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ISSN 0034-7116

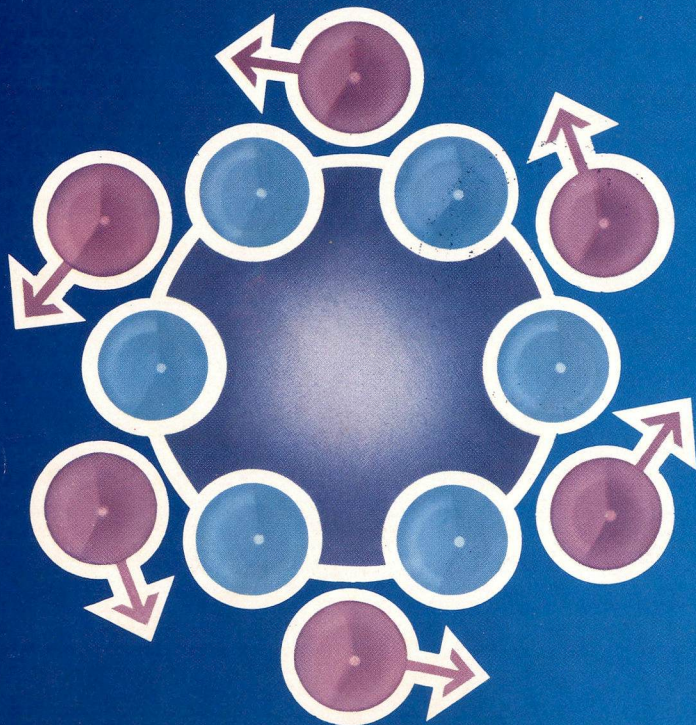
VOL. 33  
Nº 4  
DEZEMBRO  
1987

# Revista Brasileira de Cancerologia

MINISTÉRIO DA SAÚDE

Publicação da Campanha Nacional de Combate ao Câncer e da Sociedade Brasileira de Cancerologia  
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REVISTA BRASILEIRA DE CANCEROLOGIA

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A Revista Brasileira de Cancerologia (ISSN 0034-7116) é uma publicação da Campanha Nacional de Combate ao Câncer e da Sociedade Brasileira de Cancerologia. É editado um volume anual dividido em quatro números. Impresso no Brasil.

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Campanha Nacional de Combate ao Câncer, Rio de Janeiro, Brasil.

**Endereço editorial:** Revista Brasileira de Cancerologia  
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A Revista Brasileira de Cancerologia (Rev. Bras. Cancerol.) está indexada no Index Médico Latino-Americano — ISSN — 0034-7116

## EDITORIAL

O leitor da RBC, que é também, potencialmente, o autor de textos que a revista publica, dispõe — não custa que lembremos — de portas de acesso amplas para se manifestar. A primeira delas e que constitui naturalmente a razão nuclear da existência da RBC, são os trabalhos científicos originais. Aí se incluem os resultados de pesquisa clínica ou experimental, e também as "notas de técnica", as comunicações preliminares sobre artigos que serão ulteriormente desenvolvidos, as atualizações de assunto, as revisões bibliográficas, os textos de história da medicina, os relatos de caso, etc., etc. Evidentemente a prioridade de publicação vai para os trabalhos originais de pesquisas recém-concluídas e para as notas prévias, mas isso não é tudo. A RBC vem procurando ampliar o campo da comunicação através de seções tais como "Cartas ao Editor", "Opinião/Atualização", "Temas de Revisão", "Medicina e Sociedade". Embora algumas delas sejam em geral propostas por convite aos autores, a intenção da Editoria é fazer com que esses espaços de depoimento e de produção intelectual estejam abertos a todos, de modo que textos adequados à forma e ao espírito de cada uma dessas seções terão sempre o melhor acolhimento para publicação.

O presente número da RBC, dedicado ao tema dos tumores do testículo, traz seis contribuições de autores convidados. Foram ao todo convidados catorze, mas oito deles não puderam cumprir a tempo seus compromissos. Para além dos seis aqui apresentados, trabalhos sobre temas associados seriam incluídos. Entre eles, considerações sobre o tratamento desses tumores (estado atual e perspectivas), estadiamento radiológico no carcinoma de testículo, controle do câncer testicular na criança, aspectos psicológicos, radioterapia e patologia dos tumores do testículo.

Em futuro próximo esses temas e trabalhos poderão vir a ser apresentados, completando o panorama editorial pretendido.

*Jorge Wanderley*  
**Editor Chefe**

## Imaging in Testicular Tumors

FARZIN EFTEKHARI, M.D.<sup>1</sup>, BAO-SHAN JING, M.D.<sup>1</sup>, SIDNEY WALLACE, M.D.<sup>1</sup>

**Uniterms:** testicular tumors; imaging in testicular tumors

### SECTION I: INTRODUCTION AND ANATOMIC CONSIDERATIONS

#### Introduction

Prior to the advent of the newer imaging modalities, non-invasive evaluation of scrotal masses was limited to palpation and transillumination. Lymphangiography, however, has long been used in the evaluation of nodal metastases from testicular tumors and remains one of the most informative techniques in the staging of these tumors. More recently, newer non-invasive modalities, such as ultrasonography and computed tomography have become available and have had significant impact on our evaluation. It is the purpose of this article to describe and discuss the relative roles of these imaging modalities in the diagnosis of testicular neoplasms and work-up of metastatic disease. The ultimate role of MRI has yet to be evaluated. Other imaging modalities such as chest radiography, radionuclide scanning, and brain CT scanning may be performed as the need arises. Special procedures such as arteriography and venography are occasionally performed in search of undescended testicles complicated by malignancy.

Imaging techniques are also employed in preparation for transcatheter management by intraarterial infusion of chemotherapy and chemoembolization. In addition, imaging guided percutaneous biopsy and drainage techniques are of considerable value in diagnosis and treatment.

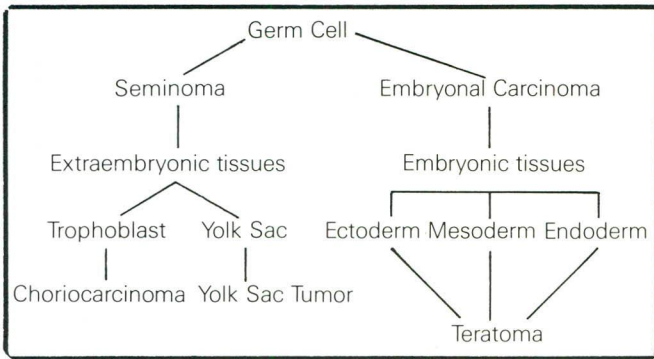
It is assumed that the reader is aware of the WHO classification shown on Table 1<sup>1</sup> and also of the multipotential nature of the germ cell tumors (Figure 1)<sup>2</sup>.

**Table 1** — W.H.O. pathologic classification testicular tumors

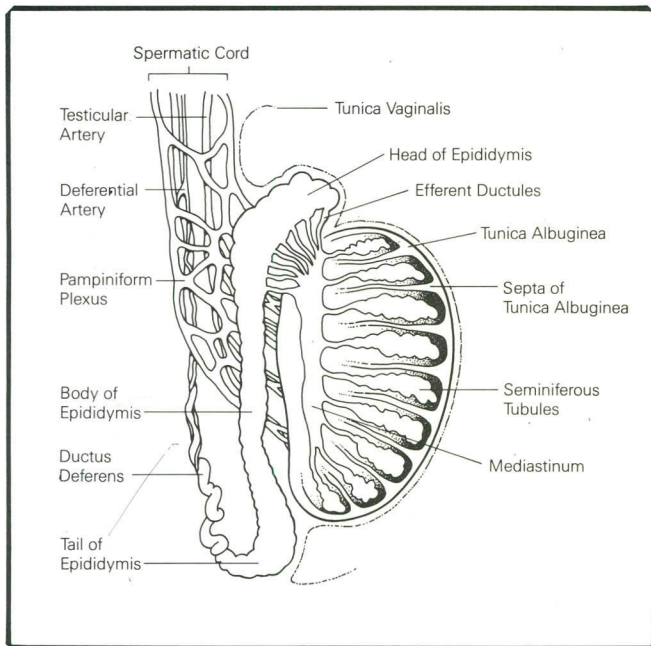
I. Germ Cell Tumor
A. Tumors of one histologic type
1. Seminoma
2. Spermatocytic seminoma
3. Embryonal carcinoma
4. Yolk sac tumor (embryonal carcinoma infantile type)
5. Polyembryoma
6. Choriocarcinoma
7. Teratomas
a. Mature
b. Immature
c. With malignant transformation
B. Tumors with > 1 histologic pattern
1. Embryonal carcinoma + teratoma (teratocarcinoma)
2. Choriocarcinoma and any other types (specify)
3. Other combinations (specify)
II. Sex Cord-Stroma Tumors
A. Well-differentiated forms
1. Leydig cell tumor
2. Sertoli cell tumor
3. Granulosa cell tumor
B. Mixed forms (specify)
C. Incompletely differentiated forms

The classification most commonly employed at M.D. Anderson Hospital is shown on Table 2. Typical spread of testicular tumors is to the retroperitoneal lymph nodes, followed by the supradiaphragmatic mediastinal chain and supraclavicular nodes<sup>3,4</sup>. The most common extranodal metastases are to the lungs and liver. However, uncommon sites of metastatic disease have also been observed involving organs such as: kidneys,

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**Figure 1** — Histogenesis and multipotential nature of testicular tumors. Adapted from Pierce G.B., Jr. and Abell M.A.: Embryonal Carcinoma of the testis. *In* Sommers S.C. (ed.): Pathology Annual. New York, Appleton-Century-Crofts, 1970, p. 28.

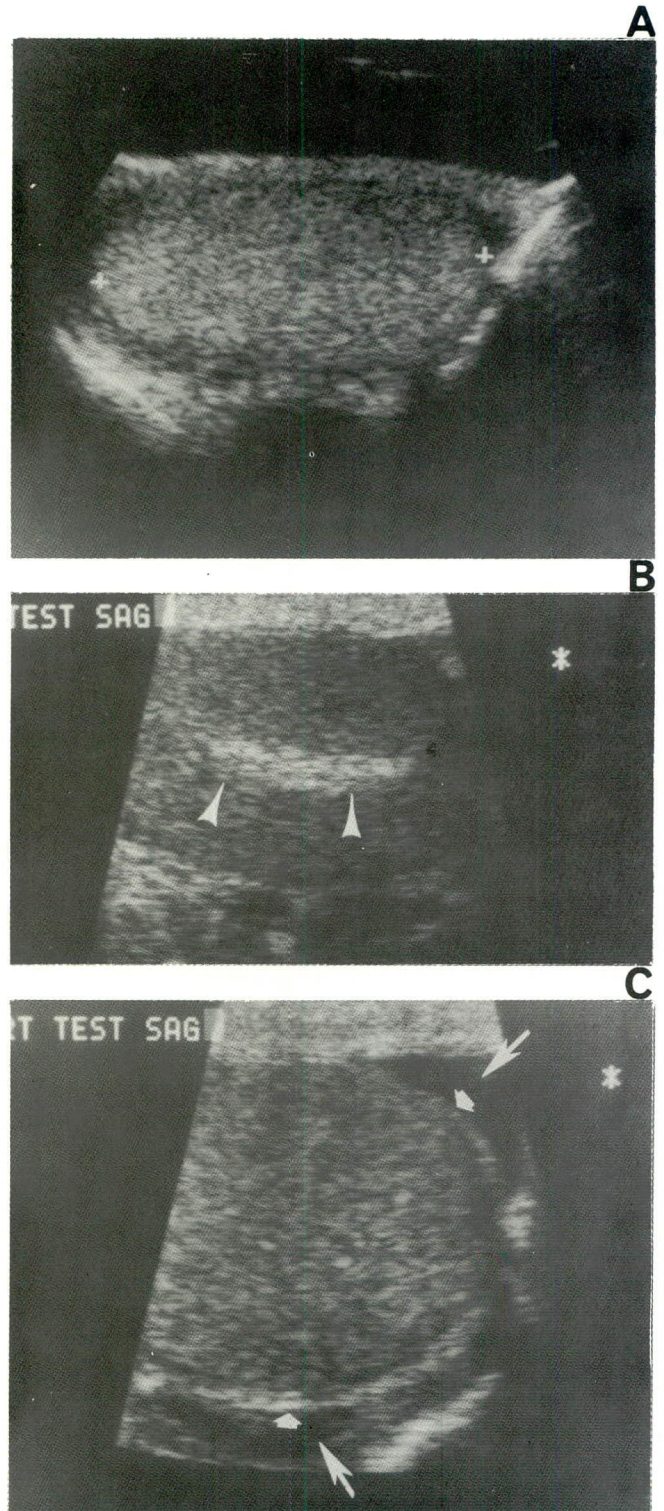


**Figure 2** — Anatomy of the scrotum. (From: The Radiologic Clinics of North America 1985; 23 (1): 122, reproduced with permission.)

adrenals, spleen, stomach and even the inferior vena cava<sup>3</sup>.

**Anatomy**

The normal testis (Figure 2) is an ovoid gland usually measuring just over 4cm in its longest dimension. The tunica vaginalis, as visceral peritoneum, covers the testis except at its site of attachment to the epididymis and spermatic cord. A capsule, the tunica albuginea, and numerous septa divide the testis into compartments, these converging toward the upper pole of the mediastinum region, which contains the rete testis (Figure 2). Each compartment contains several highly convoluted seminiferous tubules, these converging toward the rete network. Here they connect by straight tubular recti



**Figure 3** — Sonographic anatomy of the normal testis. A. Sagittal scan demonstrating uniform medium level of echogenicity (cursors). B. Sagittal scan showing echogenic band of the mediastinum testis (arrowheads). C. Sagittal scan showing a normal testis with a small hydrocele (long arrows) enabling visualization of the tunica vaginalis (short arrows).

which join to open into the head of the epididymis. At the upper pole of the testis is the appendix testis, a small vestigial pedunculated or sessile body.

Sonographically, the testis displays a uniform medium level of echogenicity similar to that of the thyroid gland (Figure 3). The head and body of the epididymis are routinely visualized and are as echogenic as the testicle or more so. The mediastinum testis, an invagination of the tunica albuginea into the testicular substance, is visualized as a highly echogenic band parallel to the long axis of the testicle (Figure 3). This should not be confused with an echogenic pathologic process. Occasionally, small echogenic foci may be seen with or without acoustical shadowing and these may represent spermatic granuloma or phleboliths<sup>5</sup>. In the presence of a hydrocele, the appendix testis may be visualized cephalad to the testicle. The various layers of the scrotum itself are indistinguishable and are often seen as a highly echogenic stripe. The tunica vaginalis may be visualized when a hydrocele is present (Figure 3)<sup>5,6</sup>.

Testicular lymphatics (Figure 4) accompany the internal spermatic artery and vein and terminate in sentinel nodes at the level of L-1/L-2 on the left and L-1/L-3 on the right, slightly lateral to the lumbar nodes. From the right testis there may be direct filling of the right lateral nodes above or below the renal vein, or directly to the left-lateral nodes. Thus, there may be immediate crossover of the right testicular lymphatics to the contralateral nodes (Figure 21), while the left testicular lymphatics only crossover after permeating the sentinel nodes. From the lumbar nodes, continuity of the lymphatic system is usually maintained through the thoracic duct<sup>7,8</sup>.

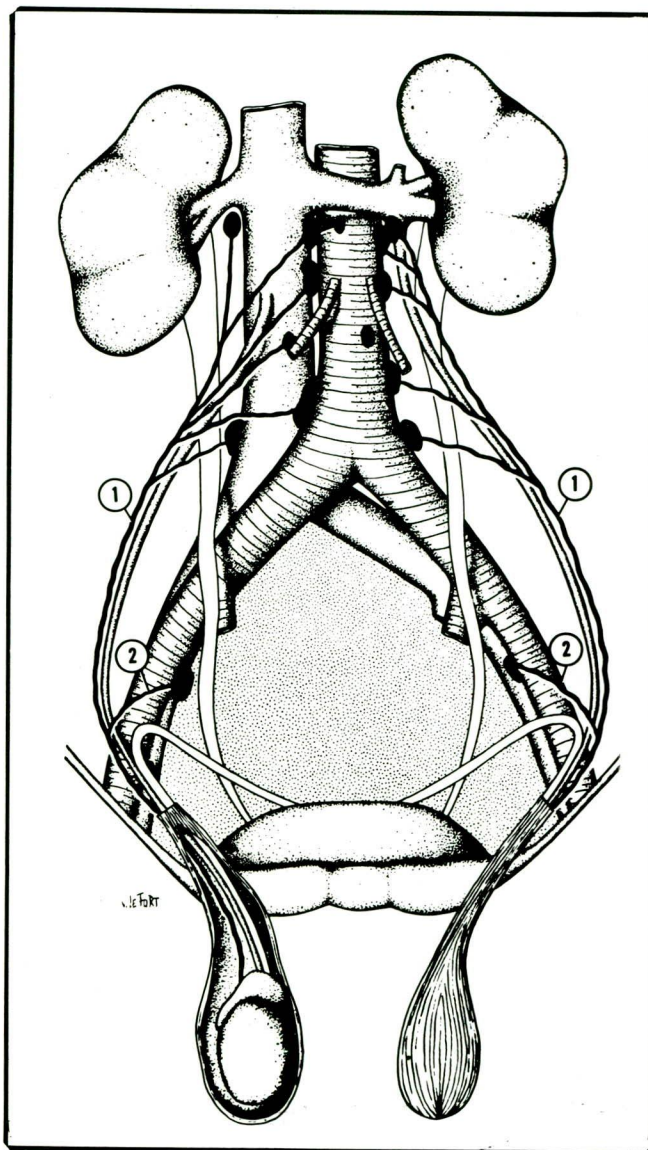
The external iliac nodes may occasionally drain the testes and on rare occasions pulmonary metastases of testicular tumors are discovered in the absence of retroperitoneal disease. This is most likely due to a variation in the normal lymphatic drainage, as shown in the rat where there may be direct communication between the testicular lymphatics and the thoracic duct. In addition, isolated metastases to the external iliac, inguinal and femoral nodes may occur as a result of surgical distortion or tumor involvement of the epididymis.

## SECTION II: MODALITIES OF IMAGING FOR DIAGNOSIS AND STAGING

### A. Ultrasonography

Ultrasound is a noninvasive, nonionizing modality which has gained wide acceptance for evaluation of the testes and other scrotal pathology. It is performed rapidly and without discomfort to the patient.

Ultrasound of the testicle is usually done in a patient presenting with an enlarged scrotum to differentiate between intratesticular and extratesticular masses (Figure



**Figure 4** — Anatomy of lymphatic drainage of the testes.

1. The major draining trunks empty into the lumbar lymph nodes via sentinel nodes from the level of the renal hilum to the bifurcation of the aorta.
2. The external iliac nodes may occasionally drain the testes.

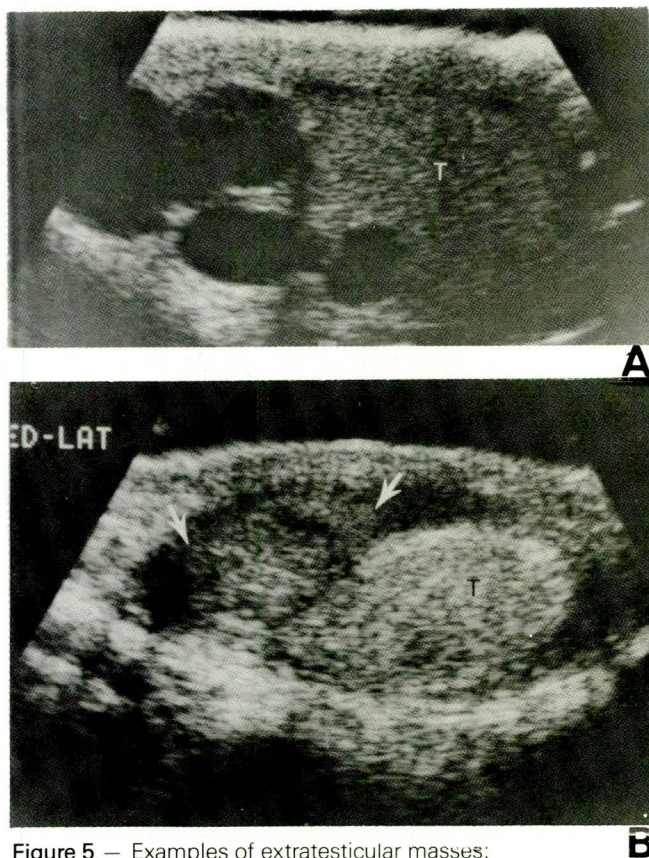
5). It is also useful in suspected testicular neoplasms, or in search of primary neoplasms which may be occult in patients presenting with metastatic disease. In addition, an undescended testicle alone or complicated by tumor may also be demonstrated by ultrasound<sup>6,9,10</sup>. Finally after orchiectomy, with or without insertion of a prosthesis, the sac may be scanned in search of residual or recurrent tumors.

*Technique.* After a brief clinical history is obtained, the patient is placed in the supine position and with gloved hands, careful palpation of the scrotum and its contents is performed. A folded towel is placed between the thighs to keep the scrotum elevated. A second towel is spread between the scrotum and the



groin. The penis is folded upward and covered by another towel. Scanning may be performed with the scrotal contents either lying on the towel or cradled within the gloved hand of the operator. In any event, care must be taken to place the epididymis posteriorly. It would be preferable to have another person to assist marking the images with appropriate numbers and planes of scanning. The room temperature should be comfortably warm to prevent contraction of the scrotum during scanning.

At UT M.D. Anderson Hospital, high resolution 7.5 and 10-MHz small parts transducers are utilized. Scanning is begun using 7.5 MHz transducer in the transverse plane (preferably including both testicles in the field) and scans are numbered from the level of the head of the epididymis through the inferior pole. This will allow comparison of the echogenicity of the testicles. In larger testicles, each testicle may be scanned separately. Sagittal slices may be obtained from midline towards



**Figure 5** — Examples of extratesticular masses:

A. Spermatoceles: 50-year-old man with an enlarged scrotum. Sagittal sonogram shows numerous fluid filled interconnected spaces along the course of the epididymis displacing the testicle (T) caudally.

B. Epididymitis: 45-year-old male with recent onset of painless swelling of the right testicle. Sagittal sonogram shows an enlarged head of the epididymis (arrows) compressing the testicle (T). The possibility of an adenomatoid tumor prompted orchiectomy which showed acute purulent and chronic epididymitis as well as orchitis.

the lateral aspect and numbered as such. Finally, both testicles and the scrotum are carefully surveyed with a 10 MHz transducer and appropriate images and measurements of the lesion(s) are obtained.

### Testicular tumors

Sonography is extremely accurate in differentiating intra- from extratesticular masses (Figure 5). This is of paramount importance as the majority of the intratesticular masses are malignant while almost all of the extratesticular masses are either inflammatory lesions or benign neoplasms<sup>5</sup>. Intratesticular masses arise either from the germ cells or the stroma. Other tumors include leukemia-lymphoma, and metastatic disease. Extratesticular masses include hydrocele, hematoma, spermatocele, abscess (Figure 5), and adenomatoid tumor<sup>5,11</sup>. Sonographic features of the malignant intratesticular neoplasms consist of single or multiple masses, bright echogenic foci and diffuse abnormality of the echo texture<sup>5,12</sup>. In one reported series of 21 patients, 72% of confirmed testicular neoplasms showed a mass on ultrasound, 66% had bright echogenic foci and 31% showed diffuse abnormality of the texture of the testicle, all these being ultrasonographic features of testicular neoplasm<sup>12</sup>. It should be noted however, that focal intratesticular masses are non-specific and while usually neoplastic may also be representative of other pathologic processes such as abscess, infarction or hemorrhage<sup>6</sup>. Thickening of the scrotum and the epididymis has been described as a differentiating sign for inflammatory lesions<sup>13</sup>, however, certain neoplasms such as embryonal carcinoma frequently infiltrate the tunica and epididymis and therefore may mimic inflammatory lesions<sup>6,11</sup>. Hyperechoic foci in a suspected neoplasm may represent "burnt-out" germ cell tumor or calcification within a teratoma. "Burnt-out" tumors are important ultrasonic findings in patients presenting with metastatic germ cell tumors and normal testicles on palpation<sup>5,12,14</sup>. Sonographically, these foci are seen at the periphery of the mass or in an area of diffusely altered texture. They measure 2 to 5mm in size. They may or may not show acoustic shadowing (Figure 11). These testicles are usually atrophic as compared to the contralateral testicle and the echogenic foci represent a regressed germ cell tumor<sup>5,12,14</sup>. Diffuse changes in the echo texture may be seen in the lymphoma-leukemia group<sup>6,15,16</sup>, seminoma and mixed germ cell tumors<sup>12,17</sup>.

While ultrasound findings are not specific, the incidence of a false-negative examination in tumors is very low. In another series, accuracy in detection of a neoplasm was found to be 80% to 90%<sup>6</sup>. This is of extreme importance in cases of metastatic germ cell tumors where no palpable mass is found in the testicle (occult testicular primary)<sup>6,17</sup>.

### Sonographic findings in specific tumors

Ninety-five percent of the testicular tumors are of germ cell origin which are highly aggressive tumors and 5% are nongerminal tumors, usually benign in nature. Of germ cell tumors, 60% are of pure cell type and 40% are mixed<sup>11</sup>. Eight percent of the patients will be expected to develop a contralateral testicular tumor either of the same or different cell type (Figure 6)<sup>11</sup>.

### Seminoma

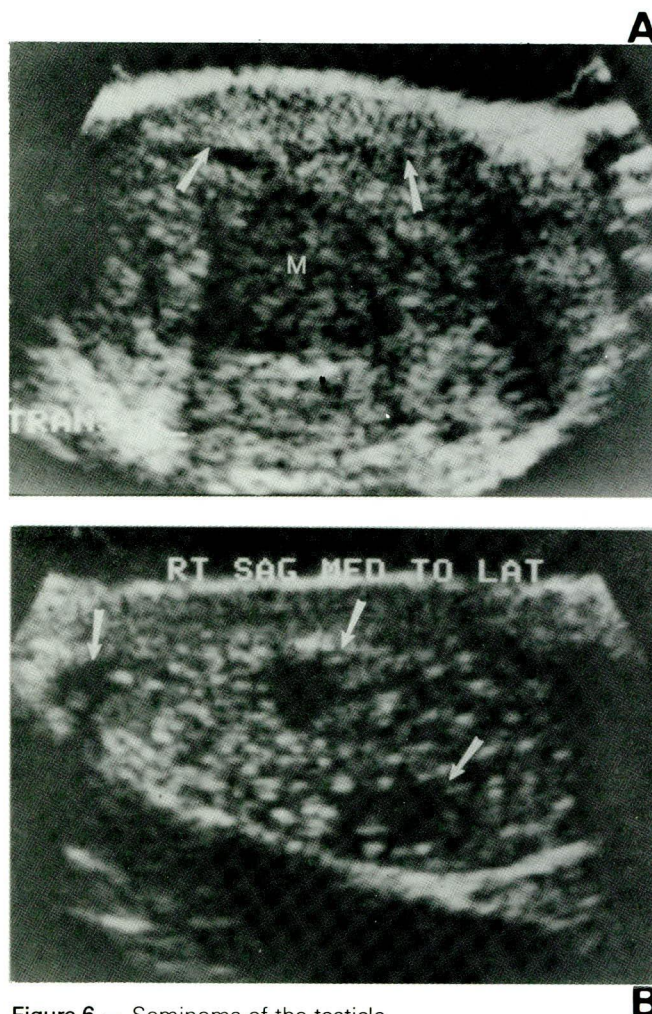
Seminomas are the most common cell type and account for 40% of the germ cell tumors. These tumors are never seen in infants and the peak age is in the fourth decade. Seminomas are less aggressive, highly radiosensitive and the cure rate for stage I disease approaches 95% to 100%<sup>3,11</sup>. Twenty-five percent of the seminomas will present with metastatic disease. These tumors are almost always confined to the tunica albuginea and represent the most common germ cell tumor arising in the undescended testicle (Figure 23)<sup>5,6,11</sup>. On sonography, seminomas usually present with solitary or multifocal hypoechoic<sup>5,6,18</sup> lesions (Figure 6). Occasionally, they produce diffuse hypoechogenicity<sup>12,17</sup>.

