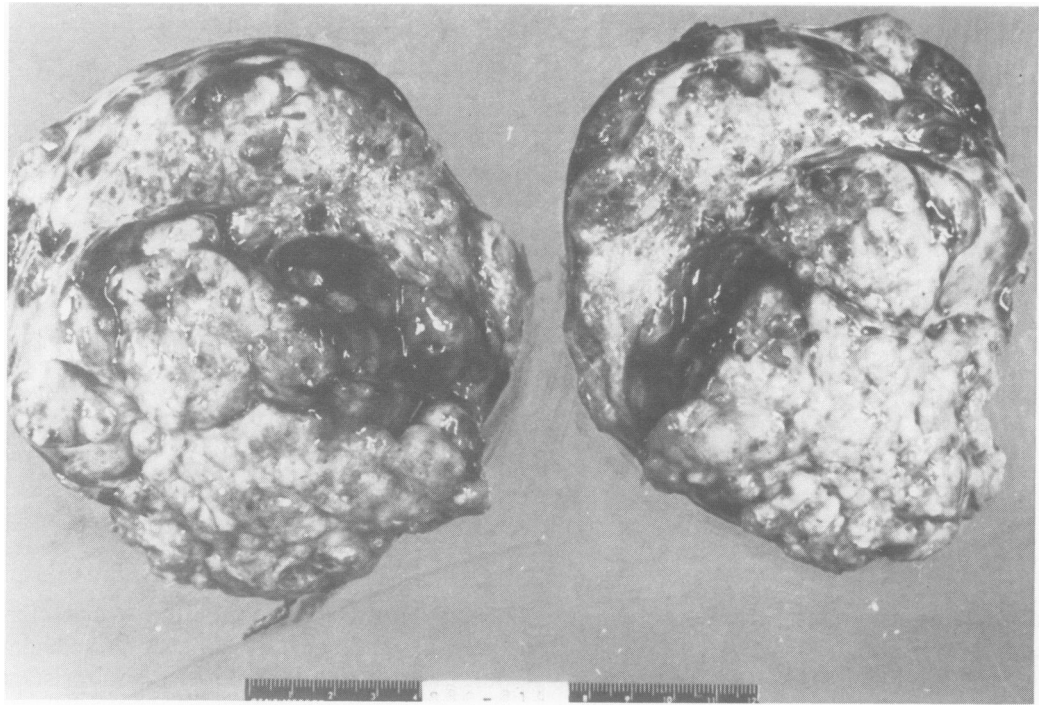

FIG. 4. Large, immature sacrococcygeal teratoma. This tumor was predominantly solid and lacked the large cystic components usually found in mature teratomas.

come (38%) (Table 3). Another patient (case 15) underwent successful resection of an immature ovarian teratoma, but 8 years later developed endodermal sinus tumor of the contralateral ovary and died with massive intraabdominal carcinomatosis 1 year later. An additional patient (case 10) (Table 3) is currently alive with presumptive evidence of metastatic immature teratoma in the lung parenchyma. Tumor-related deaths in the other areas were as follows: retroperitoneum—27% (Table 5), mediastinum—18% (Table 6), sacrococcygeal region—15% (Table 2), and head and neck region—14% (Table 5).

Within the last decade, adjuvant radiation and chemotherapy have been added to the treatment of many patients with immature teratomas or teratomas that could not be completely resected. Five patients with unresectable central nervous system tumors received radiation therapy but did not experience any curative benefit in terms of controlling local growth of the tumor (Table 8). Two patients with completely resected immature sacrococcygeal teratomas subsequently received combination chemotherapy when they developed metastatic embryonal carcinoma (Table 2). Chemotherapy was unsuccessful in preventing the progression of disease. Ten girls with immature ovarian teratomas were treated with adjuvant radiation and/or chemotherapy. Those patients with immature (grade 2 or 3) tumors and advanced stage of disease had the worst prognoses (Table 3).