### Embryonal carcinoma

Embryonal carcinoma is the most undifferentiated and the stem for all nonseminomatous germ cell tumors. These account for 20% of the germ cell tumors and occur in a younger age group than seminoma, usually between 15 and 30 years of age. They frequently invade the tunica and the epididymis and may contain necrosis and hemorrhage<sup>6,11</sup>. On sonography, they manifest as well defined lesions which are less homogeneous than seminomas and contain both cystic and echogenic areas<sup>5</sup>.

### Teratoma

Teratomas represent 5% to 10% of the primary germ cell tumors of the testicle and while they are frequently thought to be benign tumors, approximately one-third metastasize within five years<sup>5</sup>. The mature (differentiated) forms in children behave as benign tumors and almost all have a good prognosis. In the adults, it is difficult to be certain and apparently differentiated mature teratomas may harbor foci of malignant cells; therefore, it is believed that all teratomas in the adults should be considered malignant<sup>11</sup>. The sonographic appearance of the teratomas depends on the complex nature of these lesions; they may range from sonolucent to highly echogenic lesions (Figure 7). The cystic ones will present as sonolucent defects. Calcium and osseous components will create highly echogenic lesions with acoustic shadowing<sup>5</sup>. A primary teratoma in the testicle may metastasize to the retroperitoneal nodes as a



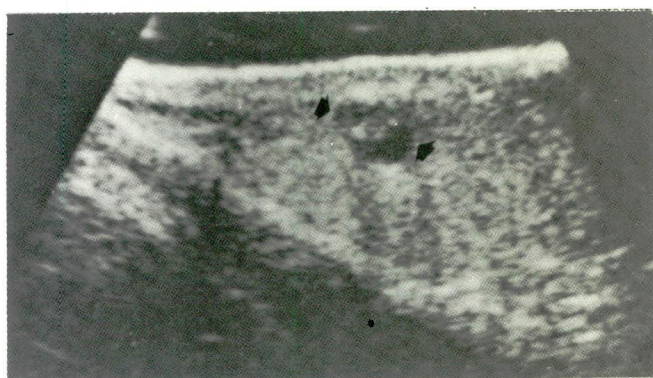
**Figure 6** – Seminoma of the testicle.

A. Unifocal pattern: 26-year-old male with right testicular mass. Sagittal sonogram showing a large centrally hypoechoic mass (M). Notice a rim of normal testicular tissue (arrows). On pathological examination, the testicle measured 5x4.5x3.5cm containing a well-circumscribed mass measuring 4.3x4x2.5cm with a rim of uninvolved tissue and extensive necrosis in the tumor corresponding to the hypoechoic area on sonogram. B. Multifocal pattern: 24-year-old male with a nodule on the right testicle. The left testicle had been removed 18 months previously for a mixed germ cell tumor (Embryonal carcinoma, teratoma and seminoma.) Sagittal sonogram shows three hypoechoic lesions (arrows). Only the upper pole lesion was palpable clinically. Detailed pathological examination revealed four nodules in keeping with the multiple lesions seen on ultrasound.

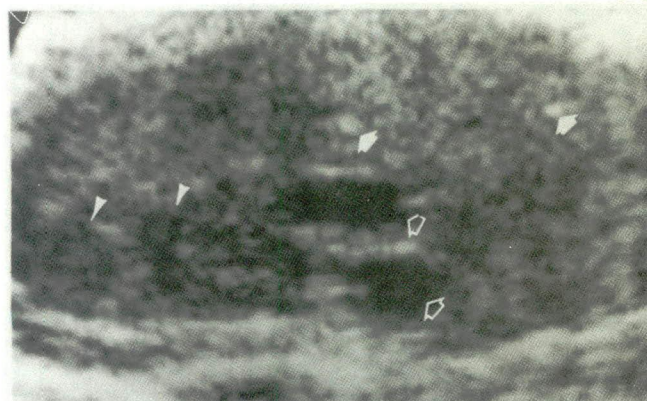
mixed germ cell tumor (Figure 7) and conversely a mixed germ cell tumor of the testicle may metastasize as a mature teratoma<sup>11</sup>. These latter metastatic lesions may enlarge in size without containing malignant cells, so called growing teratoma syndrome (Figure 19)<sup>19</sup>.

### Choriocarcinoma

Choriocarcinoma is the least common of the germ cell tumors accounting for 1-3% of these tumors. They are usually small, very aggressive tumors containing hemorrhagic and necrotic foci<sup>5-11</sup>. As expected, human



A



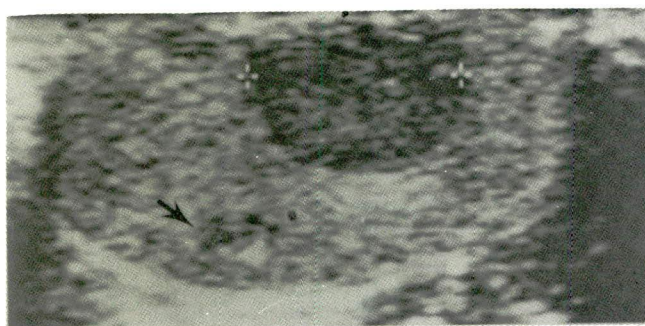
B

### Figure 7 — Teratoma of the testicle.

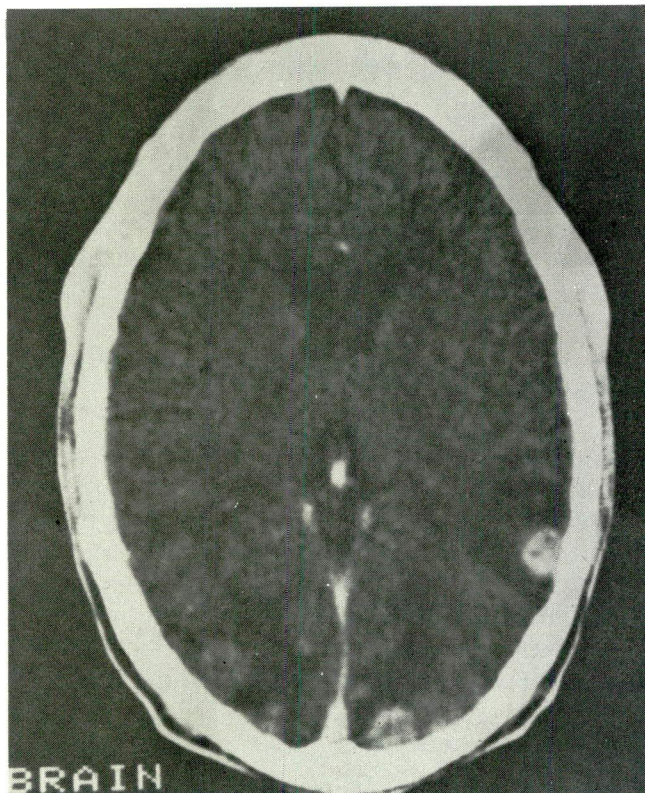
A. Cystic pattern with solid component: 37-year-old male with supraclavicular node positive for metastatic poorly differentiated carcinoma of germ cell origin. Sagittal sonogram shows small cystic lesion (arrows) with mural nodule.

Pathological examination of the testicle and retrocrural nodes revealed mature teratoma whereas the retroperitoneal nodes showed embryonal carcinoma.

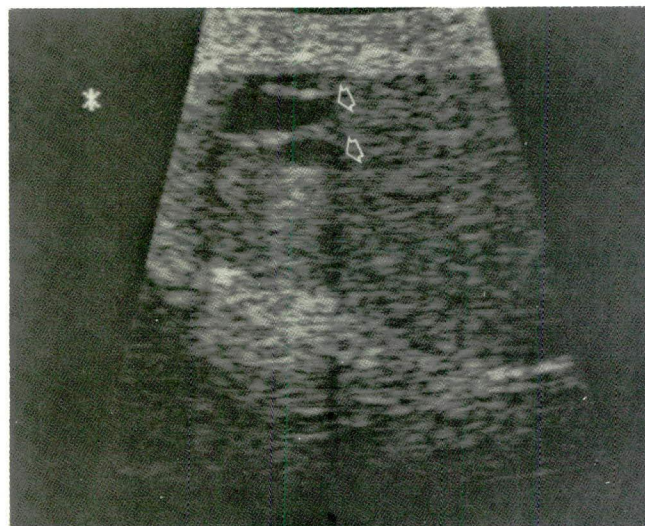
B. Diffuse and focal pattern: 22-year-old male with an enlarged testicle and pulmonary parenchymal and mediastinal metastases. Sagittal sonogram shows a diffusely abnormal echo texture with cystic (open arrows), hyperechoic (closed arrows) and hypoechoic (arrowheads) foci. Pathologically the testicle was found infiltrated by mature teratoma with partially cystic and necrotic areas.



A



B



C

### Figure 8 — Choriocarcinoma probably arising from an undescended testicle metastatic to lung and brain.

32-year-old male with disseminated choriocarcinoma diagnosed by lung biopsy. He had a history of undescended testicle, surgically corrected during infancy. Two hard nodules were palpable in the right testicle.

A. Sagittal sonogram prior to chemotherapy showing a discrete hypoechoic nodule (cursors) and a possible smaller one (arrow).

B. Postcontrast brain CT scan showing multiple enhancing metastases.

C. Postchemotherapy sonogram showing two cystic areas (arrows). Subsequent orchiectomy showed three small nodules. Pathologic diagnosis was cystic mature teratomas with 90% fibrosis. No choriocarcinoma was detected.

chorionic gonadotropin (HCG) is demonstrated in the cytoplasm of the syncytiotrophoblastic cells and as a result choriocarcinomas exclusively produce HCG. Choriocarcinomas cause early metastatic disease (Figure 8) and may be a component of other germ cell tumors. These tumors may metastasize as choriocarcinoma without choriocarcinoma being found in the testicular primary (Figure 8)<sup>11</sup>. On ultrasound, they present with mixed echogenic pattern due to necrosis, hemorrhage, and calcification.

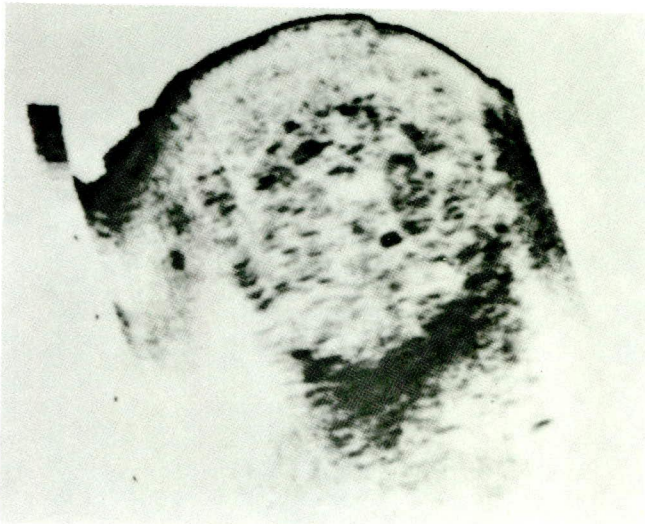
**Endodermal sinus tumor**

Endodermal sinus tumors, also known as infantile embryonal carcinoma or yolk sac tumors, are the most

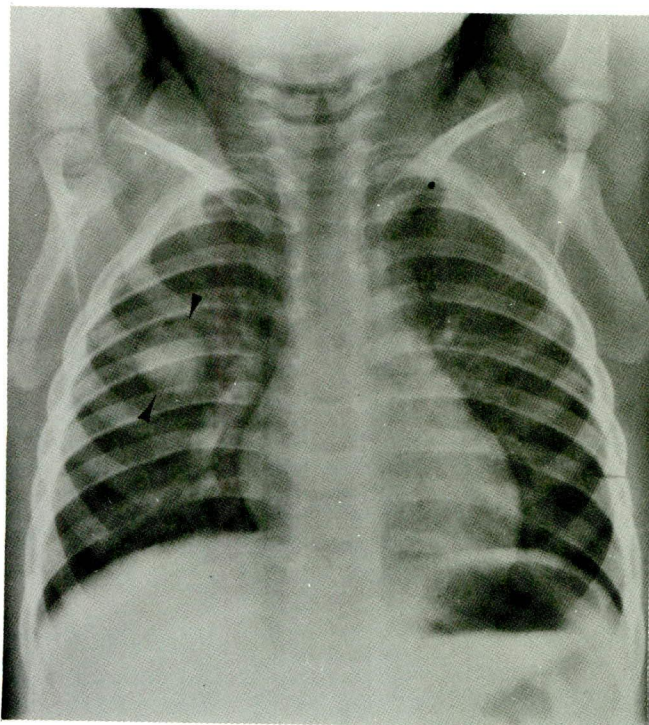
common testicular tumors in infants and children<sup>11</sup>. Pure endodermal sinus tumor is rare in adults<sup>20</sup> and is usually seen in association with embryonal carcinoma. These tumors produce exclusively alpha-fetoprotein (AFP). On ultrasound, these may present as hypoechoic or echogenic masses (Figure 9).

**Mixed tumors**

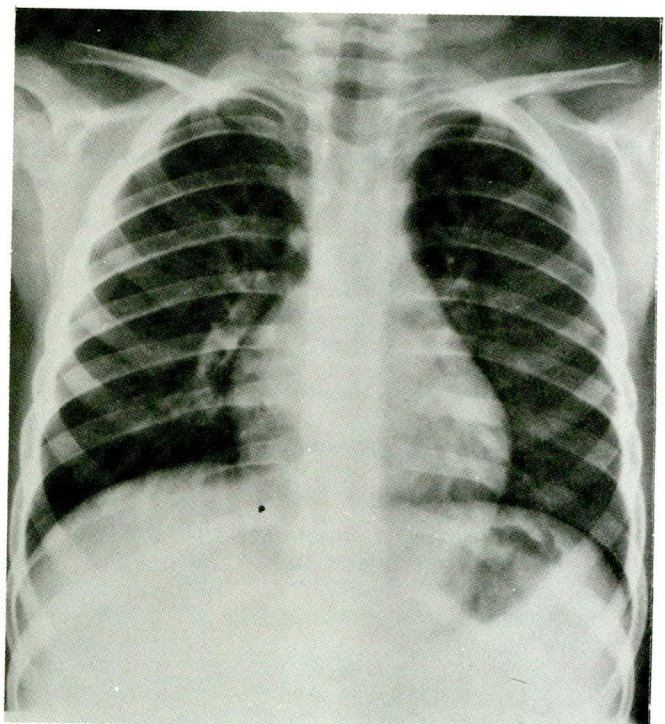
Mixed tumors constitute the remaining 40% of the germ cell tumors. The most common histologic type (25%) is the combination of teratoma and embryonal carcinoma (so called teratocarcinoma) and represents the second most common type of all germ cell tumors, second only to seminoma. These tumors contain cysts,



**A** Figure 9 — Metastatic endodermal sinus tumor of the testicle. Two-year-old boy with testicular mass, pulmonary and retroperitoneal metastases.  
 A. Sagittal sonogram shows an enlarged echogenic testicle.  
 B. Prechemotherapy chest radiograph shows a metastatic nodule (arrowheads).  
 C. Postchemotherapy chest radiography three months later shows resolution of the nodule.



**B**



**C**

hemorrhage, and necrosis. They frequently invade the tunica and epididymis and consequently lymphatic and hematogeneous metastatic disease occurs early<sup>5,6,11</sup> On sonography, these tumors may appear as solitary or multiple hypoechoic nodules, complex cystic-solid lesions or diffuse change in texture (Figure 10).

#### **Extragonadal germ cell tumors**

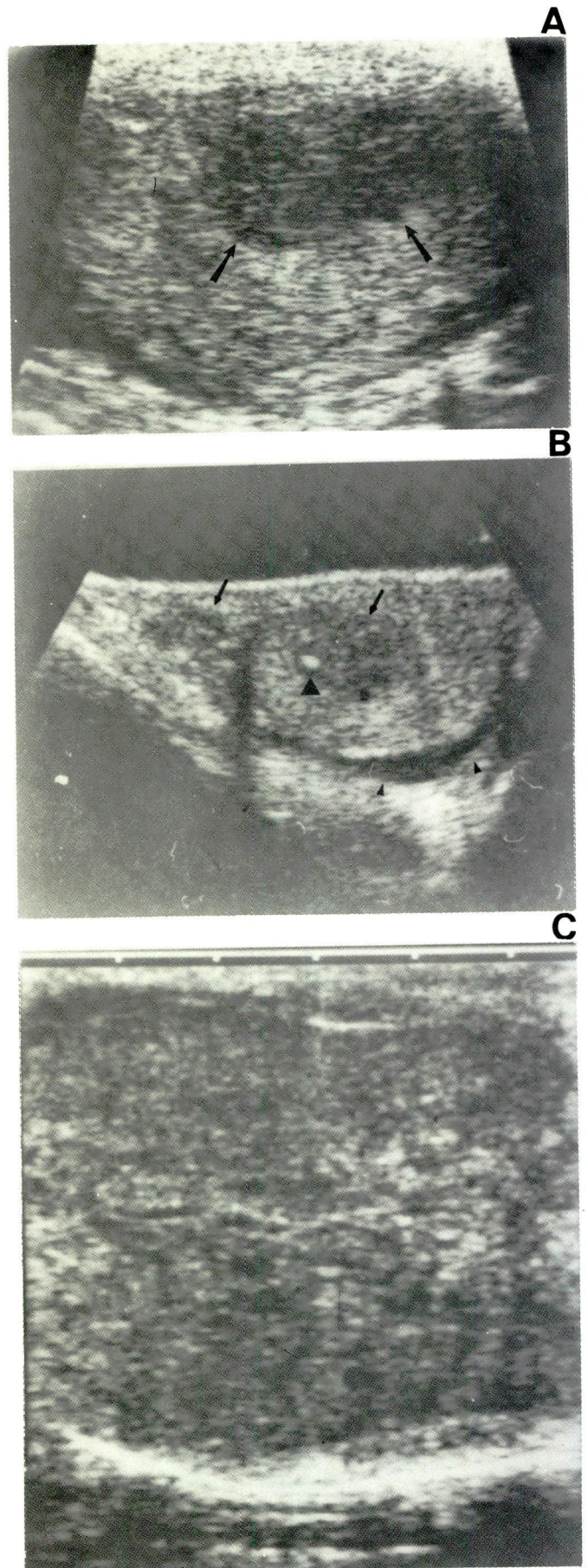
Extragonadal germ cell tumors may occur in the retroperitoneum, mediastinum, and pineal gland. Before a patient is diagnosed as having extragonadal germ cell tumor, a thorough search of the testicle by ultrasound should be performed to exclude a gonadal primary. Sonography of testicles in some patients with presumed extragonadal germ cell tumors may show bright echogenic foci representing so called "burned-out" germ cell tumors (Figure 11)<sup>5,12,14,17</sup>. Histologically these foci may contain hematoxyphilic bodies, immature bone, hyaline cartilage, calcification or tubular atrophy. These testicles are usually smaller than the contralateral testicle. These foci may or may not have distal acoustical shadowing. In one series, these foci were seen in 87% of the patients who had regressed germ cell tumor<sup>12</sup>.

#### **Non-germ cell tumors**

Non-germ cell tumors account for 5% of the testicular tumors and they are usually of Sertoli-Leydig variety. These are usually benign in nature and may produce endocrinology manifestations. On sonography, they are usually solid hypoechoic masses containing cystic foci<sup>5</sup>.

#### **Lymphoma and leukemia**

Lymphoma is not a primary tumor of the testicle and constitutes about 5% of testicular neoplasms. It is the most common testicular tumor in elderly men. Disseminated disease usually follows testicular involvement. The histologic pattern is diffuse in almost all of the cases. The sonographic appearance is that of diffusely enlarged hypoechoic testicle, although occasionally multifocal involvement may be seen (Figure 12)<sup>5-18</sup>.



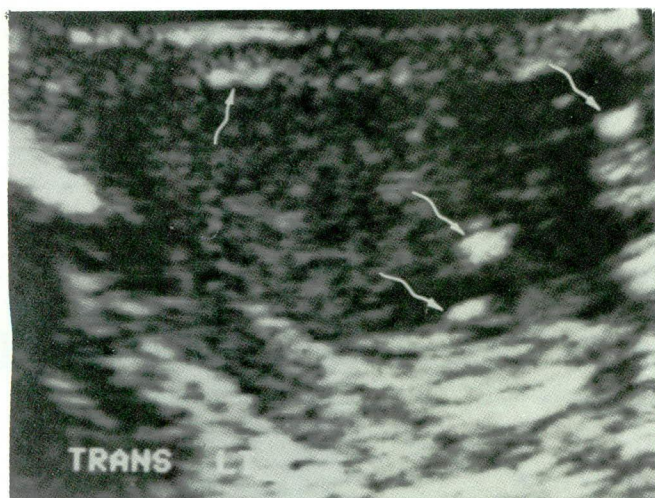
**Figure 10** — Mixed germ cell tumors of the testicle.

A. Unifocal hypoechoic pattern (arrows). (Dx: Seminoma + Embryonal carcinoma.)

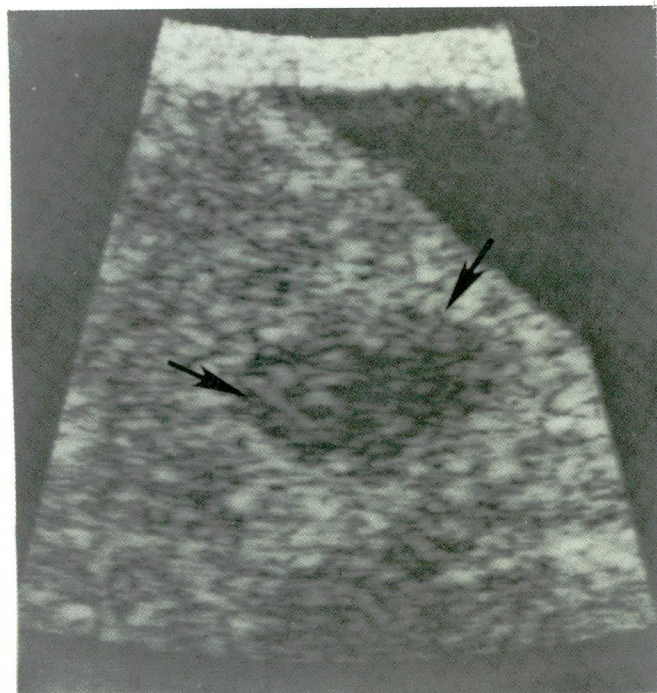
B. Multifocal hypoechoic pattern (arrows) and bright hyperechoic focus (large arrowhead). Notice small hydrocele (small arrowheads).

(Dx: Embryonal carcinoma, endodermal sinus (yolk sac) tumor and mature teratoma.)

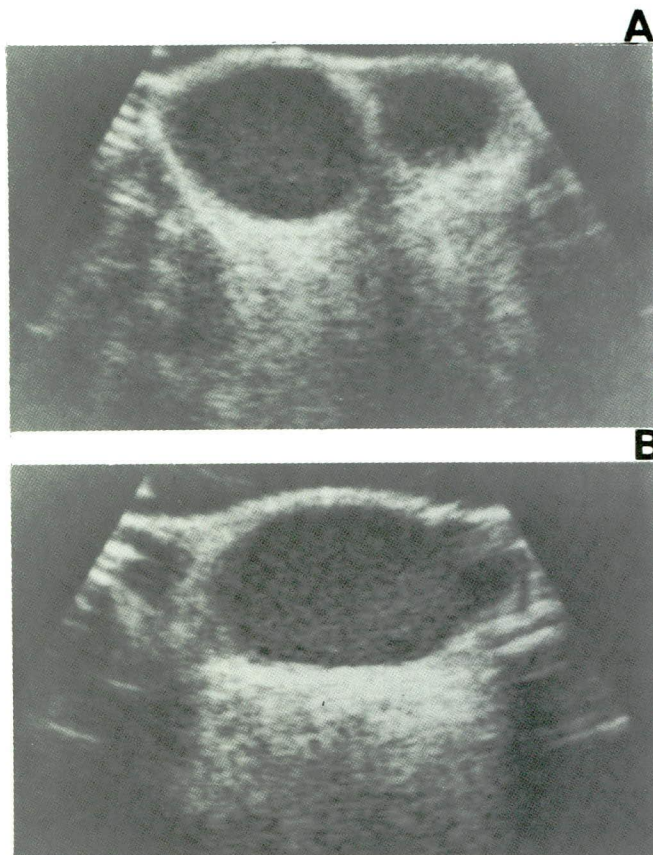
C. Diffuse pattern. Notice diffuse distortion of normal texture. (Dx: Embryonal carcinoma, endodermal sinus tumor, mature and immature teratoma, choriocarcinoma and seminoma.)



**Figure 11** — “Burnt out” germ cell tumor of the testicle. A 24-year-old man with history of metastatic germ cell tumor in retroperitoneal nodes (EST and choriocarcinoma) treated two years ago with chemotherapy. Transverse sonogram of the testicle showing abnormal texture and multiple bright hyperechoic foci (arrows). Histology showed a small cyst, an island of hyaline cartilage and extensive fibrosis consistent with “burnt out” or differentiated tumor (mature teratoma).



**Figure 12** — Lymphoma of the testicle. An 18-year-old male with lymphoblastic lymphoma presenting with bilaterally enlarged testicles and retroperitoneal adenopathy. Transverse sonogram shows one of the hypoechoic nodules (arrows).



**Figure 13** — Testicular relapse in leukemia. A seven-year-old with history of acute lymphoblastic leukemia in remission, presenting with bilaterally enlarged testicles. Transverse (A) and sagittal (B) sonograms show asymmetrically enlarged and diffusely hypoechoic testicles.