Discussion

The opportunity to examine a large series of teratomas treated at a single institution over more than 5 decades has allowed us to place into perspective and comparatively analyze their clinical and pathologic features. The differential diagnosis, treatment, and prognosis for childhood teratomas is strongly influenced by anatomic location of the primary tumor and age of the

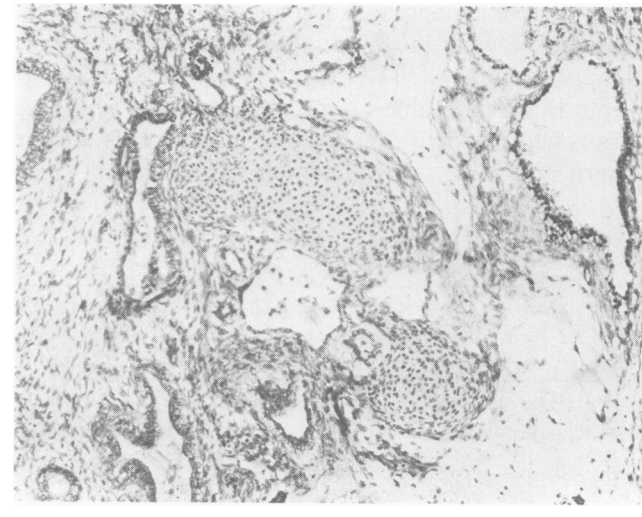

FIG. 5. Teratoma with islands of fetal-type cartilage, glandular spaces, and loose mesenchyme. Tumor was considered to be immature grade I after examination of multiple sections (H&E, ×150).

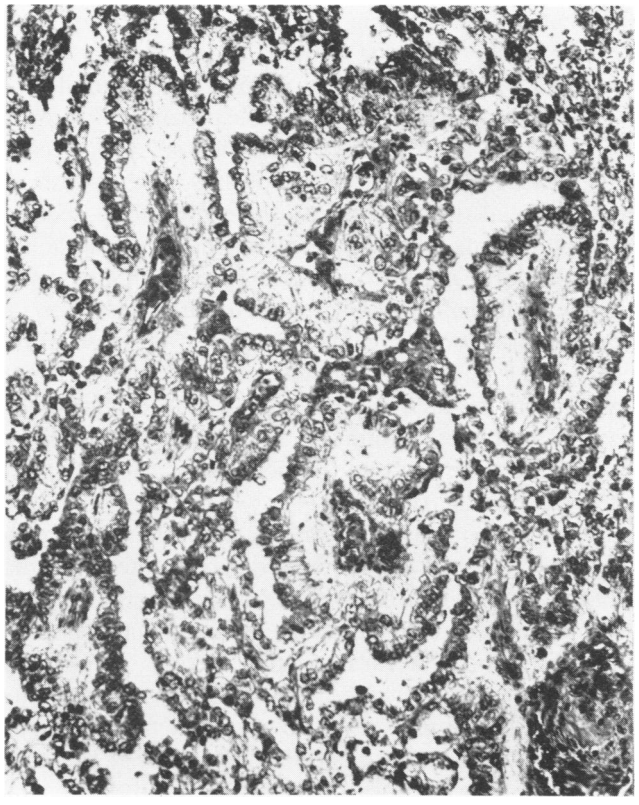

FIG. 6. Papillary configuration with tumor cells covering connective tissue core—glomeruloid body (Schiller-Duvall body) (H&E, ×150).

patient. The clinical stage or extent of disease and histologic grade of immaturity are also significant features but assume greatest importance with immature ovarian teratomas. With regard to histologic grading, it is encumbent upon the pathologist to adequately sample the primary tumor or its metastases. In general, one histologic section for every 1 to 2 cm of tumor diameter appears adequate.

The most important variable affecting long-term survival is the surgeon's ability to completely resect the tumor. Although resectability in some instances may be a reflection of size and histologic immaturity of the primary tumor, it is most often related to the strategic localization of the tumor, thus defying complete or safe removal. This is most apparent for retroperitoneal and central nervous system tumors.

The overall mortality for children with mature teratomas was significantly less than for those with immature tumors. Twenty per cent of all the tumors were classified as immature.

The most common teratomas in infancy are those arising in the sacrococcygeal region. Adverse prognostic factors include older age at diagnosis, a substantial presacral or endopelvic component (AAP type II–IV), and the presence of endodermal sinus tumor (yolk sac tumor, Teilum tumor). It is important to recognize these frankly malignant elements.

Seventy-three children with mature sacrococcygeal tumors were followed after resection. Two children experienced local recurrence, and both were alive and well years later following re-excision. Twenty children with immature sacrococcygeal tumors were followed. Three developed endodermal sinus tumor at intervals ranging from 10 months to nearly 2 years following initial surgery. Each tumor had been well sampled at the time of initial surgery to exclude the presence of frankly malignant elements. However, there is some doubt, in our opinion, as to whether the original tumor had been resected in its entirety. If this is true, it suggests that histologically immature tumors may have the capacity to spawn frankly malignant elements if allowed to persist.

TABLE 8. *Teratomas of the Brain/Spinal Cord*

Case	Age	Site	Tumor Diameter (cm)	Histologic grade	Treatment	Follow-up
1) P.G.	22 months	Floor of 3rd ventricle	6	0	Unresectable	DOD—4 months.
2) C.G.	15 months	Posterior fossa	6	0	Unresectable	DOD—3 months.
3) C.W.	11 years	Third ventricle	3.8	II	Incompl. resection	DOD—12 months. Recurrent and was more embryogenic
4) A.M.	10½ years	Posterior fossa	2	0	—	—
5) P.D.	2½ years	Cervical spinal cord	3.5	0	—	—
6) C.A.	7 months	Cervical spinal cord	4.5	0	Surgical resection	NED—10 years. Paraplegic with mental retardation
7) E.P.	11 years	Cervical spinal cord	—	0	Surgical resection	NED—20 years. Flexion deformities
8) P.S.	3 years	Intraventricular	9.5	I	Unresectable	DOD—7 months.
9) R.D.	2 months	Spinal canal, thoracic	4.0	0	Unresectable	DOD

Gonzalez-Cruzzi et al.[9,13] classified 18/40 cases of sacrococcygeal tumors as immature (40%), but included seven cases of embryonal carcinoma among the grade 3 immature teratomas. Sacrococcygeal tumors with any recognizable embryonal carcinoma at inception must be considered separately with regard to survival analysis. Noseworthy et al.[14] reported that of 19 children with sacrococcygeal tumors containing embryonal carcinoma, either pure or admixed with teratomatous elements, none survived.

With regard to ovarian teratomas, the single most important prognostic factor is clinical stage. The degree of immaturity of the primary tumor seems to correlate with extra-ovarian spread while the histologic grade of the metastases determined the ultimate prognosis. This was amply demonstrated in a series of 58 immature ovarian teratomas reported by Norris et al.[12] When survival was stratified according to histologic grade of the primary tumor, the following was observed: grade I—81% survival; grade II—60% survival; and grade III—30% survival. It should be stressed that clinical staging can yield some unreliable or misleading information, particularly in a retrospective analysis. Often, there is failure to carefully inspect the peritoneum and upper abdomen for gross or microscopic disease, which can only be revealed by biopsy or omentectomy. The combination of careful staging and accurate assessment of histologic grade is most valuable in establishing a prognostic profile. Some ovarian teratomas contain frankly malignant germ cell elements such as embryonal carcinoma, and the prognosis in these cases is significantly less favorable.[15]

Adjuvant therapy has an established role in the management of immature ovarian teratomas, particularly the use of combination chemotherapy.[16-18] In this overview of childhood teratomas, immature teratomas of the ovary are the only situation where adjuvant therapy can be recommended on a routine basis. Its use for immature teratomas in other sites must be evaluated on an individual basis, particularly for those tumors in early infancy where histology is not an entirely reliable predictor of subsequent biologic behavior. The prognosis for children with retroperitoneal teratomas and teratomas in other selected sites, such as the central nervous system, depends primarily upon the adequacy of resection. With regard to retroperitoneal tumors, there is some indication in our material that advanced histologic grade correlates with larger tumor size and, hence, unresectablility. In patients with large teratomas not amenable to complete surgical resection, adjuvant radiation and/or chemotherapy might make a subsequent complete resection possible. This approach may prove beneficial in patients with retroperitoneal teratomas, a group who had one of the highest incidences of incomplete resection and very poor survival.

A recent review of immature mediastinal teratomas by Carter et al.[19] showed a favorable prognosis for young children where tumors are characterized as space-occupying but non-aggressive neoplasms. Infants with intrapericardial tumors, mature or immature, posed different problems since they can clinically masquerade as cardiomegaly. Those correctly diagnosed often present significant technical problems due to cardiac tamponade and compression of the great vessels at the base of the heart. Since ultimate outcome seems dependent upon complete resection, it may be appropriate to aggressively try to resect these tumors. This might necessitate cardiopulmonary bypass and hypothermic arrest to completely excise the tumor.