Testicular involvement in acute lymphoblastic leukemia during the initial presentation is occasionally seen, however, most cases occur within one year of discontinuation of maintenance chemotherapy. The incidence of leukemic relapse in the testicle has been reported to be as high as 13% and probably represents an early manifestation of more occult systemic disease<sup>15,16</sup>.

Sonography at the completion of maintenance chemotherapy and thereafter may demonstrate early relapse and obviate the need for routine wedge biopsy. Sonographically leukemia manifests with enlarged diffusely hypoechoic testicles (Figure 13), although focal hypoechoic nodules are not uncommon. These focal areas of involvement may escape detection on clinical examination.

**Metastases**

Metastatic tumors to the testicle are more common than germ cell tumors in men over 50 and are usually from genitourinary primaries (prostate, kidney). On sonography these may appear as either hypoechoic or hyperechoic defects<sup>5</sup>.

### Extratesticular tumors

Among the extratesticular tumors, adenomatoid tumor is the most common and arises from the epididymis<sup>5,11</sup>. These are usually small benign tumors and are seen in the periphery of the testicle, as a solid mass usually more echogenic than the testicle<sup>5</sup>.

### Ultrasound in the evaluation of nodal metastasis

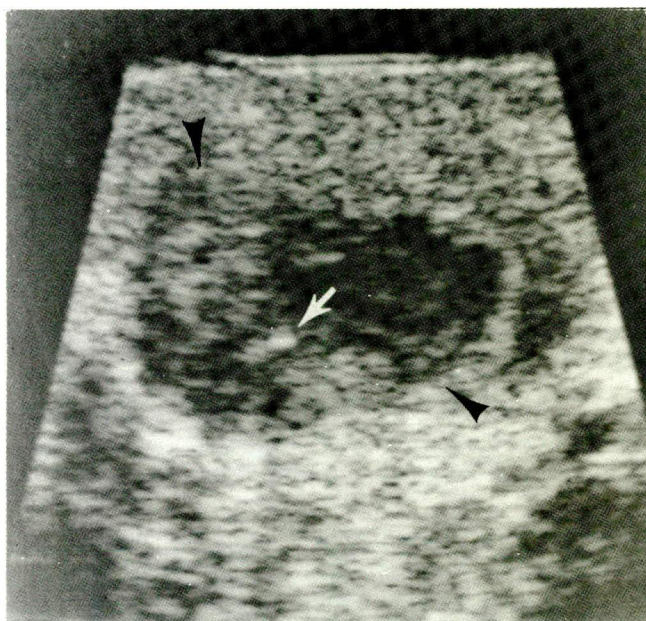
Ultrasound may be utilized in search of nodal metastasis in the abdomen and pelvis. However, the retroperitoneum is frequently obscured by gas, especially in the lower abdomen and pelvis.

### Ultrasound of the scrotum following orchiectomy

Following orchiectomy, a baseline sonogram should be obtained preferably 4-6 weeks postoperatively. This will allow time to record the status of the contralateral testicle and presence of residual or recurrent tumor in the hemiscrotum with or without prosthesis (Figure 14).

### Computed tomography

While ultrasound can be utilized in the evaluation of the retroperitoneal spread of testicular tumors, the lower paraaortic nodes are frequently obscured by the interfering bowel gas and obesity of the patient. CT scan is extremely helpful in staging because it more accurately



**Figure 14** — Tumor recurrence in the postorchietomy space. A 27-year-old male status one month postorchietomy for mixed germ cell tumor invading the capsule and epididymis. There were also retroperitoneal metastases. A 1.5cm nodule was palpable in the right sac. Saggital sonogram shows a 1.5cm hypoechoic mass (arrowheads). Notice small calcification (arrow). Following chemotherapy, both the nodule and retroperitoneal nodes regressed.

**Table 2** — UT MDAH classification of neoplasms of the testis and related structures

I. Neoplasms of testis proper	
A. Germinal tumors	
1.	Seminoma, pure
a.	Classic type
b.	Anaplastic type
c.	Spermatocytic type
2.	Embryonal carcinoma, pure, or with seminoma
a.	Juvenile variant
3.	Teratoma, pure, or with seminoma
a.	Mature
b.	Immature
4.	Teratoma with embryonal carcinoma or choriocarcinoma or both, with or without seminoma
5.	Choriocarcinoma, pure or with embryonal carcinoma or seminoma or both
B. Gonadal stromal tumors	
1.	Interstitial cell tumor
2.	Tumor of specialized gonadal stroma
a.	Androblastoma
b.	Sertoli cell tumor
c.	Granulosa cell tumor
C. Secondary neoplasms	
1.	Reticuloendothelial neoplasms
a.	Malignant lymphoma, various types
2.	Metastatic neoplasms
a.	Adenocarcinoma of prostate
b.	Malignant melanoma
c.	Bronchogenic carcinoma
d.	Other
II. Neoplasms of related structures	
A. Connective tissue neoplasms	
1.	Paratesticular rhabdomyosarcoma
2.	Nonspecific connective tissue neoplasms
3.	Granulosa cell tumor
B. Other neoplasms	
1.	Adenomatoid tumor of epididymus
2.	Papillary cystadenoma of epididymus
3.	Mesothelioma of tunica vaginalis testis

ly determines the extent of tumor preoperatively in most instances. In seminomas, it helps in radiation therapy treatment planning. In non-seminomatous tumors, the therapeutic modality chosen, namely surgery versus chemotherapy, may be guided by the CT findings<sup>4,21</sup>.

Reported accuracy of CT in the detection of retroperitoneal nodal metastasis is approximately 85% and it may detect early metastatic disease to the renal hilar nodes which are not opacified by bipedal lymphangiography (LAG)<sup>4,7,8</sup>. CT will help to depict the exact extent of the tumor, particularly in the upper periaortic regions. In addition, CT scan will demonstrate extranodal metastatic disease (liver, lung)<sup>3,21</sup>. Though larger lateral masses (> 1.5cm) can be better defined by CT, when the disease is small and the changes are subtle, the nodes are better defined by LAG (Table 3). However, CT and LAG are really complementary studies (see below)<sup>7</sup>. In addition, CT can be used for monitoring the

Table 3 — CT versus lymphangiography

Usage/Indications*	Computed tomography	Lymphangiography
To reveal flow dynamics		+
To detect small nodal lesion		+
To detect large nodal lesions	+	
To determine the extent of nodal lesions	+	
To reveal extranodal involvement	+	
To delineate nodes beyond LAG demonstration	+	
To detect internal architecture		+

\*CT and LAG are complementaries

response to treatment in patients with elevated levels of tumor markers<sup>4</sup>.

#### Technique:

CT scans of the chest are obtained at 10mm contiguous slices from the apices through the lung bases. Intravenous contrast is routinely utilized. CT scans of the abdomen are taken with 15mm slices at 10mm intervals and from the pelvis 15mm slice intervals. Oral, intravenous and rectal contrast material are routinely used. In the search for an undescended testis, smaller (10mm) slice intervals are selected. Further evaluation by scans at closer intervals (3mm to 5mm) is determined after review of the initial surgery.

#### Computed tomography in imaging of metastatic testicular tumors

CT findings of metastatic masses from testicular tumors may be divided into three different groups: cystic, solid, and mixed<sup>22</sup>.

The cystic pattern is seen in pure very mature teratomas (Figures 15, 25). The solid pattern is usually seen in pure seminoma (Figure 16) or pure choriocarcinoma. The semicystic (mixed) pattern is due to teratomatous components either metastasis from a pure primary immature teratoma or of primary mixed germ cell origin with teratomatous components (Figure 17). The degree of cystic change in a pure teratoma is directly proportional to the maturity of the teratoma, the more mature the teratoma the more cystic the appearance (Figure 25)<sup>22</sup>.

Low attenuation nodal metastases occurs in 43-46% of testicular cancer. A low attenuation mediastinal or retroperitoneal mass of unknown etiology in a young male should raise suspicion of a metastatic testicular neoplasm<sup>23,24</sup>.

Persistent masses detected by CT are common after chemotherapy of seminomas and create a diagnostic

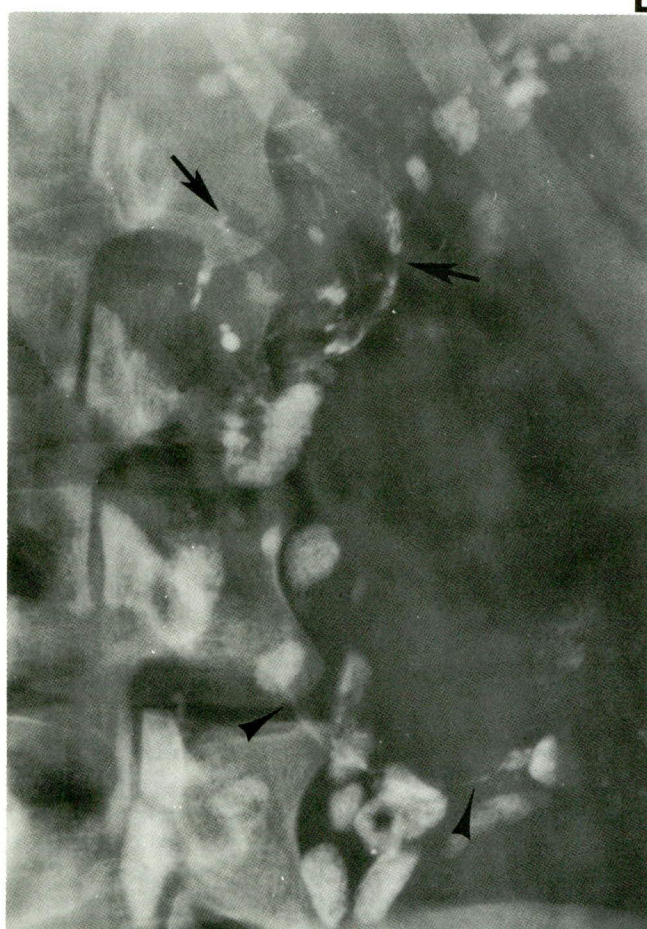
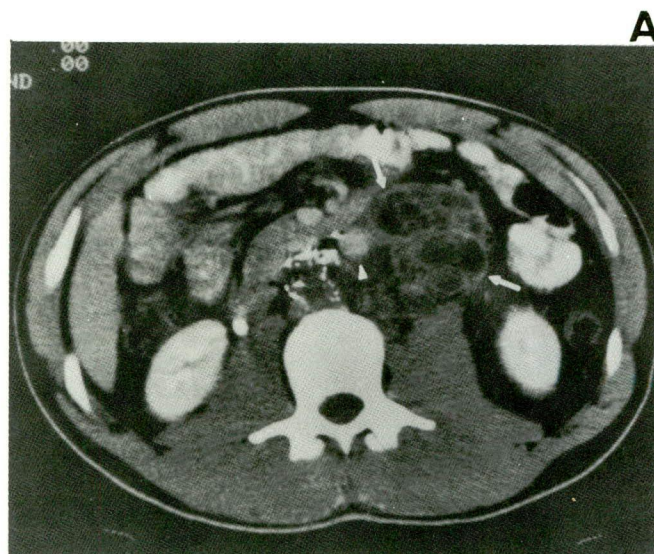
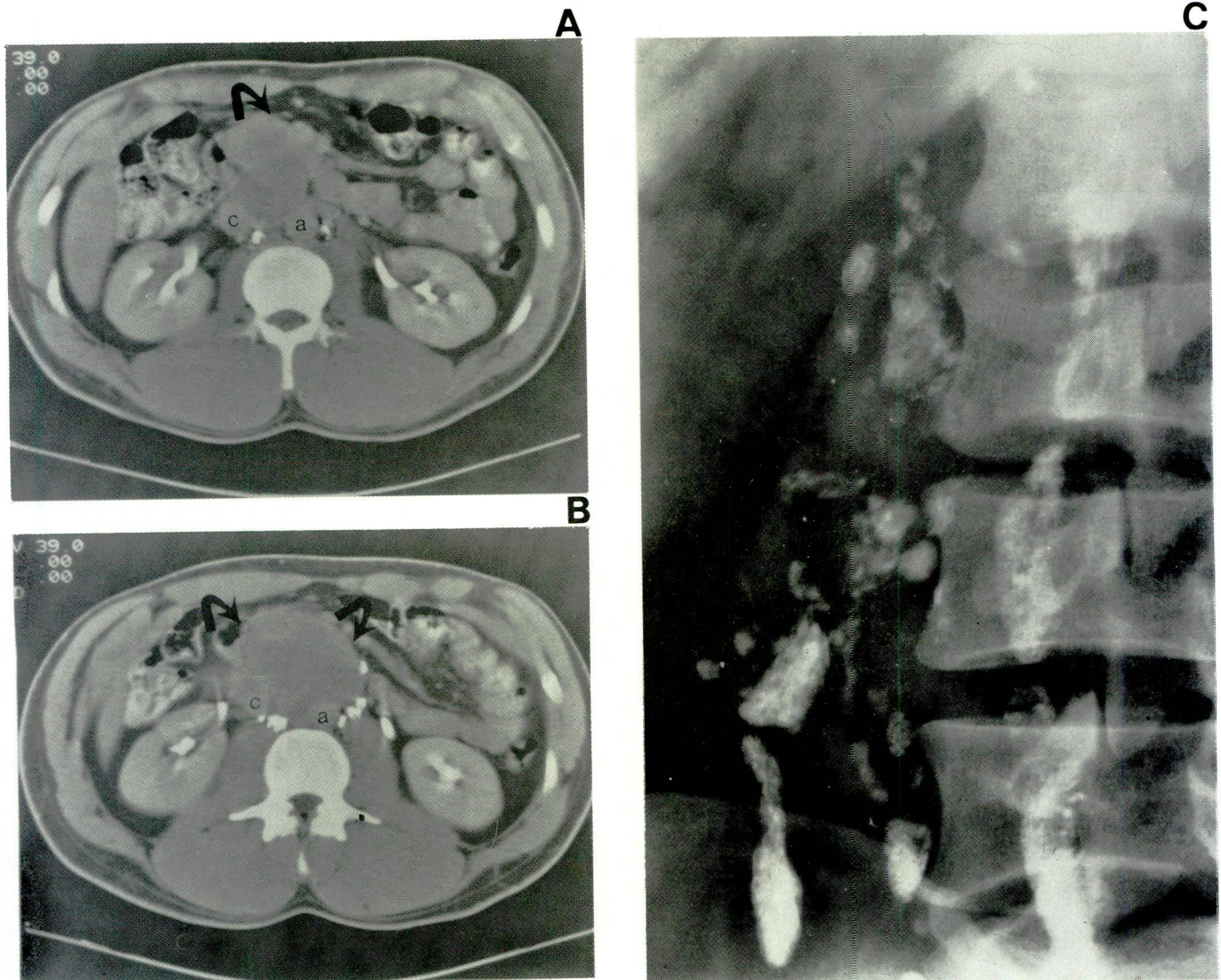


Figure 15 — Retroperitoneal metastasis from mixed germ cell tumor (Embryonal carcinoma, endodermal sinus tumor and mature teratoma) of the testicle cystic pattern:  
 A. CT scan shows septated cystic mass (white arrows) displacing the aorta (white arrowhead). The low density of the mass was consistent with its teratomatous component.  
 B. LAG shows nodal metastasis, mostly non-opacified in left upper paraaortic area (black arrows) and a huge nodal mass inferiorly (black arrowheads) almost completely filled by tumor.





**Figure 16** — Mixed germ cell tumor (seminoma embryonal carcinoma) of the testicle metastatic to retroperitoneal nodes, solid pattern.

A. and B. CT shows a large soft tissue mass anterior to the aorta (a) and inferior vena cava (c).  
C. LAG shows multiple abnormal nodes, carcinoma pattern (see text).

dilemma<sup>25,26</sup>, frequently requiring biopsy under CT guidance. Unlike their nonseminomatous counterpart they most often represent fibrosis<sup>27</sup>. Residual low attenuation masses represent necrosis with lipid-laden macrophages and cholesterol clefts (Figure 18)<sup>24</sup>.

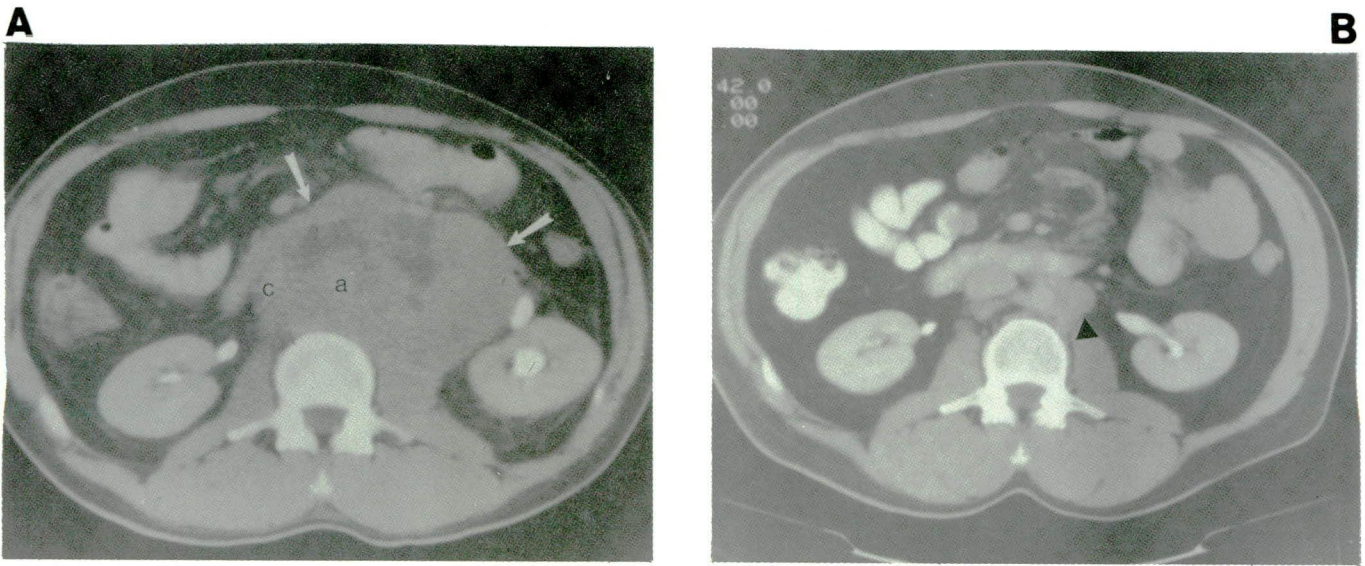
In 1.9% of patients with metastatic mixed germ cell tumors treated with chemotherapy, recurrence of a solitary enlarging mass in the chest or abdomen has been described as the "growing teratoma" syndrome<sup>19</sup>. On surgical resection, these prove to be mature teratomas with no malignant features on histology (Figure 19). In two out of six patients reported from this institution, the growth was attributed to an expanding cystic nature of the mass; the remaining four had firm masses. Tumor biomarkers were normal in these cases and surgery was curative.

Aspiration needle biopsy of the retroperitoneal nodes may be performed under CT guidance; however, if the nodes contain lymphangiographic contrast the biopsy can be done under fluoroscopy. CT is also of value in diagnostic needle aspiration and drainage of lymphoceles that result from retroperitoneal node dissection.

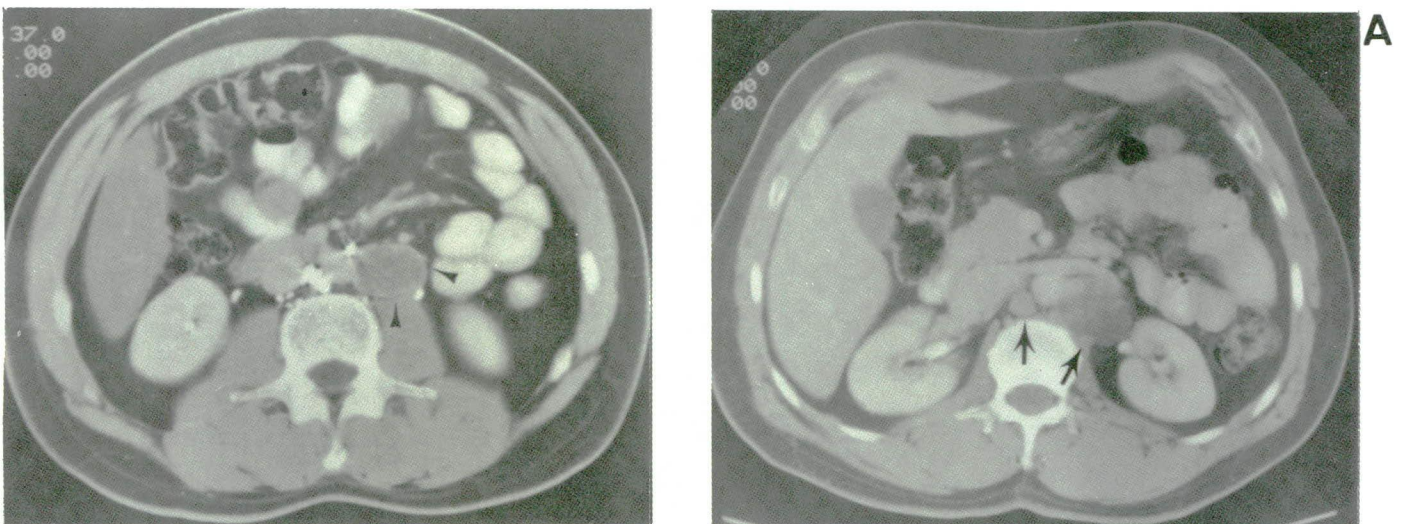
### C. Lymphangiography (LAG)

#### *Lymphangiography in tumors of the testes:*

Unlike the lumbar nodes, the sentinel nodes are usually not opacified by bipedal LAG. Thus, in the final analysis important nodes are filled by testicular LAG that are not opacified by the pedal route, necessitating

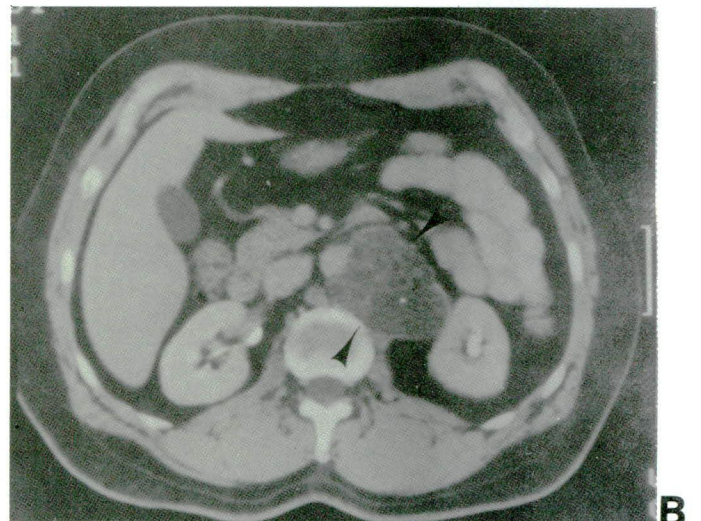


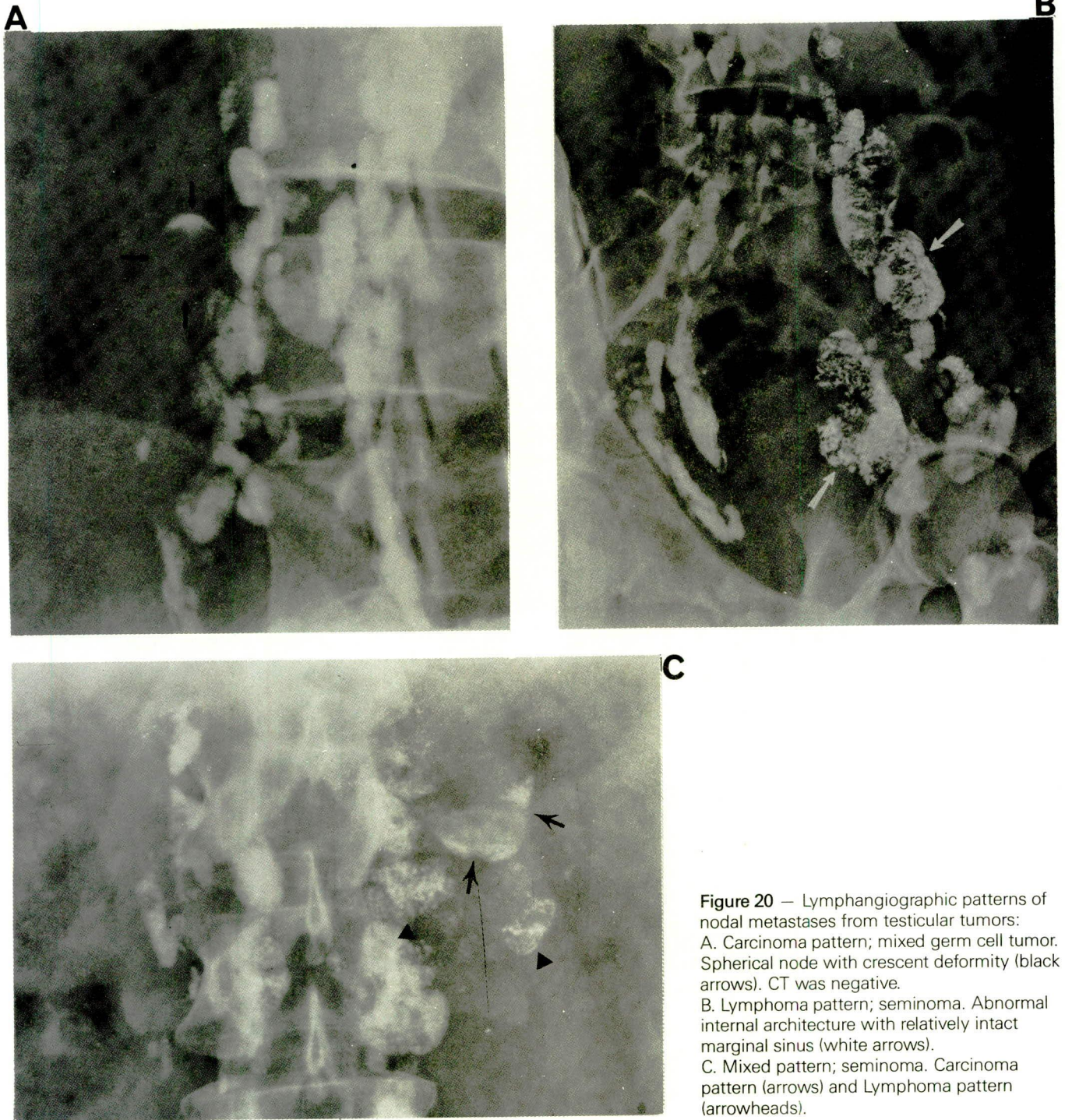
**Figure 17** — Seminoma of the testicle metastatic to the retroperitoneal nodes, mixed pattern.  
 A. CT scan one month postcommencement of chemotherapy shows huge mass (arrow) engulfing the cava (c) and aorta (a) with areas of low attenuation, presumably representing necrosis.  
 B. CT scan three years posttreatment shows residual small left paraaortic node (arrowhead).



**Figure 18** — Seminoma of the testicle with stable residual retroperitoneal mass.  
 A 29-year-old male with history of metastatic seminoma treated with chemotherapy.  
 CT scan shows a residual low density probably a necrotic mass in the left paraaortic area which has remained stable for at least 3 months.

**Figure 19** — “Growing teratoma” syndrome.  
 A 39-year-old male was treated for metastatic embryonal carcinoma of the left testicle. The patient was clinically free of disease and biomarkers were normal. Pulmonary metastases had disappeared.  
 A. CT scan in March 1986, showing low density left paraaortic and interaortacaval nodes (arrows).  
 B. CT scan in July 1986, shows increase in the size and further decrease in attenuation of the paraaortic mass (arrowheads).  
 The mass was surgically resected and a mature teratoma was diagnosed. No further therapy was given.





**Figure 20** — Lymphangiographic patterns of nodal metastases from testicular tumors:  
 A. Carcinoma pattern; mixed germ cell tumor. Spherical node with crescent deformity (black arrows). CT was negative.  
 B. Lymphoma pattern; seminoma. Abnormal internal architecture with relatively intact marginal sinus (white arrows).  
 C. Mixed pattern; seminoma. Carcinoma pattern (arrows) and Lymphoma pattern (arrowheads).

the combined approach for maximum information. However, in practice, this is seldom resorted to because of the risk of the operative procedure and the additional expense<sup>7,8</sup>.

Nodal metastases from testicular malignant disease show several different architectural patterns. Involved nodes are more spherical than normal and may have a crescent deformity with the lymphatics that fail to penetrate the marginal defects (carcinoma pattern)

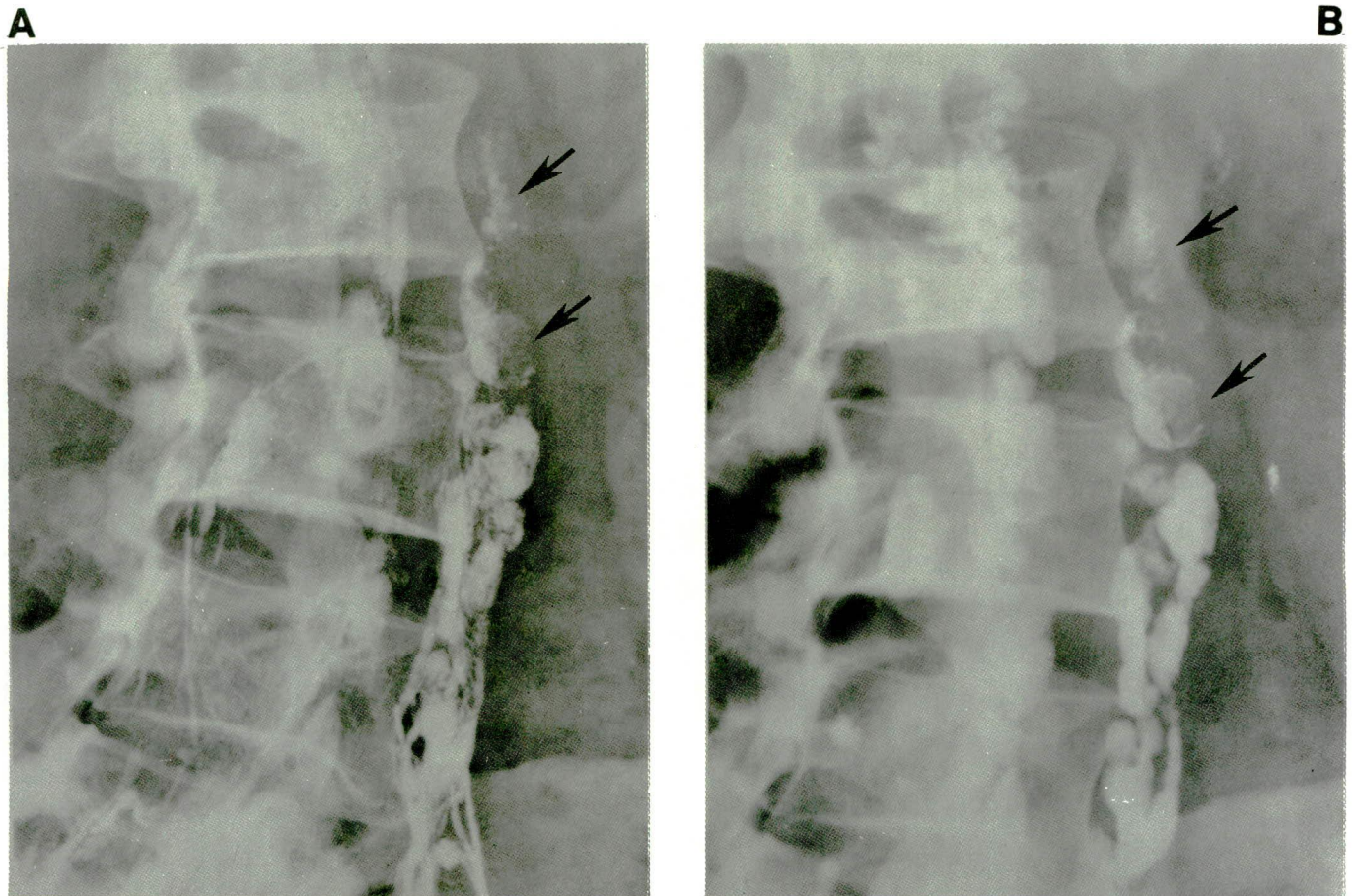
(Figures 16, 20). Occasionally, they may have an abnormal internal architecture with a relatively intact marginal sinus (lymphoma pattern) (Figure 20). The latter picture is more frequently seen in some seminomas, lymphomas, and rhabdomyosarcomas of the testes. At times, the metastatic nodes show both carcinoma and lymphoma patterns, a mixed variety (Figure 20)<sup>7,8</sup>. At times, there may be immediate crossover metastasis from the right testicular lymphatics to the contralater-

al nodes (Figure 21). In our series of a total of 83 patients considered negative by lymphangiography, 70 were negative at surgical exploration. Of the 13 patients (11%) who exhibited false negative findings, four showed microscopic lesions 3mm or less in size, one had a lesion in the interaortico-caval area, and eight were found to have metastases in nodes lateral to those usually opacified by pedal LAG. These metastasis may have been diagnosed by the testicular route, ultrasound or CT. The overall accuracy by lymphangiography was 88.4%. Following lymphangiography, the patients can be monitored by conventional radiography of the abdomen in 75% of patients for one year and in 30% for two years (Figure 21).

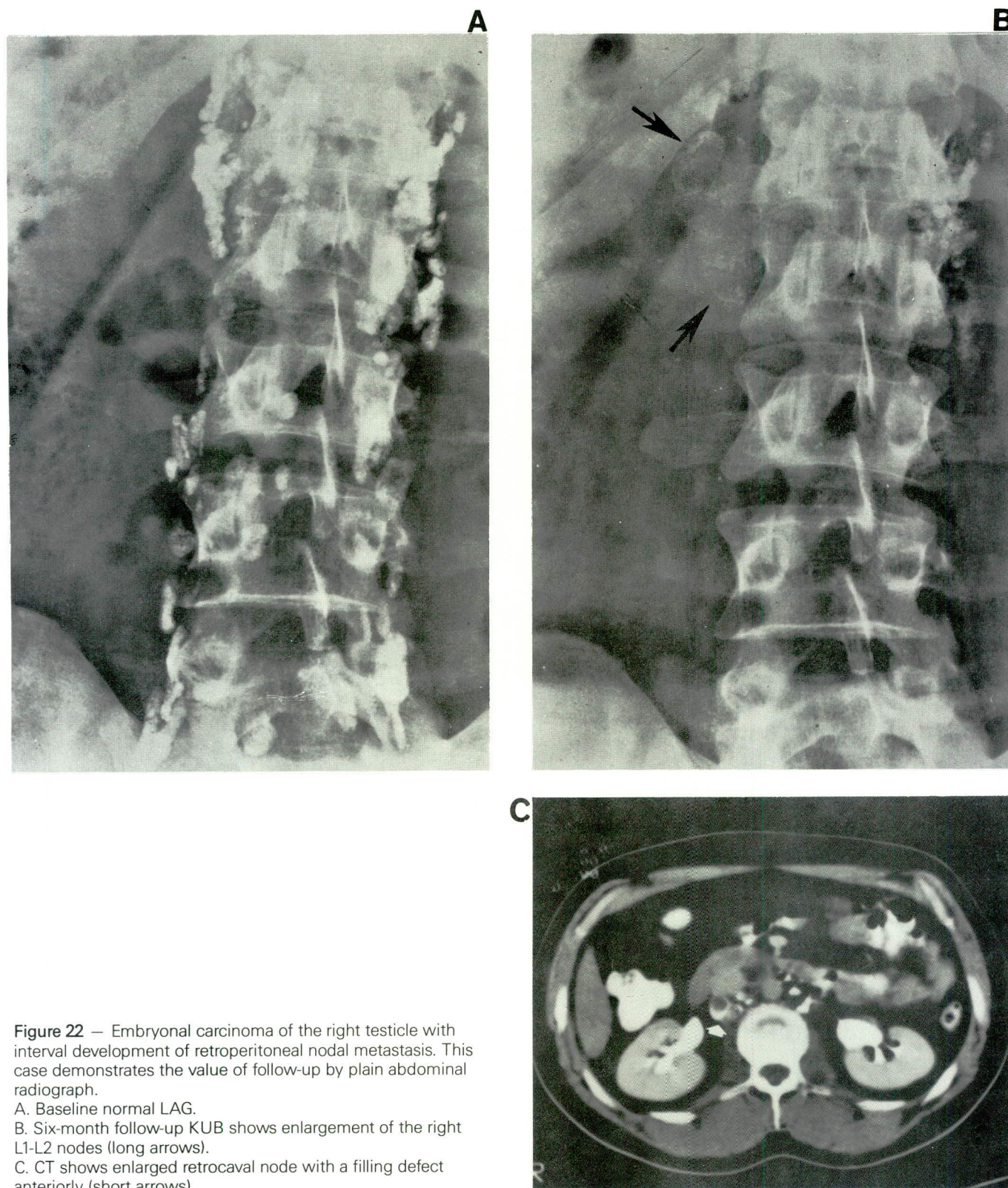
#### **Computed tomography versus lymphangiography in tumors of the testicle**

The relative indications and usage of these two modalities of imaging are outlined in Table 3. At M.D. Anderson Hospital and Tumor Institute, in a comparative study of LAG and CT, CT scans were performed within a month following LAG in 103 patients with testicular tumors (82 with carcinoma and 21 with seminoma). Of

these 103 patients (Table 4), LAG was positive for nodal metastases in 53 patients and was negative in 50. CT detected metastasis in 50 patients and no metastases in 53 patients. Thirty-nine of 103 patients had pathological correlation by retroperitoneal lymph node dissection or percutaneous needle biopsy (34 with carcinoma and 5 with seminoma) (Table 5). LAG was proven to be positive in 29 patients with an overall accuracy of 92.3%. Twenty-six patients were positive on CT, with an overall accuracy of 84.6%. The five false negatives in the CT group were due to small lesions less than 1.5-2cm. Two false negatives in LAG (5.1%) resulted from a microscopic lesion in one case and a lesion in the pre-aortic and the interaortico-caval regions in another case. One false positive (2.5%) in the CT group was due to lymphoid hyperplasia and one false positive in the LAG group was caused by a benign lesion, sinus histiocytosis. In advanced testicular tumors, LAG often failed to reveal the upper limits of the lesion; however, CT is of definite value in demonstrating the extent of the nodal metastases and the involvement of the adjacent organs<sup>4,7,8,10</sup>. Sometimes when the nodal lesion is high in the renal hilar region, it is often partial-



**Figure 21** — Embryonal carcinoma of the right testicle with cross-over metastasis to the left paraaortic nodes (arrows)  
 A. Lymphatic phase.  
 B. Nodal phase.



**Figure 22** — Embryonal carcinoma of the right testicle with interval development of retroperitoneal nodal metastasis. This case demonstrates the value of follow-up by plain abdominal radiograph.

A. Baseline normal LAG.

B. Six-month follow-up KUB shows enlargement of the right L1-L2 nodes (long arrows).

C. CT shows enlarged retrocaval node with a filling defect anteriorly (short arrows).

**Table 4** — Findings of LAG and CT in 103 patients with testicular tumors

	Lymphangiography	Computed tomography
Positive	53	50
Negative	50	53
Total	103	103

**Table 5** — Pathological correlation in 39 patients with testicular neoplasms

	Lymphangiography	Computed tomography
Positive	29	26
False negative	2	5
Negative	7	7
False positive	1	1
Total	39	39
Sensitivity	29/31 = 93.5%	26/31 = 83.8%
Specificity	7/8 = 87.5%	7/8 = 87.5%
Accuracy	36/39 = 92.3%	33/39 = 84.6%

ly visualized by LAG, and CT better delineates the extent of the lesion. Given the lack of absolute superiority of either CT or LAG in the assessment of the nodal metastasis from nonseminomatous testicular tumors, Castellino and Margulin (1982) and Lien et al. (1983) recommended computed tomography as the initial imaging procedure because of its greater patient acceptability and broader scope. It was their recommendation that abnormal results may be confirmed histologically. If the cytological results were negative or if the result of the CT examination itself was negative, lymphangiography was recommended. However, at M.D. Anderson Hospital and Tumor Institute, LAG and CT are performed as complementary procedures in the initial evaluation. In the further management of these patients conventional radiographs of the abdomen are obtained at two-month intervals while CT is used at 6-12-month intervals (Table 6).

In seminomas, when LAG and CT are positive, radiotherapy is given to the ipsilateral iliac and bilateral retroperitoneal nodes up to the diaphragm. The mediastinum and both supraclavicular areas are also treated. In the presence of a negative lymphangiogram and CT, radiotherapy is given only to the level of the diaphragm.

In nonseminomatous malignancies in the past, a patient with a positive lymphangiogram and/or CT

**Table 6** — Suggested Schedule of Tests for Patients with Testicular Carcinoma

Tests	Months						
	0	2	4	6	8	10	12
AFP	X	X	X	X	X	X	X
HCG	X	X	X	X	X	X	X
Chest radiograph	X	X	X	X	X	X	X
Lymphangiogram	X						
Computed tomography	X			X			
KUB		X	X	X	X	X	X

was treated by radiotherapy to the tumor dose of 2500 rads to the nodes up to the diaphragm. A retroperitoneal node dissection was then undertaken to remove residual tumor tissue with additional radiotherapy, 2500 rads, following the retroperitoneal node dissection. In the presence of negative lymphangiographic and CT findings, the retroperitoneal node dissection was undertaken initially. If the node dissection was negative, no further treatment was instituted.

At present with the stage I disease, normal markers, normal CT, and normal LAG, the patient is observed closely with no further treatment. Markers and follow-up examinations of the abdomen are done every two months. CT is performed every six months (Table 6). When there is a change in these parameters, chemotherapy is instituted.

In the presence of more widespread disease, stage II or stage III where chemotherapy is the initial therapeutic approach, LAG or CT is of assistance in determining the status of the retroperitoneal lymph nodes. After a favorable response to chemotherapy (that is, resolution of the pulmonary and retroperitoneal metastases), the patient is managed by utilizing the markers, CT and LAG. Surgery is reserved for instances where there are persistent defects in the nodes or residual tumor. Of twenty-five patients subjected to surgery with persistent changes on CT and/or lymphangiogram only one had residual tumor. If there is inadequate residual contrast material, a repeat lymphangiogram can be performed. We have repeated the study on many patients with a maximum of five lymphangiograms in a patient over a seven-year period. Given these circumstances, CT is of value for follow-up examinations as an alternative to repeating the lymphangiogram. While ultrasound is less specific than lymphangiogram and less sensitive than CT scan in the diagnosis of nodal metastases, it is of significant importance to diagnose postoperative lymphoceles following retroperitoneal node dissection (Figure 26) and as a guide for aspiration and drainage.

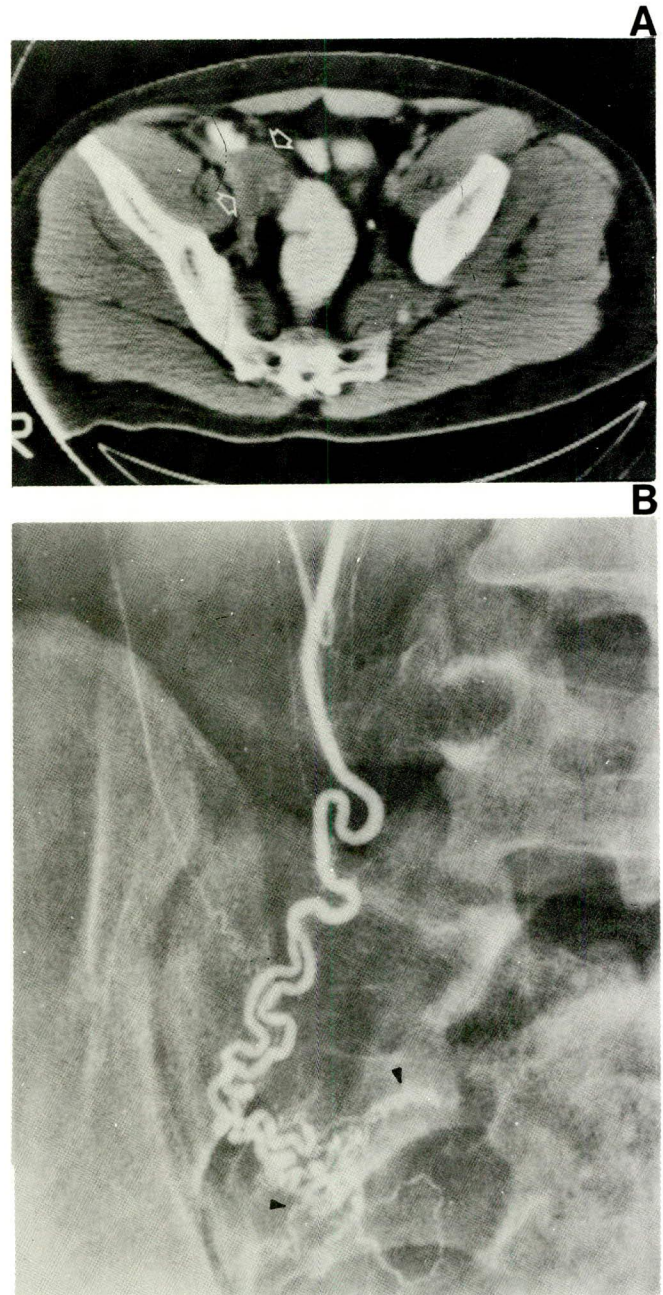
#### D. Magnetic resonance imaging

To date no studies have evaluated testicular lesions by surface coil\*. In the assessment of metastases of testicular tumors to retroperitoneal lymph nodes and other abdominal structures, MRI and CT were nearly equivalent in their ability to correctly stage retroperitoneal adenopathy<sup>31</sup>. In this study, CT surpassed MRI in detection of abnormalities other than retroperitoneal lymph nodes. However, with the advent of oral contrast medium, and technical advances, MRI may improve staging accuracy and serve as an effective substitute for CT in the evaluation of the retroperitoneum<sup>31</sup>.

### SECTION III: IMAGING IN SPECIAL CIRCUMSTANCES

#### A. Imaging in undescended testicles

The incidence of undescended testicle in the premature infant is 30% and in the term infant, 4%. In the adult population, this incidence is approximately 0.28%<sup>6,32</sup>. This anomaly represents a complete or incomplete failure of the intraabdominal testes to descend into the scrotal sac via the inguinal canal. The malposition of the testes may be found at any point from mid abdomen to the inguinal canal. The undescended testicles may be unilateral or bilateral, and when unilateral, they are somewhat more common on the right side. Seventy percent of the undescended testicles are found in the inguinal canal<sup>6</sup>. Apart from being prone to trauma and resulting in sterility, there is now agreement that the risk of testicular cancer is 12 to 40 times greater in the undescended testes than those that have descended<sup>11,13</sup>. Unfortunately, the placement of the undescended testicle within the scrotum does not preclude the possibility of a cancer developing at a later date (Fig. 8). Seminoma is the most common tumor arising from the undescended testicle<sup>11</sup>. In a series of 23 patients reported from our institution, there were 14 cases of seminoma, six cases of embryonal carcinoma, two cases of mixed germ cell tumors and one case of teratoma<sup>34</sup>. In the inguinal region, sonography can successfully detect the undescended testicle and the accuracy of



**Figure 23** — Seminoma arising in an undescended testicle: 26-year-old male with leg edema due to a large right sided abdominal pelvic mass obstructing the inferior vena cava. The right testicle was absent from the scrotum. Biopsy of the mass revealed seminoma and the patient was treated with chemotherapy.

A. CT scan following 3 courses of chemotherapy shows dramatic shrinkage of the mass as compared to an outside study (not shown) and a residual mass medial to psoas muscle (arrows).

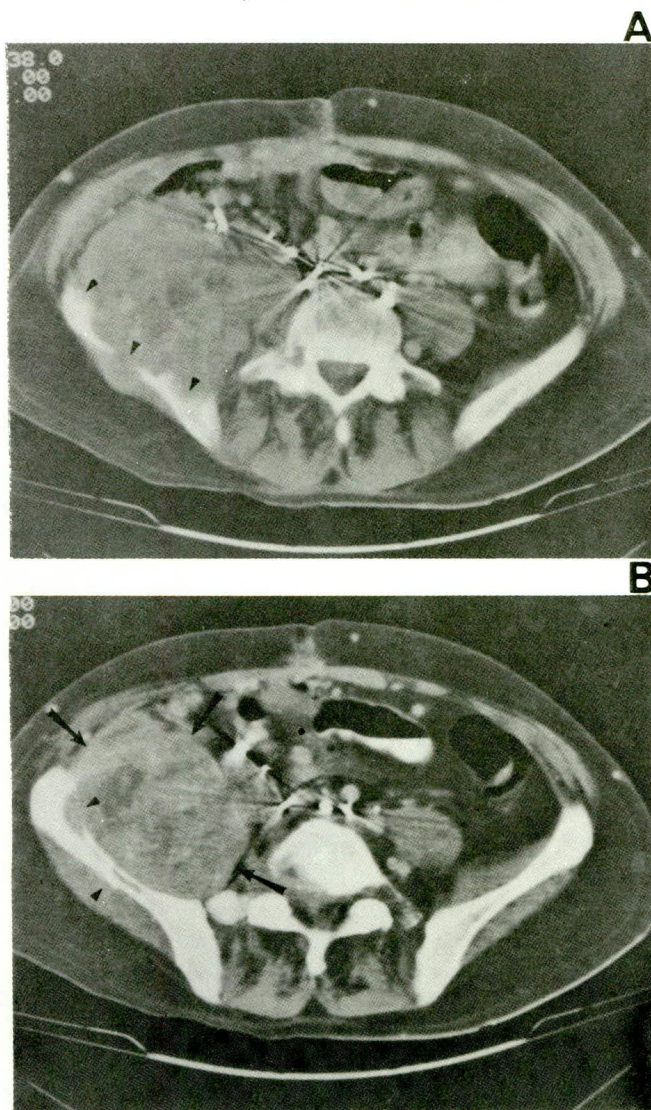
B. Testicular arteriography was performed to differentiate metastatic nodes from the presumed undescended testicle. This established that the mass on CT scan was indeed the testicle. Notice the vascular plexus outlining the testicle (arrowheads).

The surgically removed mass showed a fibrotic testicle with focal calcification and no residual tumor.

\* Since the submission of this chapter, the following articles have appeared in the literature:

- 1) Baker LL, Hajek PC, Mattrey RF et al. — High-resolution MR imaging of the scrotum: a correlative anatomic-pathologic study. *Radiology*, 1986; 161 (P): 280.
- 2) Baker LL, Hajek PC, Burkhard TK, Dicapua L, Leopold GR, Hesselink JR, Mattrey RF — MR Imaging of the Scrotum: Normal anatomy. *Radiology*, 1987; 163: 89-92.
- 3) Baker LL, Hajek PC, Burkhard TK, Dicapua L, Landa HM, Leopold GR, Hesselink JR, Mattrey RF — MR imaging of the scrotum: pathologic conditions. *Radiology*, 1987; 163: 93-98.
- 4) Rholl KS, Lee JKT, Ling D, Heiken JP, Glazer HS — MR imaging of the scrotum with a high resolution surface coil. *Radiology*, 1987; 163: 99-103.

sonography and CT in this region is about the same<sup>6</sup>. However, in the abdominal and pelvic locations, CT scan is more sensitive<sup>6,33</sup>. The sensitivity will increase when there is a complicating tumor arising from the testicle (Figure 23). In rare instances where computed tomography fails to detect the undescended testicle or differentiate metastatic nodes from the undescended testicle, spermatic venography or gonadal arteriography should be performed (Figure 23). Iliac node metastasis is rare in testicular tumors but may be seen *in tumors of undescended testicles*, alone or in combination with lumbar node metastasis. Prognosis of tumors arising from the undescended testicle is the same as in normally descended testicles<sup>34</sup>.



**Figure 24** — Embryonal carcinoma of the testicle with extranodal metastasis to the muscle and bone. History of previous pelvic node dissection. CT scans at the level of the iliac crest (A) and iliac wing (B) show a large mass involving the ilio-psoas muscle (arrows) and destroying the iliac bone (arrowheads).

## B. Extranodal metastasis in testicular tumors

Spread of the testicular tumors is usually in a predictable fashion via the lymphatic channels to the renal parahilar nodes, paraaortic nodes followed by supradiaphragmatic nodes in the posterior mediastinum and finally to the supraclavicular nodes<sup>3,7,8</sup>. Hematogenous metastasis to the extranodal sites is common in certain testicular tumors such as choriocarcinoma and embryonal carcinoma particularly in instances where there is invasion of the tunica or epididymis<sup>5,11</sup>.

The most common sites of extranodal metastases are the lungs (Figure 9) and liver (Figure 27), although metastases to brain (Figure 8) and bone also occur<sup>3</sup>. Metastasis to the lungs may occur in any type of germ cell tumors but is most common in choriocarcinomas<sup>3,11</sup>. Husband and Bellamy have noticed unusual sites of extranodal metastasis in virtually every organ system such as the kidneys, adrenals, spleen, and muscle (Figure 24)<sup>3</sup>. Computed tomography plays a major role in detection of these metastases.