In conclusion, it is encumbent upon the surgeon to make every effort to completely excise the teratoma. This might include cardiopulmonary bypass for large mediastinal tumors, adjunctive radiation and chemotherapy to shrink central nervous system or retroperitoneal teratoms to allow resectability, and careful staging of the peritoneal surfaces in an ovarian teratoma to rule out concommitant intraabdominal disease. Careful assessment of age and location is important in establishing a reliable prognostic profile. The pathologist assumes an important role in accurate determination of histologic grade, adequacy of resection, and the presence or absence of unfavorable histologic elements such as embryonal carcinoma. Tumors containing frankly malignant elements should be separated with regard to planning therapy and subsequent analysis of survival data. Survival of patients with immature teratomas in selected sites, (*e.g.*, ovary) may be improved by routine adjuvant therapy. Similar teratomas in other sites must be evaluated on an individual basis, particularly in infancy. Finally, long-term follow-up is recommended for all patients, particularly those with immature teratomas.

Acknowledgments

The authors wish to thank Mr. Carl Cobb and Ms. Jo-Anne Hutchinson for their invaluable assistance in the preparation of this manuscript.

References

1. Gross RE, Clatworthy HW Jr, Meeker IA Jr. Sacrococcygeal teratomas in infants and children: report of 40 cases. Surg Gynecol Obstet 1951; 92:341-352.
2. Scully RE. Tumors of the ovary and maldeveloped gonads. 2nd Series, AFIP Fascicle, Washington, DC, 1977.
3. Kobayaski RH, Moore, TC. Ovarian teratomas in early childhood. J Pediatr Surg 1978; 13:419-422.
4. Mostofi FK. Testicular tumors. Cancer 1973; 32:1186-1200.
5. Altman RP, Randolph JG, Lilly JR. Sacrococcygeal teratomas:

American Academy of Pediatric Surgical Section survey. J Pediatr Surg 1974; 9:389–406.
6. Grosfeld JL, Ballantine TVN, Lowe D, Baeleur RL. Benign and malignant teratoma in children: analysis of 85 patients. Surgery 1976; 80:297–305.
7. Keramedas DC, Voyatziz NG. Retroperitoneal teratoma. J Pediatr Surg 1972; 7;434–439.
8. Mahour GH, Wooley MM, Trevedi SN, et al. Teratomas in infancy and childhood: experience with 81 cases. Surgery 1974; 73:309–314.
9. Gonzalez-Cruzzi F, Winkler RF, Mirkin DL. Sacrococcygeal teratomas in infants and children. Relationship of histology and prognosis in 40 cases. Arch Pathol Lab Med 1978; 102:420–425.
10. Tobias JS, Griffiths CT. Management of ovarian carcinoma. N Engl J Med 1976; 294:919–949.
11. Robboy SJ, Scully RE. Ovarian teratoma with glial implants on the peritoneum. Hum Pathol 1970; 1:643–653.
12. Norris HJ, Zirkin HJ, Benson WL. Immature (malignant) teratoma of the ovary. Cancer 1976; 37:2359–2372.
13. Gonzalez-Crussi F. Extragonadal teratomas: atlas of tumor pathology. Sec. Series Fascile 18. AFIP, Washington, DC 1982.
14. Noseworthy J, Lack EE, Kozakewich HPW, et al. Sacrococcygeal germ cell tumors in childhood: an updated experience with 118 patients. J Pediatr Surg 1981; 16:358–364.
15. Kurman RPJ, Norris HJ. Hum Pathol 1977; 8:551–564.
16. Munnell EW. The changing prognosis and treatment in cancer of the ovary: a report of 235 patients with primary ovarian carcinoma 1952–1961. Am J Obstet Gynecol 1968; 106:790–805.
17. Frei E III, Jaffe N, Tattersall MH, et al. New approaches to cancer chemotherapy with methotrexate. N Engl J Med 1975; 292:846–851.
18. Griffiths CT, Grogern RH, Hall TC. Advanced ovarian cancer: primary treatment with surgery, radiotherapy, and chemotherapy. Cancer 1972; 29:1–7.
19. Carter D, Bibro MC, Touloukian RJ. Benign clinical behavior of immature mediastinal teratoma in infancy and childhood. Report of two cases and review of the literature. Cancer 1982; 49:398–402.