## SECTION IV: INTERVENTIONAL TECHNIQUES IN THE DIAGNOSIS AND TREATMENT OF TESTICULAR TUMORS

### A. Biopsy of the retroperitoneal nodes

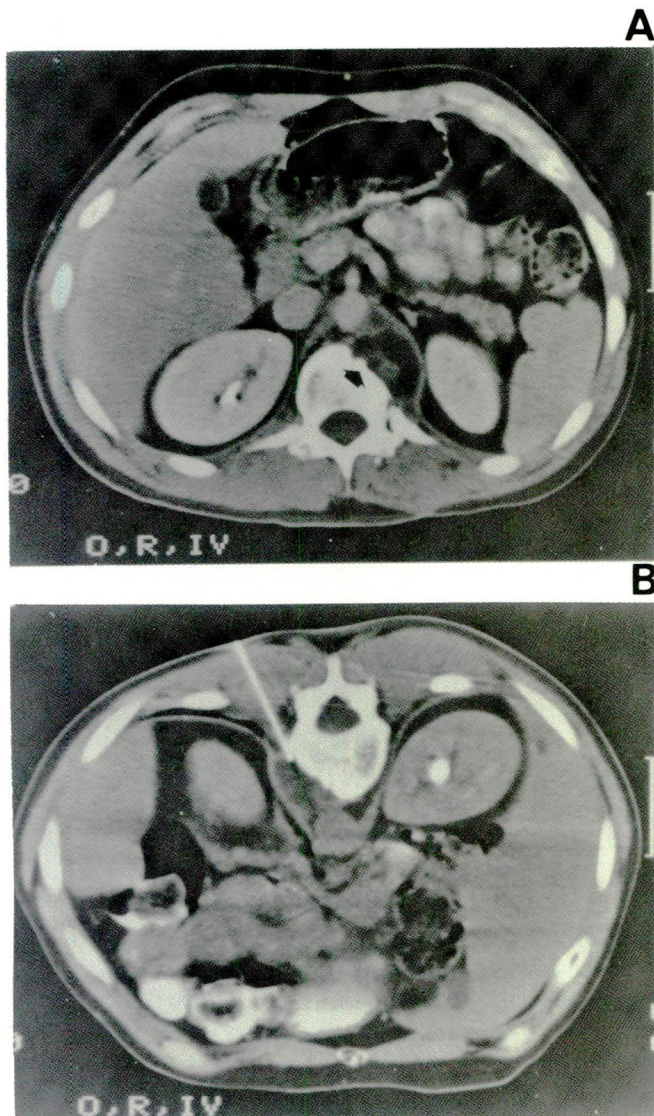
Biopsy of the retroperitoneal nodes may be necessary to verify or exclude equivocal metastatic disease, determine the radiation therapy field and monitor the response of disease to treatment<sup>34,35,36</sup>.

Occasionally, the nodes are replaced by tumor and the abnormality may not be apparent on LAG. On the other hand, non-neoplastic filling defects in the nodes such as caseous necrosis, fatty replacement and conglomerate lymph nodes may cause false positive results on LAG. Therefore, biopsy of the abnormal nodes may become an essential part of clinical management and staging<sup>35,36</sup>.

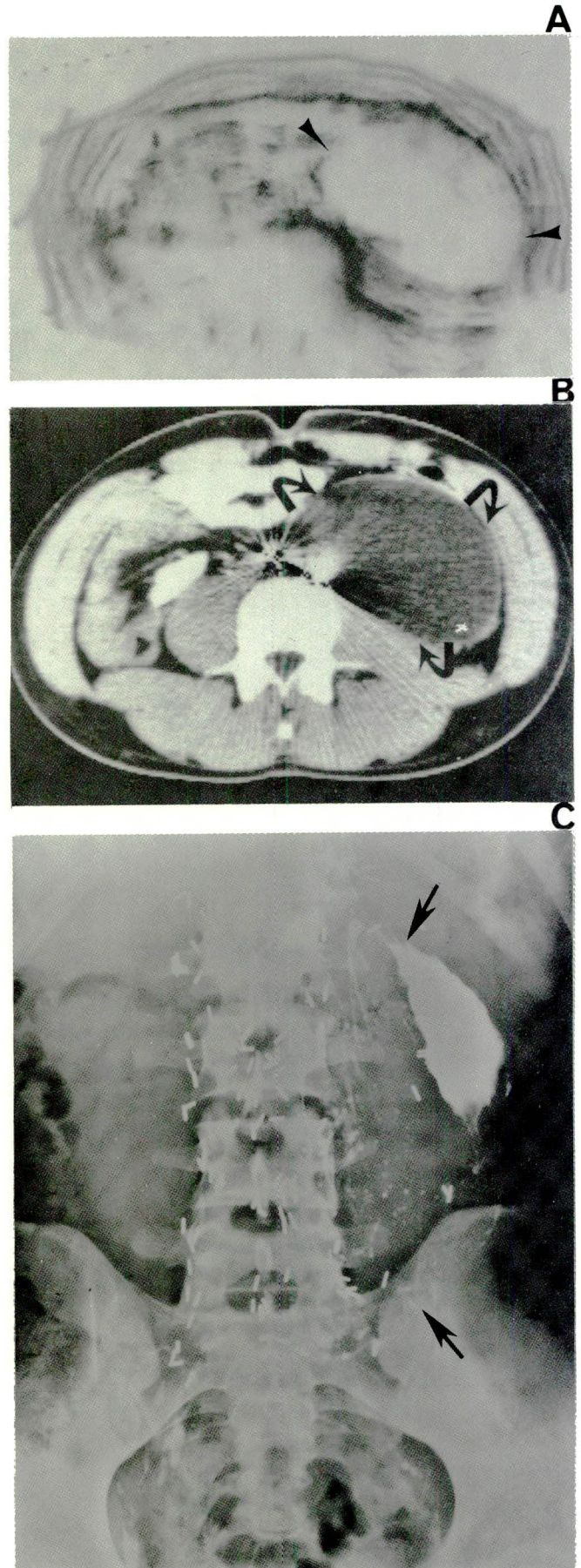
Percutaneous biopsy may be done on an outpatient basis and will obviate the need for open biopsy. Since the node is left intact, therefore, response to treatment may be monitored by repeat biopsy<sup>34</sup>. Percutaneous biopsy is also performed to establish the presence of metastases in the lung, liver, bone, soft tissues and brain<sup>35</sup>.

Biopsy of the nodes may be performed transperitoneally or retroperitoneally using different modalities. If the nodes contain lymphangiographic contrast material, fluoroscopy (preferably biplane) is the best choice. CT is used when there is no contrast present within the nodes (Figure 25) or when the nodes are replaced by tumor and not opacified. In the instances where the nodal mass is large and accessible, ultrasound may be utilized as a guide. Results of percutane-





**Figure 25** — CT guided biopsy of the lymph nodes. 31-year-old male with mixed germ cell tumor of the testicle (Embryonal carcinoma, EST and mature-immature teratoma), status postchemotherapy. A. CT scan shows low density left retrocrural mass resulting in bone destruction (arrow). B. CT scan with the patient in the prone position shows the biopsy needle in place. Biopsy revealed mature teratoma.



**Figure 26** — Postoperative lymphocele. 20-year-old male with history of the right testicular mixed germ cell tumor and retroperitoneal lymph node dissection three months previously. A. Transverse sonogram showing large fluid collection in the left side of abdomen (arrowheads). One thousand ml of clear yellowish fluid containing lymphocytes aspirated. B. CT scan 3 days later showed reaccumulation of the fluid (curved arrows). Urogram (not shown) revealed displacement and obstruction of the left ureter. C. Abdominal film following drainage of 1200ml of fluid and injection of pantopaque and ethanol. Notice the contrast material outlining the large cavity (arrows).

ous lymph node biopsy has been reported to be accurate in 70-85% of metastatic carcinoma<sup>35,36</sup>.

Transabdominal biopsy involves passage of a needle through various solid and hollow organs. Taking necessary precautions should obviate serious complications. The only relative contraindications to the procedure are bowel dilatation and abnormal coagulation profile.

### B. Diagnosis and management of lymphoceles

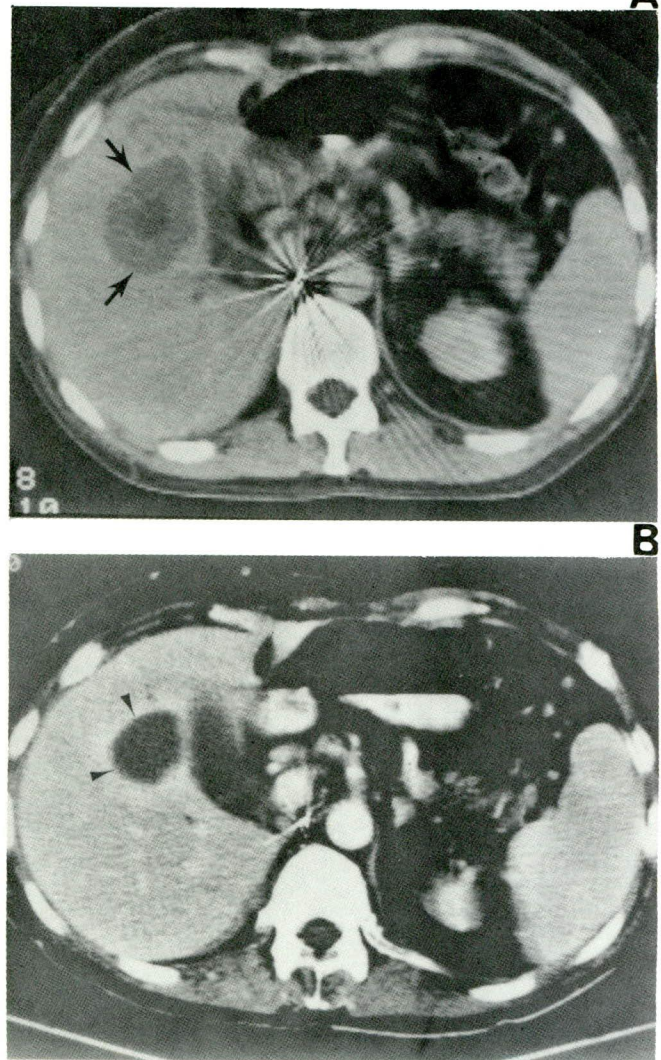
Lymphoceles usually appear immediately after surgery but may be appreciated from days to months after retroperitoneal node dissection for testicular tumors. These may initially be asymptomatic and only manifest by an abdominal mass. However, they may become infected or cause venous, ureteral (Figure 26) or bowel obstruction<sup>7,37</sup>.

Uncomplicated lymphocele would present as single or multiple fluid-containing masses with good sound transmission (Figure 26). Occasionally, they may contain debris. When abdominal sonogram is compromised by gas, CT scan can be used. CT will display a low-attenuation fluid collection in the case of uncomplicated lymphocele (Figure 26) and high attenuation in the complicated ones. Low CT numbers effectively exclude abscess or hematoma<sup>37</sup>.

Lymphocele can also be diagnosed by lymphangiography, demonstrating a contrast/fluid level in the upright position. Management of the lymphocele should be either multiple needle aspirations or catheter drainage. The indications for catheter drainage are secondary infection, persistence or growth of larger collections, symptomatic patient, or signs of obstruction in the ureters or veins. The catheter drainage requires longer intervals, lasting an average of 18 days which is considerably longer than those for an abscess drainage. When the drainage ceases, a sclerosing agent is injected and the catheter is removed (Figure 26)<sup>37</sup>.

### C. Intraarterial chemotherapy, embolization and chemoembolization

Transcatheter procedures are occasionally used in metastatic disease from testicular neoplasms to the liver, and large retroperitoneal and pelvic nodes dependent upon the availability, the ability to isolate and selectively catheterize and treat through the arterial supply<sup>38,39</sup>. These metastatic lesions are initially treated by intraarterial infusion of the chemotherapeutic agents (Figure 27). When the latter fails and radiotherapy becomes ineffective then devascularization of the lesions is attempted by embolization techniques with Ivalon, gelfoam or stainless steel coils. Chemoembolization, the combination of Ivalon or gelfoam with cisplatin, Actinomycin D, Mitomycin C, or Adriamycin has been effective in the management of liver,



**Figure 27** — Extranodal metastasis to the liver from embryonal carcinoma of the testicle treated with intraarterial chemotherapy.

A. CT scan shows a single lesion in the right lobe of the liver, the center of which has much lower attenuation (arrows).

B. CT scan following course of intraarterial 5-Fluorouracil and Mitomycin-C shows a decrease in the size of the hepatic lesion which now has a uniformly cystic density consistent with necrosis (arrowheads).

retroperitoneal nodes or osseous metastases. Treatment may provide a more demarcated and smaller avascular field for safe removal of the hepatic metastasis.

Embolization may also be utilized in patients with myelosuppression due to systemic or intraarterial infusion or in those patients who will be unable to tolerate further hepatic artery infusion chemotherapy. Failure of surgical resection is yet another indication for interventional therapy<sup>38,39</sup>.

### D. General interventional techniques

Additional interventional techniques including drainage procedures (abscess, urinary and biliary tract

obstruction, gastrostomy etc.), stent or balloon dilatation of stenoses of tubular structures, central venous catheter placement repositioning, foreign body retrieval, thrombolysis, etc. are available to assist in the management of the patient with a testicular neoplasm.

### Acknowledgements

The authors wish to thank Margaret Meza for her secretarial help in the preparation of this manuscript and, Gene Swarc and Robert Czimny, from photography, for their technical assistance.

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## Treatment of Advanced Seminoma with Dactinomycin, Cyclophosphamide, Vinblastine, Bleomycin and Cis-Platinum (The Vab-6 Protocol)

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### Summary

*Eighteen patients with advanced seminoma (stages IIc–III) were treated with: cytoxan 600mg/m<sup>2</sup>, vinblastine 4mg/m<sup>2</sup>, actinomycin D 1mg/m<sup>2</sup>, bleomycin 30mg, i.v. on day 1, followed by bleomycin 30mg/day by infusion, days 1-3, and cis-platinum 120mg/m<sup>2</sup> on day 4. 9/18 pts. achieved complete remission and have been followed clinically; no recurrences have occurred in this group. The other 9 pts. had residual masses after 3 cycles of chemotherapy; they were taken to surgery and no viable tumor was found on surgical specimens. There were 3 recurrences in this group, always distant from the site of original disease. These patients were successfully treated with salvage chemotherapy and radiotherapy. One of these patients died of hepatic failure unrelated to his seminoma. All the other patients are alive, at a median follow-up of 50 months. This chemotherapy regimen is effective in curing advanced seminoma.*

**Uniterms:** seminoma chemotherapy; advanced seminoma

Although the prognosis of patients with pure seminoma in stage I (disease confined the testis) and early stage II (few retroperitoneal lymph nodes) remains excellent with conventional radiotherapy, the same cannot be said about patients with bulky abdominal disease (stage IIc) or extra-abdominal disease (stage III). For these patients, radiotherapy yields much poorer results, with a high relapse rate and 5-year survival figures in the range of 20% or less for most of the reported series.

Advances in the chemotherapy of non-seminomatous testicular cancer (NSTC) throughout the last decade have made these tumors consistently curable. Several chemotherapy regimens containing cis-platinum, vinblastine and bleomycin as basic drugs have been developed and significantly increased the cure rate of disseminated NSTC. Paralleling the application of these protocols to disseminated NSTC, we<sup>1</sup> and several others<sup>2,3,4,5,6,7</sup> have used chemotherapy in treating disseminated seminoma. It soon became clear that seminomatous tumors are at least as sensitive — if not more sensitive — to chemotherapy than NSTC. Table I summarizes some of the international experience with

cis-platinum containing chemotherapy in advanced seminoma.

**Table I** — Results of chemotherapy regimens in advanced seminoma.

Author	Protocol	Nº Patients	Results
Simon et al. (1983)	VAB-6	10	100% *
Morse et al. (1983)	VAB-6	22	82% *
Oliver (1984)	PVB	12	83% *
Van Oosterom (1984)	PVB	73	70% §
Stanton et al. (1985)	VAB-6	30	86% §
Friedman et al. (1985)	PVB	20	90% §

\* disease-free survival § initial CR

We report here the results of treatment of 18 patients with advanced seminoma with a slightly modified VAB-6 protocol and propose guidelines for the treatment strategy of such patients.

### Material and methods

Between August 1980 and July 1984, eighteen patients with advanced (stages IIc-III) testicular semino-

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ma were treated. All patients had had no prior chemotherapy. Patients were staged with physical examination, chest roentgenogram, abdominal computerized tomography, serum markers (alpha-fetoprotein and beta-HCG in all patients, LDH in most patients) and rarely with bipodal lymphangiography. Patients characteristics are shown in Table II.

**Table II** — Patients characteristics

Age	31 (median); 25-52 (range)
Previous-chemotherapy	0/18
Previous para-aortic radiotherapy	5/18
Previous mediastinal radiotherapy	3/18
Elevated AFP	0/18
Elevated beta-HCG	6/18
Elevated LDH	4/10
Massive intra-abdominal disease	14/18
Pulmonary disease	3/18
Massive supra-clavicular/cervical disease	1/18

Patients were treated with 3 cycles of chemotherapy and submitted to surgical resection of residual masses about 4 weeks after the completion of chemotherapy. No maintenance chemotherapy was given.

The first 13 patients received classical VAB-6 chemotherapy: dactinomycin 1mg/m<sup>2</sup>, cyclophosphamide 600mg/m<sup>2</sup>, vinblastine 4mg/m<sup>2</sup> and bleomycin 30mg were given intravenously on day 1, followed by a continuous bleomycin infusion (30mg/day) from day 1 through day 3 and cisplatinum 120mg/m<sup>2</sup> with saline infusion and mannitol-induced diuresis on day 4. Cycles were repeated 21-28 days apart, depending on blood counts. Bleomycin was omitted on the third cycle.

The last 5 patients were treated with an adaptation of this protocol for outpatient use, as previously reported by us<sup>8</sup>.

Surgical resection of residual masses was carried out 4-6 weeks after completion of chemotherapy. Low concentration of inspired oxygen (maximum 28%) was used during surgery because of previous exposure to bleomycin. All patients were rendered free of disease after the operation. No further chemotherapy was given after surgery.

## Results

All patients attained a complete remission (CR) after 3 cycles of chemotherapy. In 9/18 patients there was clinical CR, shown by physical examination, x-rays, abdominal CAT scan and serum markers. These patients received no further treatment and were followed clinically. With a median follow-up of 47 months (range 36-83 months) none of these patients has relapsed.

Of interest was the extremely rapid decrease of tumor masses seen after the start of chemotherapy, with complete responses seen at the end of the first cycle of therapy in most cases. In patients with abdominal pain due to tumor there was complete relief of pain within 12-24 hours from start of therapy.

In 9/18 patients there was evidence of residual tumor mass after 3 cycles of therapy. These were all abdominal masses. These 9 patients were taken to surgery and complete removal of the residual masses was accomplished in all cases. None of these patients had histological evidence of viable tumor in the surgical specimens, which showed necrosis and fibrosis only. Of significance was the fact that extensive fibrosis was present in the retroperitoneum of these patients, which precluded effective lymphadenectomy in some cases<sup>9</sup>. With a median follow-up of 54 months (range 38-76 months) there have been 3 relapses in this group, at 5, 5 and 8 months after surgery for removal of residual masses. One patient had a relapse in the supra-pubic area and the other 2 patients had hepatic recurrences. These 3 relapses occurred in areas previously uninvolved by disease. The 3 patients with recurrent disease were re-treated with a combination of VP-16-213 and cisplatinum for 4 cycles, followed by radiotherapy to the affected areas (2,500 r). Two of these patients are alive at 76 and 60 months, with no evidence of disease. The third patient died at 49 months of hepatic failure following blood transfusion-related cirrhosis of the liver. He had no evidence of disease at autopsy.

## Toxicity

Despite the apparent aggressiveness of this protocol, toxicity was considered mild to moderate. Nausea and vomiting were universal but this was dramatically ameliorated with the introduction of high-dose metoclopramide and dexamethasone. Total alopecia was seen in 16/18 patients. Chemical phlebitis was seen in 4/18 patients. Leukopenia of moderate degree (leukocytes below 2,000/mm<sup>3</sup>, granulocytes below 1,200/mm<sup>3</sup>) was seen regularly. There were 7 febrile episodes requiring antibiotics. None of these had a documented site of infection or positive blood cultures. Mild elevation of serum creatinine (up to 2,8mg/ml) was seen in 2 cases and reverted to normal with further saline hydration. Ototoxicity consisting of mild hearing loss and tinnitus was reported by 2 patients. This symptoms subsided in both patients after a few months. One patient had a "idiosyncratic" reaction with the first cycle of chemotherapy, consisting of severe arthralgias, abdominal pain, fever, paresthesias in the lower limbs and an acute dermatitis. This patient received no further VAB-6 chemotherapy and on surgery was found to have had complete necrosis of his residual tumor. This patient went on to develop hepatic recurrence of his disease

and was re-treated successfully with VP-16 and cisplatin without significant toxicity. This same patient developed clinically significant hypocalcemia after the first cycle of chemotherapy, requiring oral and intravenous calcium supplementation. There were no treatment-related deaths.

Toxicity data is summarized in table III.

**Table III** — Toxicity of VAB-6 chemotherapy in seminomas

	N° Patients
Alopecia (complete)	16/18
Nausea	18/18
Vomiting (3 episodes/cycle)	14/18
Phlebitis	4/18
Sepsis	7/51 cycles
Renal failure (transient, mild)	2/18
Hearing loss (transient)	2/18
Hypocalcemia, symptomatic	1/18
"Idiosyncratic" reaction	1/18
Treatment-related deaths	0/18

## Discussion

Our data shows a remarkable sensitivity of seminomas to chemotherapy. This is in agreement with other data in the literature also showing an initial CR to chemotherapy in excess of 80%.

Our data shows that the concept of "high-risk" patients — as defined by any of the current definitions — does not apply to patients with disseminated seminomas of testicular origin. All our patients would have been considered "high-risk" by current criteria; nonetheless, all of them showed an initial CR to chemotherapy.

We question the value of post-chemotherapy resection of residual masses in seminomas. This procedure, which is of value both therapeutically as well as in assessing the need for further treatment in cases of non-seminomatous tumors, proved to be of no value in our seminoma patients. It had no therapeutic value (all our relapses occurrences occurred far from the residual necrotic masses), nor had it value in assessing the need for further treatment (all the re-

sected specimens showed only necrosis and fibrosis). This finding seems to be in agreement with other data from the literature<sup>10,11</sup>.

The role of radiotherapy is also questioned. Pre-chemotherapy radiotherapy in advanced seminoma should be definitely discouraged, since it is not only ineffective in most cases but also increases the risk of life-threatening leukopenia should chemotherapy be needed in case of treatment failure.

Post-chemotherapy radiation therapy, as recommended by some authors<sup>12</sup> routinely in the treatment of advanced seminoma seems also unnecessary. Our series show that only had the original tumor masses no viable tumor cell after chemotherapy but also that relapses occurred far from the initial site of disease.

Our experience shows that the treatment of advanced seminoma should always be started with chemotherapy. Our proposed regimen is extremely effective in inducing complete remissions and we recommend 3 cycles of therapy as optimal treatment. Residual tumor masses need not be irradiated nor resected, but should be monitored closely, without treatment. Further treatment will be indicated only if there is evidence of progression of disease.

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## Serum and Cellular Biologic Tumor Markers in Testicular Cancer

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During the past two decades, a dramatic improvement has been made in the treatment of testicular germ cell tumor. This progress has been due to finding more efficacious systemic chemotherapeutic agents and the availability of specific and sensitive biologic tumor markers to detect early recurrence and monitor the therapy. In this review, I will update my 15 years of experience in establishing and utilization of these serum and cell markers in testicular cancer.

### Historical Landmarks

My interest in these markers initiated in 1967 when I was serving at the American Urological Association in the Armed Forces Institute of Pathology in Washington, D.C. The development and utilization of testicular tumor models in syngeneic strain 129J mouse helped to understand the original and biological characteristics of this tumor<sup>1</sup>. In 1963, Abelev and associates demonstrated an alphafetoprotein (AFP) in serum of the mouse embryo<sup>2</sup>. In 1972, a radioimmunoassay (RIA) was developed that measured serum hCG in the presence of physiological amounts of luteinizing hormone with minimal cross reactivity<sup>3</sup>. Also, the development of a RIA to measure AFP in minute amounts prompted us to study the frequency and usefulness of these markers in testicular cancer. Although we found a number of specific and nonspecific serum and cell markers in patients with testicular cancer (Table 1). However, none were more accurate than serum AFP and/or hCG when measured by sensitive and specific RIAs.

**Table 1** — Testicular tumor markers.

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#### Specific Markers

1. Alpha-fetoprotein (AFP)
2. Human chorionic gonadotropin (hCG)
3. Placental alkaline phosphatase (PLAP)
4. Gamma-glutamine transpeptidase (GGT)
5. Placental proteins number 5, 10, 15
6. Placental lactogen

#### Nonspecific markers

1. Lactic dehydrogenase<sup>(LDH)</sup>
  2. Polyamines (putrescine, spermine, spermidine)
  3. Carcinoembryonic antigen
- 

### Serum AFP

Human AFP is a glycoprotein having a molecular weight of 70,000 and containing about 41% carbohydrate. It is produced in the liver, yolk sac, and gastrointestinal tract of the fetus. AFP is present in human fetal serum at a concentration of 3ng/ml by the 12<sup>th</sup> week of gestation. At birth, the concentration is approximately 30ng/ml and drops to much lower levels by 1 year of age; in normal adults it is found in concentrations of approximately 1-16ng/ml. AFP has been clinically useful primarily as a diagnostic tool for hepatoma and certain other malignant diseases.

In a prospective study, data from our clinical program of testicular cancer the following distributions for AFP and hCG were obtained.

One hundred and two of 145 (70%) patients with embryonal carcinoma, 36 or 56 patients (69%) with embryonal carcinoma with or without teratoma (64%), 3

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of 4 patients with yolk sac tumors (75%) and none of 5 patients with choriocarcinomas had an elevated level of serum AFP. Eighty-seven of 145 patients (60%) with embryonal carcinoma, 32 of 56 patients (57%) with embryonal carcinomas with/without teratoma, one of 4 patients (25%) with yolk sac tumors. None of the patients with seminoma and/or choriocarcinoma had elevated serum AFP.

### Serum hCG

hCG is a glycoprotein secreted by the normal placenta. It is normally found in the serum only during pregnancy, hCG has a molecular weight of 38,000 and is composed of two dissimilar subunits. Alpha and beta subunit is the basic subunit of the pituitary glycoprotein hormones; luteinizing follicle-stimulating, and thyrotropin. The beta subunit comprising two thirds of the molecular weight, is unique to the hCG and is distinct from the subunits of luteinizing, follicle-stimulating and thyrotropic hormones particularly in the terminal 29 amino acids. The subunit was isolated, purified and used to immunize rabbits to produce an antibody specific for hCG which does not cross-react with physiologic concentrations of the other glycoprotein hormones<sup>3</sup>.

Data from our laboratory showed that 14 out of 140 (9%) of patients with seminoma, 4 out of 16 (25%), 87 of 145 (60%) of embryonal carcinoma and 1 out of 4 yolk sac tumor and all with choriocarcinoma had elevated serum hCG.

### Combined Serum AFP and hCG

When both markers were considered, 9.0% of seminoma, 44% of teratoma, 88% of embryonal carcinoma, 86% of embryonal carcinoma with teratoma, 75% of yolk sac tumors had elevated levels of serum hCG and/or AFP<sup>6</sup> (Table 2).

The frequency of markers in testicular seminoma was unsatisfactory. Therefore, we embarked in studying multiple markers in seminoma.

### Multiple Serum Markers in Seminoma

We studied the role of placental alkaline phosphatase (PLAP), gammaglutamyl transpeptidase (GGT), and hCG in testicular seminoma. In 89 seminoma patients with negative beta-glycoprotein, total serum GGT was measured and values about 30 IU per liter were considered abnormal<sup>7</sup>. Serum PLAP was measured by enzyme-linked immunoabsorbent assay and values greater than 1.85mg per ml were considered abnormal. Serum hCG and AFP were measured by double antibody radioimmunoassays normal less than 1ng/per ml and greater than 20ng per ml, respectively. At the time of this study, 30 patients had detectable seminoma, 10 were histologically unconfirmed and the remaining 49 had no evidence of tumor. Only six of 30 patients (20%) with active tumor had elevated levels of serum hCG. Twelve of 30 patients with active tumor (40%) had elevated serum PLAP, and 10 of 30 (33%) of these patients had elevated serum levels of GGT. When these three serum markers were considered together, over 80% of the patients with clinically active tumours had detectable serum levels of one or more of these biochemical serum markers. It should be emphasized that the false positive, false negative rates of these markers, especially false positive rates for GGT, due to occasional concomitant liver disease and the biologic half-lives of these markers should be taken in consideration.

A nonspecific marker that may be useful in the management of seminoma is lactic dehydrogenase (LDH) (Figures 1 and 2). Serum lactic dehydrogenase is a nonspecific enzyme made up of five heterogenous isoenzymes in man that can be measured electrophoretically. Cancer cells have increased glycolysis leading to an increased synthesis of lactate, and it may be utilized as a nonspecific tumor markers in several cancers<sup>7</sup>.

### Role of AFP and hCG in Staging

Clinically, when these markers were considered in staging testicular tumor the staging errors decreased

Table 2 — Frequency of Elevated hCG and AFP in Patients with Testicular Cancer.

	AFP		hCG		AFP and/or hCG	
	No. of patients	Percent of patients	No. of patients	Percent of patients	No. of patients	Percent of patients
Seminoma	0/160	0	14/160	9.0	14/160	9.0
Teratoma	6/16	37.5	4/16	25.0	7/16	43.7
Embryonal carcinoma	102/145	70.3	87/145	60.0	127/145	87.5
Embryonal carcinoma with teratoma	36/56	64.2	32/56	57.0	48/56	85.7
Choriocarcinoma	0/5	0	5/5	100.0	5/5	100.0
Yolk sac tumor	3/4	75.0	1/4	25.0	3/4	75.0



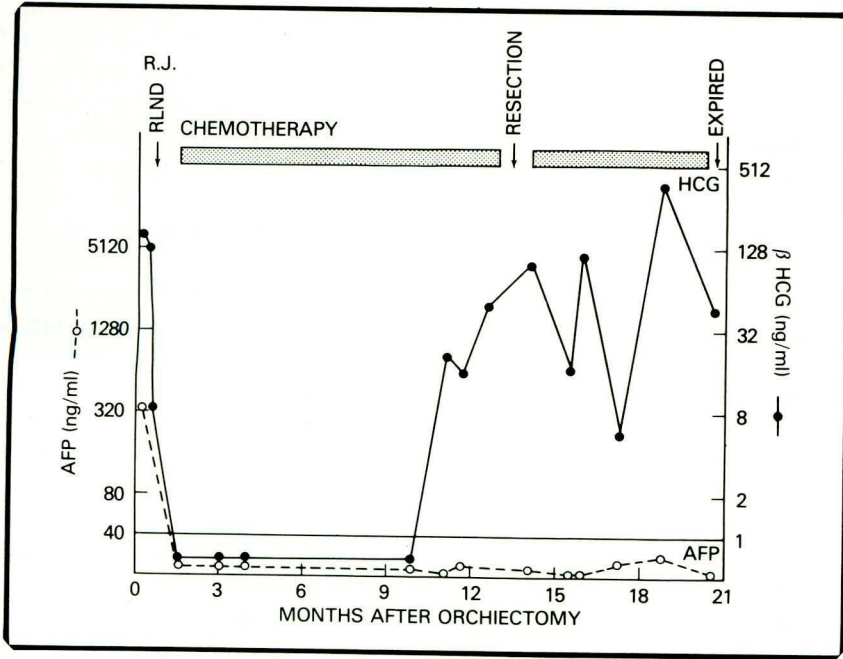


Figure 1 — hCG and AFP in monitoring a patient with embryonal carcinoma and an element of choriocarcinoma. Note the discordance between the serum hCG and AFP.

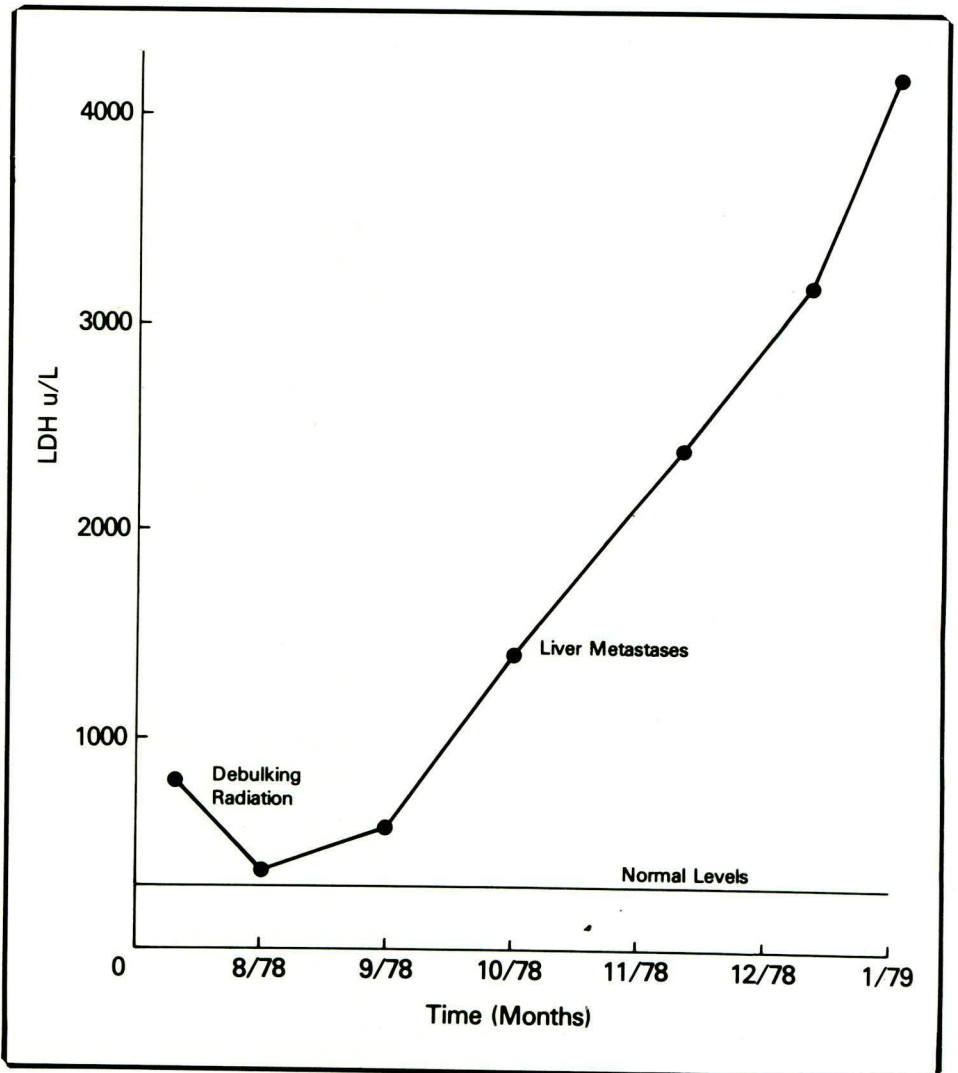


Figure 2 — LDH in monitoring of a patient with bulky testicular seminoma.

to 5-14%, an improvement when compared to a high clinical staging error of 15-20%.

The important feature which tumor markers add to the understaging of testicular cancer are as follows:

- (1) Improved staging based on clinical investigation markers, therapy and pathological findings.
- (2) Persistently elevated serum markers after orchietomy for testicular cancer invariably indicate stage II or III disease.
- (3) Persistently elevated serum markers after lymphadenectomy indicate stage III disease or an inadequate lymphadenectomy.
- (4) When lymphadenectomy is negative for tumor but postlymphadenectomy serum markers are persistently elevated, patients invariably have stage III disease. However, surgery still remains the most accurate means of assessing retroperitoneal metastases.
- (5) Perhaps, the most important application of these markers are in monitoring of testicular tumor when serially measured.

### Monitoring the Response to Therapy

Serial measurements of serum hCG and AFP by RIA reflect the efficacy of surgical, radiation, and/or chemotherapeutic regimens in patients with testicular tumor. When these therapies are effective, they produce an immediate decrease in serum levels of hCG and AFP that reflects the decrease in tumor size and could be as rapid as the catabolic rate for these markers. In our series, elevated markers were found, often months before the patients were symptomatic or recurrence was detectable by any other clinical tests. Consequently, the markers proved to be sensitive indicators of the presence of otherwise undetectable metastases.

It is important to consider the biologic half-lives of the markers (AFP 5 days and hCG 18 to 24 hours) to avoid any confusion from the progressively decaying markers of the already excised tumor. Preorchietomy serum markers are not always available but this should not disturb the proposed system since the original orchietomy specimen is usually available and immunohistologic techniques, such as immunoperoxidase, can determine the presence of cellular markers when serum is not available.

### Discordance, Limitations and Clinical Guidelines

The discordance between various testicular tumor markers is well known and may be explained on the basis of the findings that different cells produce these various markers. Also, during chemotherapy of a patient with elevated levels of serum hCG and AFP, one may return to normal whilst the other remains elevated

(Figure 1). This may occur if some of the cells producing a given marker are resistant to the therapy. To avoid errors, currently we submit the following guidelines. (1) The physician should discuss the sensitivity and specificity of a given commercial assay with the laboratory, and perhaps, occasional inclusions of normal serum or serum with known levels of AFP and/or hCG may serve as negative and positive controls when blindly coded.

(2) These markers should not replace scrotal exploration for histopathologic diagnosis of the primary tumor and retroperitoneal lymphadenectomy to detect or exclude the presence of retroperitoneal metastases. However, the elevated levels of tumor markers are indicative of the presence of tumor and the necessity for further treatment. They are also helpful in monitoring the efficacy of and the need for changes in therapy.

(3) The problem of impurity of certain antisera against the subunit of the hCG of the possibility of high levels of luteinizing hormones (LH) in patient undergoing orchietomy and/or chemotherapy causing a false positive result should also be kept in mind. The false positive results may be clarified by the testosterone suppression test, determination of serum LH, and measurement of hCG on urinary concentrate utilizing a carboxy-terminal RIA that is currently available to all urologists through the NCI laboratories as a courtesy.

(4) In monitoring the therapy or following the patients with testicular tumor, one should utilize frequent clinical examination, chest x-rays, and other tests as physicians find them necessary, along with determination of serum AFP and hCG. In patients on chemotherapy the normalization of these serum markers does not mean tumor-free status; as a matter of fact, on exploration of the retroperitoneum and chest, it is not unusual to find cystic fibrotic markers should not deter the surgeon from looking for tumor. Appropriate utilization of chemotherapy, surgery, radiotherapy, and tumor markers can make a dramatic improvement in the prognosis and survival of these patients.

### Other Placental Proteins

Over the past several years, we have studied a number of placental proteins including pregnancy specific beta glycoprotein and placental proteins number 5, 10 and 15 utilizing immunoperoxidase. We have localized these markers in syncytiotrophoblastic components of the human placenta, choriocarcinoma and syncytiotrophoblastic giant cells associated with testicular cancer.

### Cellular Localization of AFP and hCG

In 1972, as we embarked on serum measurements of AFP and hCG we also concentrated on detecting cellular localization of these markers<sup>5,10,11</sup>. First, utilizing

immunofluorescence technique, we were able to localize AFP and hCG to their cellular origin. However, this technique is mainly a research tool requiring fresh tissue and needs storing in dark areas. Later, we utilized immunoperoxidase.

Immunoperoxidase methods have much in common with established immunofluorescence procedures. Both have the potential for demonstration of specific cell and tissue antigens with similar limitations demanding rigorous control of specificity. In any study, the choice of an immunofluorescence method of an immunoperoxidase method can be and on rational grounds, according to the desired objective, the degree of morphologic detail required, the materials available for study, and the ease of access to specialized ultraviolet microscopy. The major advantage of immunoperoxidase is that it can be utilized in either a prospective or a retrospective study, since the tissue to be stained can be fixed in formaldehyde and this is usually available as opposed to immunofluorescence requiring fresh or frozen tumor specimens. Therefore, these properties of immunoperoxidase have the necessary features that make immunocytochemistry more convenient and practical.

This technique utilizes a 4 to 6 micron thick section of formal formaldehyde fixed tumor that is deparaffinized in xylene and cleared in the usual fashion. The section is incubated in a humid chamber for 30 to 60 minutes with appropriate antisera to a given marker. The second antibody is a gamma-globulin that is conjugated with horse-radish peroxidase. The section is washed again and exposed to Diaminobenzidine. The slides are counter-stained with hematoxyline. Utilizing this technique, we reported for the first time that the yolk sac tumor is mainly responsible for AFP and syncytiotrophoblastic giant cells (STGC) are producers of hCG (Table 3). Later utilizing antisera to hCG and AFP tagged to I<sup>(3)</sup> we were able to detect and localize tumors producing these markers by gamma scintilla-

tion cameras as a specific radioimmunodetection technique<sup>12</sup>.

**Table 3** — Immunohistologic Classification of Germ Cell Tumors.

Tumor	AFP	hCG	SP <sub>1</sub>
Placenta	—	+	+
Yolk Sac Tumor	+	—	—
Seminoma	—	—	—
Seminoma with STGC	—	+	+
Embryonal carcinoma	+	+	—
Choriocarcinoma	—	+	+
Teratoma	—	—	—

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## New Advances and Directions in Testicular Cancer

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### Summary

*Major advances have taken place in the overall management of patients with all forms of testicular cancer. The current article reviews the approach to diagnosis, staging, and treatment of patients with both seminomatous and nonseminomatous germ cell cancer of the testis. The use of radiation therapy for patients with seminoma, as well as new treatment modalities for patients with advanced forms of germ cell cancer of the testis, are outlined in full. Future directions are discussed, with an emphasis on new chemotherapeutic modalities in the overall management of the disease.*

Uniterms: testicular cancer

### Introduction

Carcinoma of the testis is a rare but extremely important disease, as it serves as a model of a curable, solid neoplasm<sup>1,2</sup>. When present in its early, nonmetastatic form, patients with germ cell cancer have enjoyed a high cure rate when treated with the modalities of either surgery or radiation therapy. However, the great excitement associated with the disease today focuses on the curability of advanced, metastatic forms which, in the past, have been almost universally fatal. The successful, multidisciplinary principles and strategies which have evolved for the management of patients with advanced testis cancer are now being applied to other advanced cancers with encouraging results. Because this type of cancer is most common in young males, the ability to cure the majority has a major emotional, socio-economic, and psychological impact.

Approximately, 5,500 new cases will be diagnosed in the United States in 1987, with peak age incidence between 20-35 years; a second peak occurs in early childhood. Caucasians have the world's highest incidence; blacks have the lowest. The disease is uncommon after the age of 40. A testis lesion suggestive of neoplasm in a patient over the age of 50 should suggest a testicular lymphoma rather than primary germ cell carcinoma.

Patients with a history of a cryptorchid (maldescended) testicle are most susceptible to developing testis cancer, with a 10 to 100 fold increased risk. Other factors include a prior history of mumps orchitis, and in-

guinal hernia. Although some investigators have suggested an association with in utero exposure to DES, the overwhelming body of data suggest that no such association exists. The unilaterally cryptorchid testis itself may be at increased risk of developing a neoplasm, as is the contralaterally, normally descended gonad. Most pediatric urologists now recommend performing an orchiopexy for cryptorchidism at an age less than 2 to help decrease the subsequent testicular cancer risk and improve subsequent fertility potential. The management of adults with an unilaterally cryptorchid testis is controversial. Some advocate exploration and removal of an inguinal cryptorchid testis under the age of 50; in those over 50, the low risk of developing a subsequent testis cancer justifies no surgical intervention<sup>3</sup>.

Based upon statistics generated in 1977, testis cancer was the third leading cause of cancer death in males between the ages of 15 and 34. Advances in therapeutic strategies for advanced forms of the disease has been associated with a marked reduction in mortality. In data generated from 1981, testis cancer is no longer listed among the top five causes of cancer mortality in that same age group.

### Clinical features and diagnosis

The manifestations of testis cancer are protean and range from detection of an asymptomatic nodule or swelling while performing testicular self examination to the development of dyspnea secondary to massive

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pulmonary metastases. Most patients will first seek medical attention because of the self detection of a painless mass or nodule. Other symptoms, such as testicular pain, dysuria, and pain after intercourse are relatively uncommon. Patients who present with a painful lesion in the scrotum are often initially diagnosed and treated for epididymitis before the actual diagnosis of testis cancer is established. It is important to realize that epididymitis can concomitantly occur in patients with testis cancer and may help explain the associated pain. If a testis lesion persists after an adequate course of antibiotics for epididymitis, the possibility of an underlying testis neoplasm must be strongly considered and ruled out. Diffuse induration of one testis, too, may be the first physical abnormality detected. The sudden, acute appearance of a rapidly enlarging testis is usually associated with hemorrhage into a neoplasm and is seen with certain histologic subtypes. Torsion of the testis itself or torsion resulting from a neoplasm can sometimes confuse the clinical picture and may not be resolved until a surgical exploration is performed.

Back or abdominal pain, secondary to retroperitoneal adenopathy, weight loss, dyspnea, secondary to pulmonary metastases, gynecomastia, supraclavicular lymphadenopathy, and urinary obstruction may also occur at presentation.

A testicular ultrasound can complement the physical examination in determining the presence of a testicular parenchymal abnormality. Once the diagnosis of a testis neoplasm is suspected, a blood sample should be set aside for subsequent determination of the tumor marker glycoproteins, alpha fetoprotein (AFP) and human chorionic gonadotropin (hCG) (vide infra) prior to orchiectomy. The operative approach to establish the diagnosis of testis cancer demands that a high radical inguinal orchiectomy be performed. A trans-scrotal biopsy of the testis or a trans-scrotal orchiectomy should never be performed if the diagnosis of testis cancer is a possibility. Because the lymphatic drainage of the testis (to the retroperitoneal lymphatics between L1 and L3) differs greatly from that of the scrotum (to superficial and deep inguinal groin nodes), a "scrotal violation" in the presence of a testis cancer may predispose to the development of local recurrences and metastases to the inguinal lymphatics. This rarely, if ever, happens if a proper, radical, high inguinal orchiectomy is performed appropriately.

### Pathology

Germ cell cancers of the testis can be conveniently divided into *seminomas* or *nonseminomas*, based upon the histopathology of the orchiectomy specimen. The former must be in pure form; the latter may either be a mixed germ cell cancer with both seminomatous and nonseminomatous components or a pure form of a non-

seminoma, such as embryonal cell carcinoma, teratoma, yolk sac cancer, or choriocarcinoma. The term "terato-carcinoma" generally refers to a mixed germ cell, nonseminomatous cancer consisting of teratoma and embryonal cell cancer.

The distinction between seminoma and nonseminoma is important, as the staging evaluation and subsequent management differ considerably. These different approaches have been dictated because of the relative radioresponsiveness (sensitivity to radiotherapy) of seminomas compared to the radio-resistance of the nonseminomas. Thus, radiation therapy to the lymphatics of the abdomen and/or chest has been the mainstay of therapy in patients with various stages of pure seminoma. Such treatment is generally not utilized in the management of patients with nonseminoma.

The clinical behavior of seminomas and nonseminomas have distinct characteristics. Most often, seminomas spread via the regional lymphatic to the retroperitoneal nodes of the abdomen and/or the mediastinal and supraclavicular lymph nodes before gaining access to other visceral structures. While pulmonary or other hematogenous metastases can occur in patients with seminoma at initial presentation, such metastatic spread is more common in patients with nonseminomas. Not infrequently, patients with nonseminoma in advanced stages of disease will have pulmonary, hepatic, osseous, small bowel, or central nervous system metastases at some point during their clinical course in addition to lymphatic metastases of the retroperitoneum.

### Biological tumor markers

Germ cell cancers of the testis will often secrete biological tumor "markers" which can be detected in the peripheral blood using sensitive immunoassay techniques. If elevated following orchiectomy, these markers often will reflect the presence of metastatic disease. They can be extremely valuable in monitoring therapy (markers fall with disease regression and increase with disease progression) and may even predate the onset of new clinical or radiological metastatic disease by weeks to months. The two most common markers are the AFP and hCG. AFP is commonly secreted by embryonal cell cancer, yolk sac tumors and endodermal sinus tumors; its biological half life is approximately 6 days. AFP is not produced by seminoma and its detection implies the presence of nonseminomatous elements, either occultly in the primary testis itself or in a metastatic site, despite the fact that the primary orchiectomy specimen is "pure" seminoma. hCG is secreted by syncytiotrophoblastic giant cells present most commonly in choriocarcinomas; not infrequently, such giant cells may be present in embryonal cell components, as well as pure seminomas. The biologi-

cal half life of hCG is approximately 24 hours.

The use of immunohistochemical staining for AFP and hCG of primary testis cancers has allowed excellent clinico-pathologic correlations to emerge. Pure seminoma will usually stain negatively for both AFP and hCG. Approximately 5% of pure seminomas may stain positively with hCG, helping explain the clinical situation of a patient with a pure seminoma and an elevated hCG value. These patients often have syncytiotrophoblastic giant cells within their primary lesion. Nonseminomatous components, such as embryonal cell carcinoma, will stain for AFP, while choriocarcinomas will stain positively for hCG. Teratomas usually stain for neither AFP nor hCG.

### Staging evaluation

The major mission of staging is to determine whether or not the cancer is localized to the testis, regional lymphatics or is widely disseminated. Since the approach to staging and management is dictated by the pathological diagnosis of the orchiectomy specimen, the appropriate evaluation will be outlined for each.

### Pathology results indicate a pure seminoma

A careful physical examination, an abdominal-pelvic computerized tomographic (CT) scan, to assess the presence of retroperitoneal adenopathy or visceral involvement, a chest x-ray, with or without whole lung tomography, routine chemistries, and the biological markers (AFP and hCG) are ordinarily obtained. In most cases, the biological markers will be normal. If the AFP is elevated, the patient should be treated as a nonseminoma, even though the pathologic interpretation is pure seminoma.

If therapy is going to include irradiation for a pure seminoma, bipedal lymphangiography will often be performed to help delineate radiation therapy portals. However, the necessity of lymphangiography for such determination seems to be less imperative today as newer and more sophisticated body computerized tomographic scanners may provide similar information.

If the hCG is elevated in a patient with a pure seminoma, the pathologist should attempt to identify syncytiotrophoblastic giant cells to help explain the hCG elevation. Otherwise, there may be some uncertainty of whether or not the patient is harboring occult foci of nonseminomatous components which are responsible for the hCG production. Also, if the physical or radiographic examinations fail to reveal any evidence of metastatic disease and the hCG is elevated pre-orchiectomy, it is imperative to sequentially follow the decline of the hCG. If the marker does not decline along its biological half-life, the suspicion of occult metastatic cancer should be raised.

### Pathology results indicate a nonseminoma

The staging evaluation outlined for the seminoma generally employed for the patient with a non-seminomatous germ cell tumor of the testis. However, the use of bipedal lymphangiography is generally not employed.

Following the establishment of these non-invasive staging studies, patients can be categorized as either having stage I, early stage II, advanced stage II, or stage III disease. Patients with stage I disease have no clinical, radiographic or marker evidence of tumor presence beyond the confines of the testis. Patients with early stage II have evidence of non-palpable, small, retroperitoneal adenopathy on CT scan, usually measuring < 4-5cm. A patient with advanced stage II has retroperitoneal lymphadenopathy measuring > 5cm on CT scan or palpable retroperitoneal adenopathy with disease limited to lymphatics below the diaphragm (Palpable abdominal masses > 5cm may also be considered as stage III disease). Stage III disease includes visceral involvement below the diaphragm (e.g., liver or bowel) or disease above the diaphragm (e.g., lung or supraclavicular lymphadenopathy). Furthermore, patients with stage III disease can be further subdivided according to anatomic location of disease and disease bulk. Stage III disease of "minimal" to "moderate" risk include supraclavicular lymphadenopathy (stage IIIA), gynecomastia + elevated biological markers (III B-1), or > 5 pulmonary lesions, none of which are > 2cm in greatest diameter (III B-2). More advanced forms or stage III disease include pulmonary presentations with mediastinal or hilar involvement, positive pleural effusion or pulmonary metastases greater than 2cm, palpable abdominal mass, ureteral displacement or hydronephrosis (III B-4), hepatic, gastrointestinal, central nervous system, osseous or vena caval involvement (III B-5).

Conceptually, patients with testis cancer can be categorized pathologically as having either *seminoma* or *nonseminoma* and staged as either "early" or "advanced" disease. Patients with *early* disease would be considered to have stage I and early stage II disease, while patients with *advanced* disease have advanced stage II or any form of stage III disease. This conceptualization allows rational decision making for nearly all categories or disease.

### Treatment modalities according to histology and stage (Table 1)

#### *Early seminoma*

These patients have either a normal abdominal CT scan or retroperitoneal lymphadenopathy measuring less than 5cm in greatest diameter. Most of these pa-

**Table 1** — Testis Cancer — General Approach to Management.

	Seminoma	Non-Seminoma
Stage I	XRT <sup>1</sup>	RPLND <sup>2</sup> or orchiectomy alone/observation
Early Stage II	XRT <sup>1</sup>	RPLND ± Chemo <sup>3</sup> or Chemo <sup>3</sup>
Advanced Stage II	Chemo <sup>3</sup> ± XRT <sup>4</sup>	Chemo <sup>3</sup> ± TRS <sup>5</sup> ± Chemo <sup>6</sup>

XRT<sup>1</sup>: Radiation therapy, delivered to subdiaphragmatic lymphatics (3000-3700R)

RPLND<sup>2</sup>: Retroperitoneal lymph node dissection

Chemo<sup>3</sup>: Combination chemotherapy (see Table 2)

XRT<sup>4</sup>: Radiation therapy to residual radiographic abnormalities

TRS<sup>5</sup>: Tumor reductive surgery

Chemo<sup>6</sup>: Additional chemotherapy given if surgical specimen reveals viable cancer

From: Garnick MB — Testicular cancer. In: Braunwald E et al, eds. *Harrison's Principles of Internal Medicine*. 11<sup>th</sup> edition. New York, McGraw Hill Book Co., 1987; 1578-1581, with permission.

tients are generally treated with abdominal radiotherapy, delivering 3000 to 3700 rad to the subdiaphragmatic lymph nodes and ipsilateral groin. Although prophylactic mediastinal and supraclavicular radiation therapy was used in the past, this practice is generally not employed today. Patients with clinical stage I generally have a 95%-97% cure rate; patients with early stage II disease generally enjoy an 85%-90% survival rate, when treated with radiation following orchiectomy.