Discussion

DR. JUDSON G. RANDOLPH (Washington, D.C.): I wish to corroborate the authors' conclusions in one area of this study by referring to the data accumulated several years ago in a national review of sacrococcygeal teratoma. My co-workers in this were Dr. Peter Altman, now at Columbia Presbyterian, and Dr. John Lilly, now at Colorado; and these data have the inherent strengths and weaknesses of all combined national studies; that is, large numbers, but individual variation.

(Slide) This shows a comparison of types of sacrocoxxygeal teratoma, and we noticed, as would be obvious, that when there is an external position, then complete surgical excision is much more likely; and as the tumor extended into the abdomen, fewer could be excised completely, and so the survival rate was influenced.

(Slide) This particular slide shows a point that I think Dr. Tapper made very well, and that is that malignant changes occur in teratoma as time runs on. In those tumors which were resected before 2 months, the survival rate was about 90%, whereas after 2 months biologic changes had occurred with respect to malignancy which made curative resection much more difficult to achieve.

I think that the temporally related changes in teratoma are significant, and will influence, in spite of the best surgical effort, certain results.

I have two questions for the authors. Do teratomas in different locations behave differently with respect to their propensity to mature and develop malignant potential? Second, with respect to decisions at the operating table, can we get representative biopsies from these tumors in one or two places, or can frozen sections sometimes be misleading?

DR. J. ALEX HALLER, JR. (Baltimore, Maryland): I am sure we are going to be able to get information from the published data that will be invaluable to us in the prospective evaluation of children who are being treated currently in our different children's centers. One of the things that has been of great concern to me and, I am sure, others who care for these children, particularly with the large presacral teratomas, is the return, or lack of return, of function as a result of the distortion of the rectum, urethra and vagina.

(Slide) Dr. Tapper indicated that there was striking distortion in this area as a result of these very large masses of tumors. Sometimes the rectum lies almost over the sacrum; at other times, the perineum is distorted completely above the pubic symphysis. Although there is good survival, the real question in my mind has been, are we going to have incontinent children, or problems with that perineal area? I would like to ask Dr. Tapper, in his follow-up studies, has he noted a major problem with functional disturbance?

We have now followed seven children into teenage with large presacral teratomas, and each of those children has had absolutely normal rectal and urinary function. There has been a delay in toilet training in several of them, simply because of the time required for the return of some of these structures to normal anatomic relationship, but all are currently continent, and I wonder if that has also been his experience.

I would like to ask him one final question. Dr. Tapper implied that chemotherapy may be indicated in the treatment of the presacral teratoma on the basis of good results from similar management of ovarian teratomas. This concerns me somewhat, because, if I understand the statistics correctly, the long-term results of the surgical resection of ovarian teratomas and presacral teratomas are just about exactly the same. I am concerned that, while there may be a response in ovarian tissue, that may be specific rather than because of its being in that particular position. What evidence is there that we should begin projecting the use of potential poisons in children who have a 90% long-term survival with adequate resection initially?

DR. JAMES A. O'NEILL, JR. (Philadelphia, Pennsylvania): These are relatively rare tumors, and in most major institutions really occur only a very few times a year. This series is a classic in terms of difficulty of pathologic interpretation. For example, in a recent instance, only one of 22 slides was characteristic of malignant change; and therefore this becomes a problem.

My first question relates to one of the things we have had a recent interest in. In order to differentiate those tumors which may be more mature from those which have a greater malignant potential, we have been looking at tumor markers, such as AFP, HCG, and CEA, either in serum or in tissue. From your series, Dr. Tapper, have you any additional information regarding the use of markers?

I too agree with Dr. Haller's concern regarding the addition of adjuvant chemotherapy. We are dealing with very small, delicate subjects. The adjuvant chemotherapeutic approach is an exceedingly toxic one, and all of us have patients who have died primarily on the basis of application of chemotherapy in the neonatal age group. Therefore, if one is to take on a, perhaps, prophylactic approach under these circumstances without more definitive evidence of probable malignancy, what regimens would you select in terms of modifying very toxic chemotherapeutic regimens?