### Advanced Seminoma

In the past, these patients with large retroperitoneal masses or mediastinal involvement were often treated with either radiation therapy to fields including subdiaphragmatic lymphatics, whole abdomen, mediastinum and supraclavicular nodes; however, survival rates of only between 40%-70% were achieved. If these patients subsequently relapsed outside of the radiation therapy field, the ability to administer myelosuppressive combination chemotherapy was diminished and was associated with a substantial degree of drug related morbidity. Today, most patients with advanced forms of seminoma should receive initial combination chemotherapy with a cisplatin-containing program. Substantial tumor shrinkage will occur in the majority of patients. However, the proper management for partially regressed retroperitoneal masses following chemotherapy for patients with advanced seminoma remains controversial. Often, patients will receive post-chemotherapy radiation therapy to areas of bulk disease, and, in rare instances, surgical removal of residual tumor masses. However, residual masses following chemotherapy only may actually continue to shrink even after therapy is discontinued. Nonetheless, one

treatment strategy allows for cisplatin-combination chemotherapy to be given over a span of 12 to 14 weeks. Patients are then restaged; decisions regarding further chemotherapy, radiation therapy, or surgery are then made.

There is controversy today regarding the management of residual radiographic masses after chemotherapy for seminoma. In one series, residual masses measuring  $\geq 3$ cm were surgically removed. Residual seminoma was found in 6/14 cases. Others would advocate careful observation after chemotherapy and the possible consideration of radiation therapy if the mass persists or enlarges.

### Early (clinical stage I) nonseminoma

Patients who are clinical stage I nonseminoma are routinely treated with a retroperitoneal lymph node dissection (RPLND), using either a transabdominal or a thoracoabdominal approach. The rationale justifying this operation is based upon the inexact data generated from the non-invasive staging evaluation of the retroperitoneal lymphatics. The false negative rate of abdominal CT scans in patients with clinical stage I is 35-50%. Thus, surgical removal of the retroperitoneal lymph nodes not only serves as therapy but it determines the need for possible additional therapy. If microscopic disease is detected and surgically removed, an 85-90% cure rate can be expected following RPLND.

### Early (stage II) nonseminoma

The optimal management of the patient with retroperitoneal lymphadenopathy measuring between 2-5cm on the CT scan is controversial. While the technique of RPLND may be a curative procedure, a relapse rate of 30-45% can be expected. If RPLND is performed and the patient then relapses, combination chemotherapy can be administered or chemotherapy may sometimes be given as an adjuvant to RPLND. Alternatively, combination chemotherapy can be given prior to RPLND. If complete resolution of disease is achieved following chemotherapy, RPLND would not be performed, thus obviating the need for the operation in this subset of patients.

### Advanced stage (bulk stage II or stage III) nonseminoma<sup>4-8</sup>

#### Chemotherapy for advanced forms of nonseminomatous germ cell cancer

Testis cancer has been responsive to varying antineoplastic agents of differing mechanisms of actions. The early encouraging results using chloroambucil,

methotrexate, and actinomycin D were then followed by the more successful programs of vinblastine and bleomycin. The introduction of cisplatin was associated with marked improvement in both the response rate and duration of response of advanced testis cancer. In nearly universal use today are cisplatin-containing programs, either with vinblastine and bleomycin (PVB) or the combination of cisplatin with vinblastine, actinomycin D, bleomycin, and cyclophosphamide (VAB programs). Additionally, recent data suggests that the use of VP-16-213, cisplatin and bleomycin may be therapeutically equivalent and less toxic than vinblastine, bleomycin and cisplatin and associated with less gastrointestinal toxicity and myalgias<sup>6</sup>. The programs listed in Table 2 have rendered approximately 80%-85%

**Table 2** — Commonly used chemotherapy programs for advanced testis cancer.

PVB		
Vinblastine	0.15mg/kg/D	IV D* 1,2
Bleomycin	30mg	IV D 1,8,15
Cisplatin	20mg/m <sup>2</sup> /D	IV D 1-5
Repeat cycles q 21 days x 4 cycles		
VAP-6		
Induction:	Cyclophosphamide	600mg/m <sup>2</sup> IV D 1
	Bleomycin	30mg IV D 1, then 20mg/m <sup>2</sup> /D CIV** D 1-3@
	Actinomycin D	1mg/m <sup>2</sup> IV D 1
	Vinblastine	4mg/m <sup>2</sup> IV D 1
	Cisplatin	120mg/m <sup>2</sup> IV D 4
Maintenance:	Vinblastine	6mg/m <sup>2</sup> IV D 1
	Actinomycin D	1mg/m <sup>2</sup> IV D 1
Induction: Repeat cycles q 21-28 days x 3-5 cycles;		
D* = day;		
**CIV = continuous intravenous infusion;		
@ Bleomycin omitted after cycle 2;		
Maintenance: Repeat cycles q 21 days; total duration of "induction and maintenance" is 1 year.		
PEB		
Etoposide	100mg/m <sup>2</sup>	IV D 1-5
Bleomycin	30mg	IV D 1, 8, 15
Cisplatin	20mg/m <sup>2</sup>	D 1-5
Repeat cycles q 21 days x 4 cycles		

Adapted from: Garnick MB — Testicular cancer. In: Braunwald E et al, eds. Harrison's Principles of Internal Medicine. 11<sup>th</sup> edition. New York, McGraw Hill Book Co., 1987; 1578-1581, with permission.

of patients with advanced nonseminomatous germ cell cancer in complete remission and potentially cured.

Following such therapy, patients are then restaged (with physical, radiographic, and biochemical examinations) to assess the response of areas which previously contained disease and to determine the need for additional therapy. Large abdominal masses can undergo astonishing regression. Pulmonary nodules often completely resolve, and biological markers frequently normalize following 12 weeks of intensive combination

chemotherapy. If following combination chemotherapy, a residual abdominal or pulmonary mass remains in the setting of normal markers, surgical removal of the mass(es) should be performed. Table 3 outlines current recommendations. Preoperatively, it is difficult to determine the histology of such residual masses. Approximately one-third will contain residual, viable cancer; one-third will be fibrosis, necrosis or hemorrhage, and an additional third will demonstrate the phenomenon of "teratomatous transformation". This latter finding is thought to result from either chemotherapy induced differentiation of the primary mass into a teratoma or from chemotherapy selection of more malignant elements in the mass with residual teratomatous components remaining. If either fibrosis, hemorrhage or teratoma are found following chemotherapy, additional post-surgical chemotherapy is usually not indicated. If, however, viable cancer is demonstrated, additional chemotherapy is generally administered.

If biological markers are persistently positive following remission induction chemotherapy, additional chemotherapy is generally required. "Tumor reductive" surgery will not be attempted until biological markers are normalized.

A proportion of patients will have complete resolution of physical, radiographic, and biochemical marker abnormalities after cisplatin-containing chemotherapy. These patients generally require no additional chemotherapy or surgery following their active 12-week program of chemotherapy.

All patients with testis cancer, regardless of pathology or stage, will require meticulous follow up with monthly physical exams, monthly chest x-rays, and markers for 18 to 24 months. The frequency of these tests can be decreased in the second and third year following diagnosis. The goal of such meticulous follow up is to detect relapse when the tumor burden will hopefully still be minimal. In addition, most relapses from

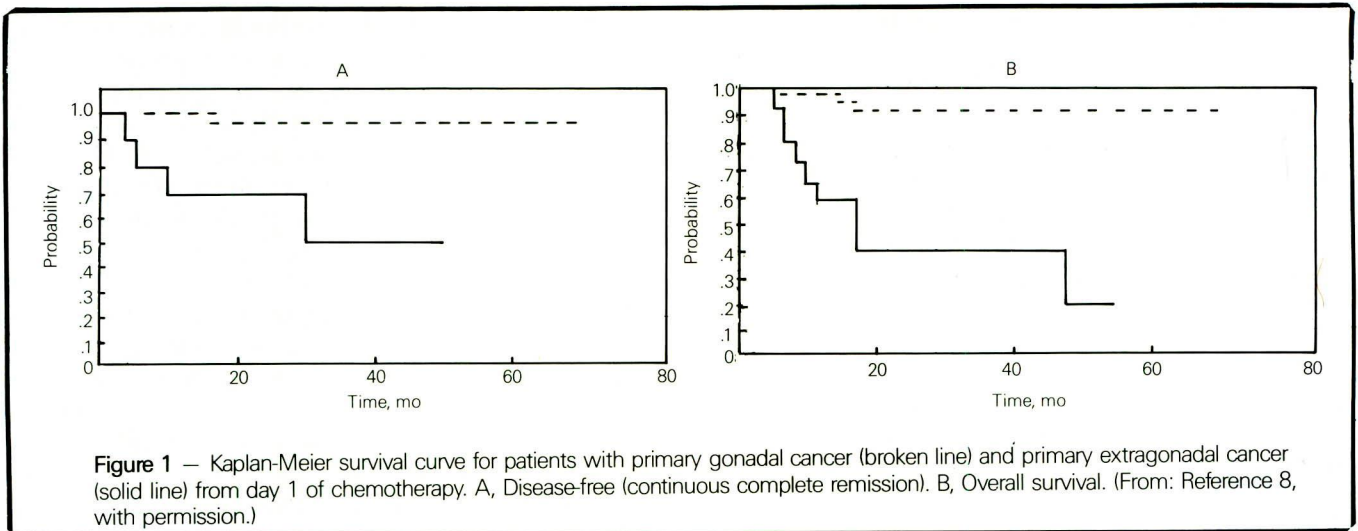
**Table 3** — Advanced testis cancer — nonseminoma approach to management after initial chemotherapy.

Biological "Markers"*	Radiographic Abnormalities	Therapeutic Choice
Positive	Present or Absent	Additional Chemotherapy†
Normal	Present	TRS‡ ± Chemotherapy§
Normal	Absent	Observation

\* = Alpha fetoprotein and human chorionic gonadotropin  
 † = Chemotherapy with a "second-line" program, with attempts to "normalize" biological markers  
 ‡ = tumor reductive surgery  
 § = additional chemotherapy determined by presence of "viable" cancer in surgical specimen. Chemotherapy usually withheld if surgical specimen contains only fibrosis or teratoma

From: Garnick MB — Testicular cancer. In: Braunwald E et al. Harrison's Principles of Internal Medicine. 11<sup>th</sup> edition. New York, McGraw Hill Book Co., 1987; 1578-1581, with permission.





testis cancer occur within the first 2 years following original diagnosis.

The treatment results for patients with advanced nonseminomatous testis cancer reveal that approximately 85% of patients will enter a complete remission and are potentially cured (Figure 1). Additionally, the relapse rate from a complete remission status is extremely low. However, there are certain subsets of patients with "high risk" forms of advanced disease that are associated with a lower complete remission, low cure rate, and high relapse rate. Such patients require different treatment strategies. These include patients with extragonadal presentations (the presence of extensive nonseminomatous germ cell cancer in areas such as the anterior mediastinum or retroperitoneum with clinically and radiographically normal testes), patients with bowel, caval, central nervous system, or bony involvement, or patients with extremely high biological markers (usually  $> 5000$  mIU/ml hCG). Alterations in the duration of therapy and doses of chemotherapy are currently being tested to improve treatment results in this "high risk" population.

#### Side effects of curative cancer therapy — selected aspects

##### Radiation therapy and surgery

The loss of fertility potential can accompany both the use of radiation therapy and RPLND. Because these two modalities are generally reserved for the management of early stage patients, a full discussion regarding the potential loss of fertility in a young population who are likely to be cured to their disease is mandatory. Although of questionable benefit, the possibility of sperm banking should be discussed prior to the initiation of either definitive radiation therapy for early stage seminomas or RPLND for early stage nonseminomas.

Recently, modifications in the surgical technique of RPLND ("limited" dissection) have decrease the incidence of fertility loss and ejaculatory disturbances.

##### Combination chemotherapy

When standard cisplatin, vinblastine, bleomycin, programs are employed, the major side effects are myelosuppression, potential for nephrotoxicity, nausea and vomiting, weight loss, anemia, ileus, pulmonary toxicity, ototoxicity, peripheral neuropathy, Raynaud's phenomenon, hypomagnesemia and stomatitis. Infertility is the rule during therapy, although it may return years after completion of therapy. The use of these chemotherapy programs requires skill on the part of the treating physician and should not be attempted by the occasional user. With proper expertise, these side effects can be minimized.

Special precautions must be taken in the patient who has received bleomycin and is scheduled for a tumor reductive surgical procedure. The acute respiratory distress syndrome has occurred in a minority of patients and is thought to be related to excessive fluid overload and high inspired oxygen concentration during the operative procedure. Current recommendations now call for the  $FIO_2$  to be maintained at  $< 24\%$  and to keep patients in a hypovolemic or euvolemic state in the perioperative period. Such measures seem to minimize the postoperative pulmonary complications.

##### Orchiectomy alone for clinical stage I disease<sup>9,10</sup>

Because combination chemotherapy + tumor reductive surgery can cure 80-85% of patients with advanced disease, the possibility of "orchiectomy alone" for clinical stage I patients has gained support. Treatment with chemotherapy (or radiation therapy) is instituted if relapse occurs. Such an approach prevents

a RPLND (or radiation therapy) from being performed in the 60-70% of patients who would have negative nodes and are already "cured" by the orchiectomy. Current data indicate that patients who do relapse can nearly always be treated successfully with chemotherapy at the time of first relapse, assuming patient compliance. However, patients selected for an "orchiectomy only" policy must fulfill very strict criteria relating to their clinical stage of disease, pathologic interpretation of the primary lesion, and willingness to undergo meticulous follow up.

### "Second line" treatment programs

Testis cancer which is refractory to PVB or VAB-6 programs may sometimes respond to the addition of the epipodophyllotoxin derivative, VP-16-213 (Etoposide). The combination of cisplatin with etoposide may induce second complete remissions, many of which are durable, in approximately 25-30% of patients. Also, the use of the drug ifosfamide may be able to induce second or third remissions in patients with refractory germ cell cancer.

### The extragonadal germ cell syndrome

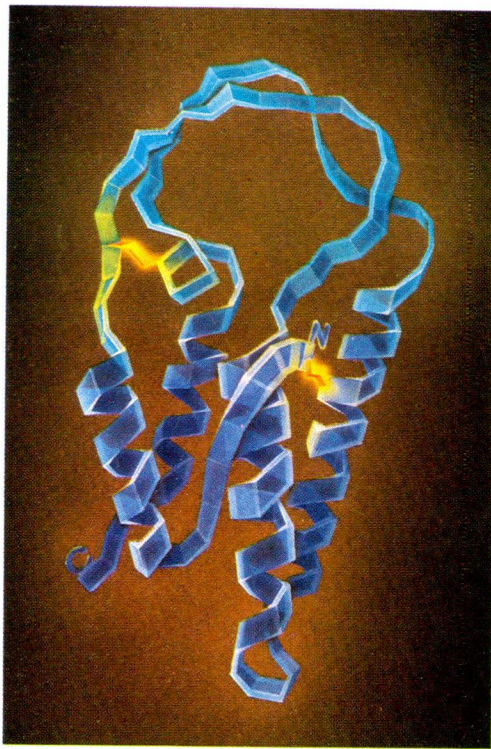
Patients who present with a large anterior, mediastinal mass, central nervous system abnormalities or retroperitoneal disease, consistent with a germ cell histology in the presence of clinically and ultrasonographically normal testes constitute the extragonadal germ cell cancers. The response to therapy is generally lower when compared to primary tes-

ticular cancer, which justifies the need for more intensive therapies. However, a proportion of these patients may be cured when treated with chemotherapy + tumor reductive surgery. In addition, patients with "undifferentiated" cancer of the mediastinum or retroperitoneum may have an unrecognized form of extragonadal germ cell cancer syndrome. Biological markers and immunohistochemical staining for AFP or hCG of the biopsy material may often provide useful clues. If positive, these patients should be treated as if they have potentially curable advanced testicular cancer.

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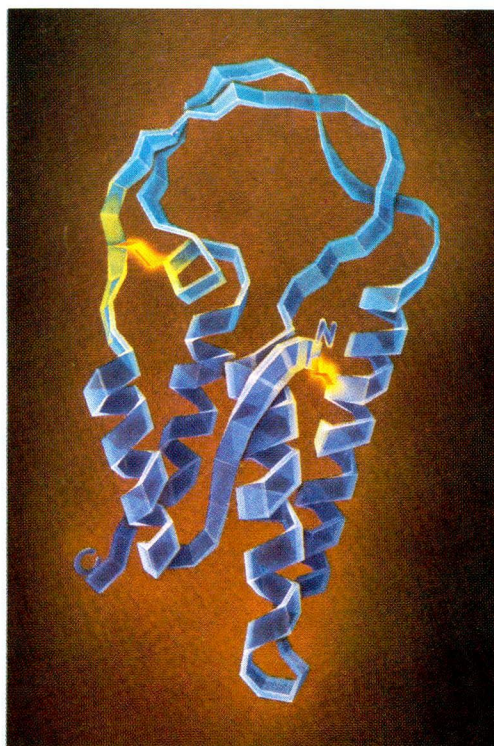
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## Tratamento Cirúrgico dos Tumores Germinativos do Testículo

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### Resumo

Os autores discutem, no presente trabalho, o papel da cirurgia dentro da estratégia global de tratamento dos pacientes com tumores germinativos do testículo. Desta forma, são abordados o tratamento da lesão primária e dos casos de violação tumoral, a importância da cirurgia nos estádios avançados dos pacientes com seminomas e tumores não-seminomatosos e as indicações para a realização de linfadenectomia retroperitoneal em estádios iniciais dos casos de tumores não-seminomatosos. Finalizam o trabalho discutindo aspectos técnicos da cirurgia neste grupo de pacientes.

**Unitermos:** tumores germinativos de testículo; orquiectomia; linfadenectomia retroperitoneal

A abordagem e tratamento dos pacientes com tumores germinativos do testículo evoluiu de forma notável após a identificação de marcadores humorais produzidos por estes tumores<sup>10,30,65</sup>, após a introdução clínica da tomografia computadorizada<sup>18,70</sup> e com o advento de esquemas quimioterápicos de grande atividade contra estas neoplasias<sup>16,59,67</sup>. Com o emprego combinado e criterioso de cirurgia, radioterapia e quimioterapia, os índices de sobrevivência de 5 anos, que antes da década de 60 situavam-se em torno de 50%, aproximam-se atualmente de 90%, transformando as neoplasias de testículo em doença consistentemente curável<sup>54</sup>.

### Planejamento terapêutico

O tratamento dos pacientes portadores de tumores germinativos do testículo baseia-se fundamentalmente em 3 parâmetros: 1) tipo histológico do tumor; 2) estadiamento do tumor; 3) níveis séricos dos marcadores tumorais, essencialmente alfa-fetoproteína e fração  $\beta$  da gonadotrofina coriônica humana.

Embora existam pequenas diferenças na história natural dos diversos tipos histológicos de tumores germinativos do testículo, estas neoplasias podem ser agrupadas sob o ponto de vista terapêutico em seminomas e tumores não-seminomatosos. Os coriocarcinomas, os carcinomas embrionários, os teratomas e os teratocarcinomas têm um comportamento biológico mais ou menos parecido e respondem de forma relati-

vamente semelhante às diferentes modalidades terapêuticas. Por este motivo, podem ser considerados em conjunto e denominados genericamente de tumores não-seminomatosos. Os seminomas, por outro lado, costumam se manifestar de forma menos agressiva e são mais radiosensíveis que os tumores não-semino-

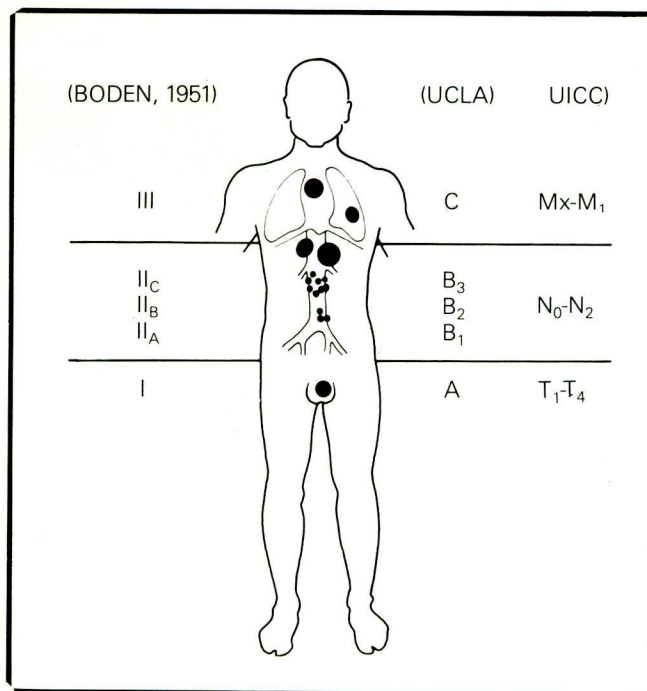
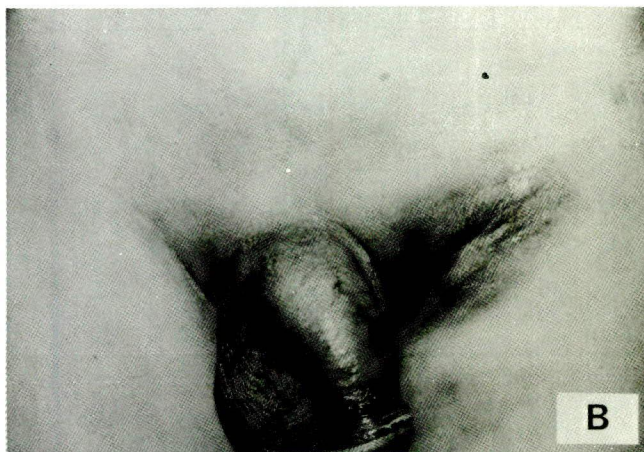


Figura 1 — Estadiamento dos tumores germinativos de testículo.

matosos<sup>1</sup>. Devem, desta forma, ser discriminados dos demais tumores germinativos.

O estadiamento das neoplasias do testículo serve para estabelecer a extensão da doença. Várias classificações foram propostas mas as mais utilizadas são aquelas apresentadas por Boden<sup>2</sup> e por Hussey e col.<sup>29</sup>, representadas na Fig. 1. De acordo com esta última classificação, que é por nós preferida, define-se: *estádio I* = tumor restrito à bolsa escrotal; *estádio II* = metástases em linfonodos abdominais (II<sub>A</sub> = metástases microscópicas em menos de 6 linfonodos; II<sub>B</sub> = metástases microscópicas em mais de 6 linfonodos ou metástases macroscópicas com menos de 2cm de diâmetro; II<sub>C</sub> = metástases macroscópicas com mais de 2cm de diâmetro); *estádio III* = tumor acima do diafragma, em linfonodos mediastinais ou pulmão e tumores metastáticos viscerais. Como veremos adiante, a seqüência terapêutica nos pacientes com neoplasias do testículo é estabelecida em função do estadiamento inicial da doença.

Os tumores germinativos do testículo apresentam a capacidade de sintetizar proteínas específicas que po-



**Figura 2** — A) Recidiva inguinal em paciente com seminoma do testículo esquerdo, tratado através de orquiectomia por via escrotal. B) Regressão completa da lesão 4 semanas após quimioterapia com VAB<sub>6</sub>.

dem ser identificadas no soro, mesmo em quantidades reduzidas. Cerca de 8% dos seminomas puros secretam gonadotrofina coriônica humana ( $\beta$ -GCH) e cerca de 85% dos tumores não-seminomatosos produzem  $\beta$ -GCH e/ou alfa-fetoproteína (AFP)<sup>30</sup>. Níveis elevados destes marcadores refletem a presença certa de tumor, mesmo quando os depósitos neoplásicos não são detectados por outros métodos. Ademais, elevação da AFP em pacientes com diagnóstico inicial de seminoma indica a existência de elementos não-seminomatosos no tumor, não identificados pelo patologista. Este achado é bastante relevante, pois estes casos devem ser tratados de acordo com o componente neoplásico mais agressivo, ou seja, com os protocolos para os tumores não-seminomatosos<sup>21,31</sup>.

### Tratamento do tumor primário

A orquiectomia representa a primeira medida terapêutica em pacientes com tumor do testículo e deve ser sempre realizada através de incisão inguinal alta. Esta abordagem permite que o tumor seja mobilizado e exteriorizado, após o clampeamento do cordão espermático, sem que haja violação dos envoltórios vaginais. A exploração da massa através de incisão escrotal é absolutamente inadequada, já que se acompanha quase sempre da abertura *in situ* do tumor com possível derramamento de células neoplásicas e recidiva local da lesão<sup>22</sup>. Este fenômeno de violação tumoral, que também ocorre em casos de biópsia transescrotal do testículo ou em casos de manipulação prévia da gônada (orquipedia, correção de hérnias), é responsável por recorrência local da neoplasia em 10% a 24% dos pacientes<sup>9,36,40</sup>. Esta recorrência manifesta-se por crescimento de tumor ao nível da cicatriz escrotal ou de gânglios inguinais (Fig. 2-A).

Alguns pacientes com doença metastática são tratados de imediato com quimioterapia antes da orquiectomia. Independente da resposta observada, estes pacientes devem ser submetidos à orquiectomia secundária, já que mesmo nos casos de clareamento completo das lesões sistêmicas, doença residual testicular é encontrada em 23% a 43% dos pacientes<sup>7,57</sup>.

Na presença de violação tumoral, torna-se necessário tratamento complementar, a fim de reduzir os riscos de recidiva local (Fig. 3). Os pacientes com doença disseminada são tratados com quimioterapia, independente do tipo histológico do tumor, de modo que eventuais depósitos neoplásicos locais são destruídos concomitantemente (Fig. 2-B). Por outro lado, nos pacientes com doença aparentemente localizada, a abordagem complementar é planejada em função da histologia do tumor primário. Nos casos de seminoma deve-se realizar irradiação escrotal e inguinal homolaterais e nos pacientes com tumores não-seminomatosos



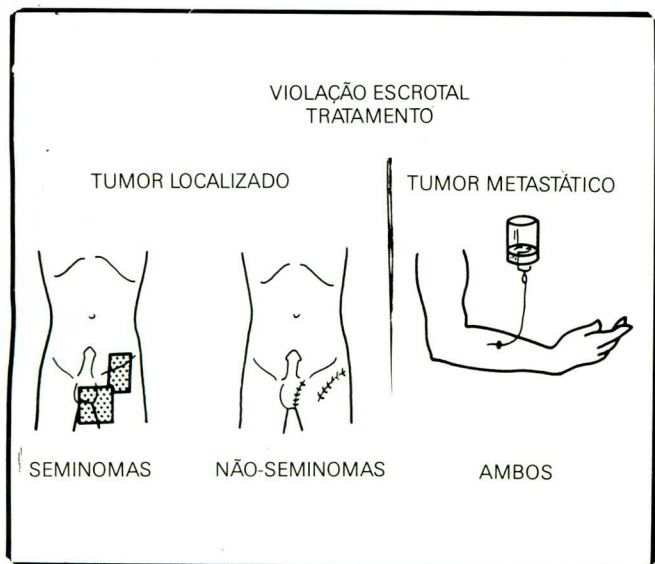


Figura 3 — Estratégia terapêutica nos casos de violação tumoral.

está indicada a resecção da cicatriz cirúrgica escrotal ou hemi-escroteciomia, associando-se linfadenectomia inguinal nos casos com linfonodos locais suspeitos (Fig. 3). Nos pacientes que puderem ser acompanhados de forma precisa e que não têm lesões suspeitas ao exame local, pode-se adotar uma orientação mais conservadora, representada por avaliações periódicas das regiões escrotal e inguinal<sup>35</sup>.

### Tratamento dos seminomas

Os seminomas puros são bastante radiosensíveis e a radioterapia representa a principal forma de tratamento profilático dos linfonodos retroperitoneais e mediastinais nos casos de doença aparentemente localizada<sup>1,18,63</sup>. Por outro lado, a grande eficiência de esquemas quimioterápicos como o VBP ou o VAB<sub>6</sub>, tornou a quimioterapia sistêmica o método preferencial de tratamento complementar em pacientes com doença disseminada<sup>24,45,60,68</sup>.

A Fig. 4 resume nossa orientação nos diferentes estádios de seminoma do testículo. Pacientes com doença em estágio I são tratados com orquiectomia seguida de radioterapia retroperitoneal, a fim de destruir eventuais metástases microscópicas em linfonodos locais, não detectadas clinicamente. A adição de radioterapia mediastinal e em área supraclavicular não aumenta a sobrevida dos pacientes em estágio I e por isto estas regiões não precisam ser irradiadas neste grupo<sup>5,63</sup>. Em pacientes com estágio II<sub>A</sub> e II<sub>B</sub> empregamos radioterapia retroperitoneal com o objetivo de tratar os depósitos metastáticos locais e irradiação preventiva do mediastino e regiões supraclaviculares. Nos casos de doença em estádios II<sub>C</sub> e III os resultados obtidos com a utilização da radioterapia são relativamente

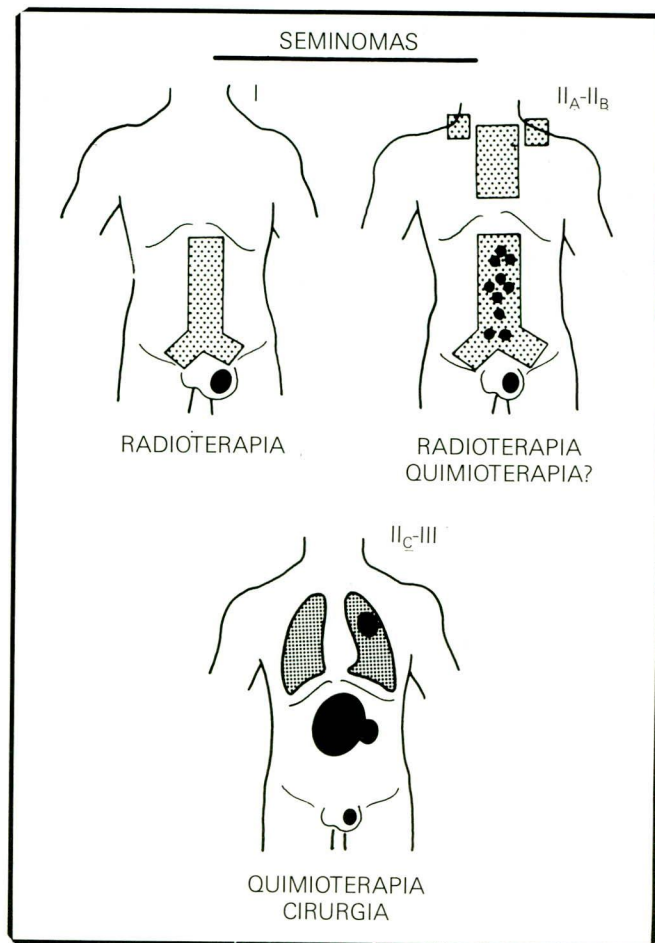


Figura 4 — Estratégia de tratamento dos seminomas.

precários<sup>5,58</sup>. Por outro lado, os seminomas são extremamente quimiossensíveis e, por isto, nossos pacientes com estádios II<sub>C</sub> ou III são tratados primariamente com quimioterapia, seguida de exploração cirúrgica nos casos com massas residuais<sup>60</sup>.

### Papel da cirurgia nos tumores em estádios I, II<sub>A</sub> e II<sub>B</sub>

Embora linfadenectomia retroperitoneal tenha sido preconizada por alguns autores nos casos de seminomas em estádios I, II<sub>A</sub> e II<sub>B</sub><sup>37,56</sup>, a evolução satisfatória dos mesmos com o emprego de radioterapia retroperitoneal e mediastinal reduziu o interesse pelo emprego da cirurgia nestes casos. A linfadenectomia retroperitoneal só está indicada nos pacientes com seminoma que apresentam níveis séricos de alfafetoproteína elevados, já que isto implica na existência de elementos não-seminomatosos, não identificados pelo patologista na lesão primária ou presentes isoladamente em depósitos metastáticos<sup>21,31</sup>. A menor sensibilidade dos tumores não-seminomatosos à radioterapia torna inadequada sua utilização neste grupo especial de pacientes.

### Papel da cirurgia nos tumores em estádios II<sub>C</sub> e III

Dentro da estratégia de tratamento dos seminomas avançados, tem-se recorrido à cirurgia no sentido de explorar a natureza de lesões residuais que persistem após a quimioterapia. Enquanto que em tumores não-seminomatosos esta abordagem é extremamente importante, como veremos adiante, nos casos de seminoma a cirurgia pós-quimioterapia talvez seja menos relevante. Em 10 pacientes com seminomas por nós explorados após quimioterapia com VAB<sub>6</sub>, não encontramos nenhum caso de câncer residual, atestando a grande sensibilidade deste tipo de tumor à quimioterapia e questionando a necessidade da intervenção nesta situação (Tabela 1). No passado, elementos não-semino-

**Tabela 1** — Resultados da exploração cirúrgica de massas retroperitoneais residuais em 30 pacientes submetidos à quimioterapia com VAB<sub>6</sub>.

Achado cirúrgico	Seminomas		Não-seminomas	
	Nº	Recorrência	Nº	Recorrência
Necrose/Fibrose	10	2 (20%)	8	1 (13%)
Teratoma Maduro	0	—	5	1 (20%)
Câncer Residual	0	—	7	7 (100%)
Total	10	2 (20%)	20	9 (45%)

matosos eram encontrados em até 44% das lesões metastáticas de pacientes com seminoma<sup>4</sup>, o que poderia acarretar falências terapêuticas ou a transformação tumoral após a quimioterapia. Estas eventualidades justificariam a exploração cirúrgica de todos os casos de massas residuais pós-quimioterapia em seminomas. É provável, contudo, que pela impossibilidade de se medir no passado os marcadores séricos, estes pacientes tenham sido incorretamente classificados como portadores de seminoma e já representassem, desde o início, tumores mistos. Atualmente, a natureza mista dos mesmos é mais facilmente reconhecida e eles são tratados como tumores não-seminomatosos. Portanto, pacientes com seminoma e massas residuais estáveis após quimioterapia podem ser acompanhados clinicamente, estando a exploração cirúrgica das lesões indicada nos casos com evidência de progressão das mesmas<sup>24,60</sup>.

### Tratamento dos tumores não-seminomatosos

Os tumores não-seminomatosos são relativamente radioresistentes e por isto não devem ser tratados primariamente com radioterapia. A abordagem terapêutica destes casos é feita através de linfadenectomia retroperitoneal ou quimioterapia sistêmica, dependen-

do do estágio clínico da doença. Embora exista atualmente alguma controvérsia quanto ao papel e momento adequado da cirurgia, a maioria dos autores acredita que a linfadenectomia retroperitoneal meticulosa representa a medida terapêutica mais importante nos pacientes com tumores limitados, enquanto que a quimioterapia constitui o principal recurso terapêutico nos casos de doença disseminada<sup>12,18,22,53,69</sup>.

A estratégia global de tratamento que adotamos em tumores não-seminomatosos está representada na Fig. 5. Pacientes em estágio I são tratados com orquiectomia seguida de observação clínica nos casos de baixo risco de envolvimento retroperitoneal ou de linfadenectomia retroperitoneal quando estes riscos são elevados. Em pacientes com estágio II<sub>A</sub> — II<sub>B</sub>, nossa orientação é a de realizar orquiectomia seguida de linfadenectomia retroperitoneal meticulosa. Nos casos de remoção completa dos linfonodos e sem evidência de doença residual (marcadores negativos e tomografia computadorizada normal), nenhum tratamento adicional é realizado. Quando ocorre remoção incompleta do tumor, estes pacientes são submetidos à quimioterapia sistêmica com VAB<sub>6</sub> por 3 ou 4 ciclos. Nos pacientes com estádios II<sub>C</sub> e III nossa conduta é a de realizar orquiectomia e, em seguida, quimioterapia intensiva com VAB<sub>6</sub>, por 3 ou 4 ciclos. Cerca de 30 dias após o término da quimioterapia estes pacientes são submetidos à exploração abdominal ou torácica, com remoção completa de todas as massas identificáveis. Nos casos com câncer residual, reinstitui-se quimioterapia com VAB<sub>6</sub> (3 ciclos) ou com a associação de VP-16, cisplatino e adriamicina (4 ciclos).

### Papel da cirurgia nos tumores em estágio I

Em pacientes com estágio I, a chance de existirem metástases microscópicas em linfonodos retroperitoneais situa-se em torno de 20%<sup>47,69</sup>, o que justifica a realização de linfadenectomia nestes casos. Como cerca de 80% dos pacientes tratados desta forma evidenciam linfonodos normais, tornando a cirurgia supérflua, alguns autores passaram a questionar o emprego rotineiro da linfadenectomia nos casos de tumores não-seminomatosos em estágio I<sup>26,44,47,48,69</sup>. Segundo estes mesmos autores, eventuais recorrências retroperitoneais da neoplasia após a orquiectomia poderiam ser tratadas com sucesso por meio de quimioterapia e desta forma 80% dos pacientes seriam poupados dos inconvenientes da linfadenectomia, ou seja, cirurgia de maior porte e infertilidade por ausência de ejaculação. Peckham e col. estudando 84 pacientes submetidos apenas à orquiectomia e seguidos por até 56 meses, observaram recorrência da neoplasia em 16 casos (19%), todos eles levados novamente a estado de remissão da doença com emprego de quimioterapia<sup>45</sup>. De forma semelhante, Johnson e col. adotando a mes-

ma orientação em 31 pacientes, constatou recidiva da neoplasia em 5 deles (16%). Com o emprego de quimioterapia, todos os casos de recorrência puderam ser resgatados, atestando a viabilidade desta orientação<sup>33</sup>. Outros estudos acompanharam-se de resultados parecidos<sup>26,44</sup> demonstrando que pelo menos em alguns pacientes, seguimento clínico rigoroso após a orquiectomia poderia ser adotado no lugar da linfadenectomia retroperitoneal.

A possibilidade de se instituir uma abordagem conservadora em pacientes com tumores não-seminomatosos em estágio I fez com que se tentasse definir fatores de risco de recorrência retroperitoneal. Desta forma, recidivas foram observadas em 43% dos casos de carcinoma embrionário e em apenas 3% dos pacientes com teratocarcinoma<sup>48</sup>. Ademais, num trabalho posterior, estes autores verificaram recorrência da doença em 75% dos pacientes com invasão vascular microscópica presente no tumor primário e em cerca de 25% dos casos sem tal fenômeno<sup>47</sup>. Moriyama e col., analisando parâmetros que pudessem prever o aparecimento de metástase, verificaram que o tamanho da lesão primária não tinha maior significado prognóstico mas que a extensão local da mesma relacionava-se com a incidência de metástases<sup>42</sup>. Assim, demonstraram que a presença de invasão do epidídimo e infiltração do cordão espermático acompanha-se de riscos muito mais elevados de recorrência da doença. Observações semelhantes foram feitas por outros estudos, que confirmaram a maior propensão ao desenvolvimento de metástases em pacientes com lesões primárias representadas por carcinoma embrionário ou que se acompanhavam de invasão vascular microscópica, ou envolvimento das estruturas adjacentes<sup>32,51</sup>.

Considerando-se as desvantagens da linfadenectomia, mas também levando-se em conta os riscos e a possibilidade de falência da quimioterapia, principalmente se eventual metástase retroperitoneal não for identificada precocemente, parece-nos razoável que os pacientes com tumores não-seminomatosos em estágio I e baixo risco de recidiva da doença sejam apenas acompanhados clinicamente após a orquiectomia ("surveillance"). Por outro lado, nos casos de maior risco de recorrências, estaria indicada a linfadenectomia retroperitoneal. Aqui incluir-se-iam as seguintes situações:

- 1) Pacientes cujo seguimento clínico após a orquiectomia não pode ser feito de forma assídua e confiável.
- 2) Persistência de marcadores séricos elevados após a orquiectomia, sem evidências de lesões metastáticas.
- 3) Adenomegalia retroperitoneal de natureza não bem definida.
- 4) Pacientes com lesão primária constituída por carcinoma embrionário puro.
- 5) Presença de invasão vascular neoplásica na lesão primária.
- 6) Neoplasias com invasão do epidídimo ou infiltração do cordão espermático.

### **Papel da cirurgia nos tumores em estádios II<sub>A</sub> e II<sub>B</sub>**

Em pacientes com estádios II<sub>A</sub> e II<sub>B</sub> o emprego da linfadenectomia retroperitoneal exclusiva acompanha-se de índices de sobrevida de cerca de 70%, aparentemente superior aos resultados da radioterapia exclusiva, onde a sobrevida se situa em torno de 45%<sup>1,12,22,53</sup>. Como cerca de 30% dos pacientes tratados cirurgicamente apresentam recidiva da neoplasia quando seguidos por 2 anos, tem-se preconizado nestes casos o emprego de quimioterapia profilática associada à linfadenectomia, com a finalidade de reduzir este risco. Apesar do aumento dos índices de cura com esta forma de abordagem combinada, existem alguns autores que preferem realizar somente a linfadenectomia retroperitoneal, com introdução posterior de quimioterapia sistêmica nos casos de recorrência da doença<sup>13,50</sup>.

De acordo com esta orientação, que se apóia na grande eficiência de quimioterapia intensiva, evitar-se-ia o emprego desnecessário de drogas quimioterápicas em cerca de 70% dos casos, que são curados exclusivamente com a linfadenectomia. Esta idéia foi corroborada por Donohue e col. num estudo que incluiu 62 pacientes, onde se observou remissão completa da doença em 96% dos casos tratados com quimioterapia profilática e em mesma percentagem de casos tratados com quimioterapia tardia, por ocasião de recidiva da doença<sup>13</sup>.

### **Papel da cirurgia nos tumores em estádios II<sub>C</sub> e III**

Dentro da estratégia de tratamento dos pacientes com tumores germinativos avançados do testículo deve ser detectado o papel da cirurgia após a quimioterapia. Este procedimento visa não somente a monitorizar os efeitos da quimioterapia, permitindo a reinstituição precoce do tratamento citotóxico nos casos de resposta incompleta, mas serve também para remover resíduos neoplásicos nesta última situação, contribuindo para o controle definitivo da doença. Até recentemente todos os nossos pacientes eram explorados cirurgicamente, mas esta orientação é atualmente adotada apenas nos casos que evidenciam lesões residuais após a quimioterapia.

Enquanto que em todos os nossos casos de seminoma a exploração destas massas revelou apenas necrose e fibrose (Tabela 1), nos pacientes com tumores não-seminomatosos o exame histológico das lesões ressecadas revelou necrose e fibrose em 40% dos casos, teratoma maduro em 25% dos pacientes e neoplasia maligna em 35% dos mesmos. Estes achados são bastante significativos, uma vez que a persistência de massas residuais após a quimioterapia não indica necessariamente falência terapêutica. Outros estudos confirmaram estas observações, atestando a im-

portância da cirurgia na monitorização dos efeitos da quimioterapia<sup>15,19,28,45,66</sup>. Apesar disto o benefício terapêutico direto da cirurgia no controle da doença é ainda controverso. Tem-se afirmado que entre 14% e 24% dos pacientes tratados apresentam neoplasia residual passível de remoção cirúrgica completa, que os torna livres de doença<sup>17,25,67</sup>. Contudo, em quase todos estes trabalhos, os pacientes considerados curados com a intervenção cirúrgica foram também tratados com quimioterapia alternativa adicional. É provável que nestes casos a cirurgia tenha tido um papel adjuvante, reduzindo a massa tumoral e aumentando a eficiência da reindução quimioterápica<sup>19,28,66</sup>.

Em resumo, cirurgia exploradora deve ser sempre feita em pacientes com tumores não-seminomatosos e massas residuais pós-quimioterapia. Quando somente necrose e fibrose é encontrada, confirma-se a remissão completa da doença e o paciente é poupado dos inconvenientes de quimioterapia adicional. Nos casos com tumor viável, pode-se melhorar a evolução do paciente com a administração precoce de quimioterapia alternativa. Finalmente, a remoção de teratomas maduros serve para prevenir complicações posteriores, já que estas lesões tendem a evoluir localmente, acarretando fenômenos compressivos indesejáveis em órgãos adjacentes<sup>38,64</sup>.

Alguns pacientes em remissão após a quimioterapia podem evidenciar, no seguimento, massas retroperitoneais sólidas. Conquanto isto represente, na maioria das vezes, recorrência da doença, deve-se lembrar que lesões benignas decorrentes de cirurgia local prévia podem simular recidiva da neoplasia. Fibrose retroduodenal resultante da manipulação local (Fig. 6) ou

linfocelos, que surgem em cerca de 3% dos pacientes submetidos à cirurgia retroperitoneal<sup>41</sup>, representam causas freqüentes de falsas recorrências. Nos casos de dúvida quanto à natureza da lesão, deve-se recorrer à cirurgia exploradora antes de se instituir quimioterapia. Obviamente, as massas benignas têm um caráter não-progressivo, que pode ser definido através de exames sucessivos e que permite, por vezes, a adoção de conduta conservadora e expectante (Fig. 6).

Sob o ponto de vista técnico, as massas retroperitoneais devem ser exploradas por via tóraco-abdominal, quando situadas acima dos vasos renais ou através de incisão abdominal mediana, quando localizadas abaixo dessa região<sup>11,39</sup>. A ressecção completa de todas as lesões visíveis é fundamental para a avaliação e remoção eficiente do tumor, já que estas massas são heterogêneas, com áreas de necrose entremeadas com outras contendo neoplasia ativa<sup>15,18</sup>. Durante a anestesia deve-se dar atenção especial às condições ventilatórias, uma vez que são freqüentes nestes pacientes graus variados de lesão pulmonar induzida pela bleomicina<sup>27,46</sup>. Neste sentido, recomenda-se que os pacientes sejam mantidos durante o ato cirúrgico com pressão parcial de O<sub>2</sub> reduzida e recebam preferencialmente soluções colóides ao invés de cristalóides, de modo a atenuar os riscos de infiltração líquida pulmonar<sup>27</sup>.

### Linfadenectomia retroperitoneal

Dois fenômenos biológicos relevantes devem ser considerados quando se planeja a linfadenectomia retroperitoneal em tumores do testículo: 1) as metástas

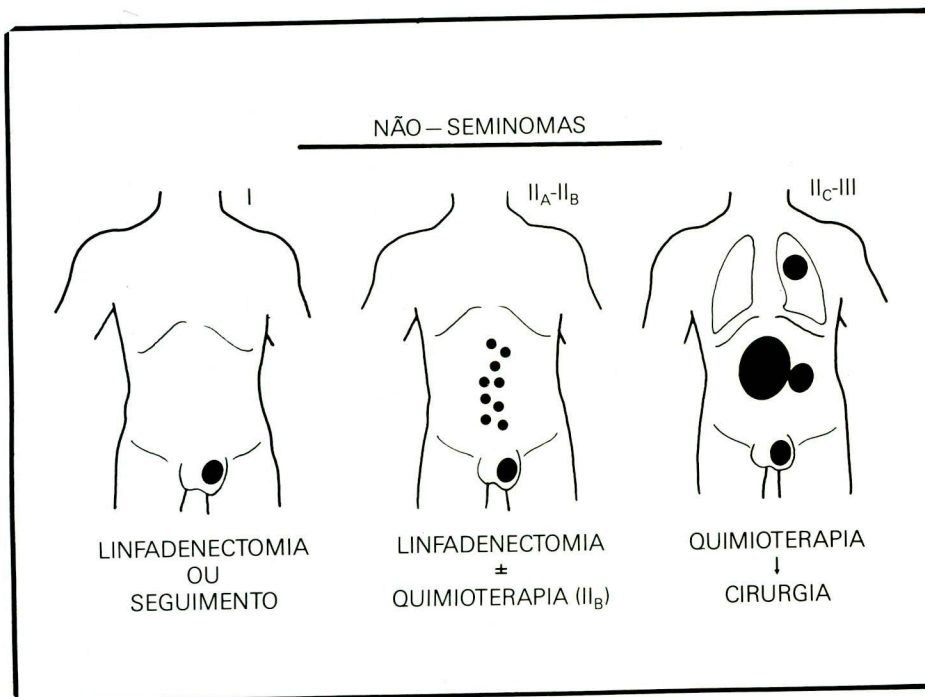
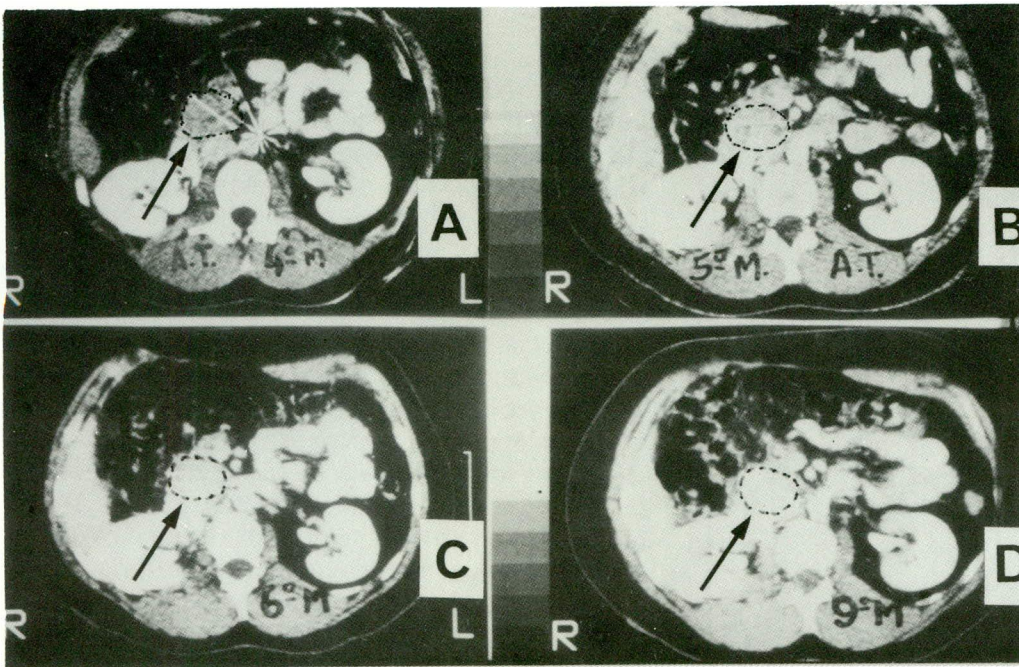


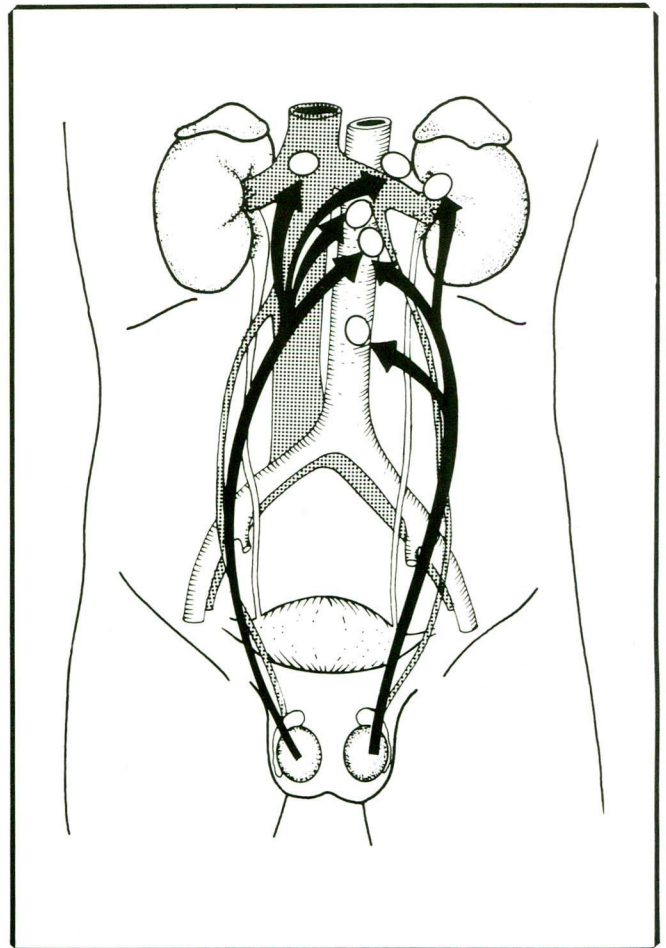
Figura 5 — Estratégia de tratamento dos tumores não-seminomatosos.



**Figura 6** — Massa fibrótica anterior à v. cava, detectada após linfadenectomia retroperitoneal (A). A natureza não-evolutiva da lesão foi confirmada por tomografias sucessivas realizadas 30, 60 e 150 dias após o primeiro exame (B, C e D).

ses ganglionares abdominais instalam-se inicialmente nos linfonodos situados na altura dos vasos renais (Fig. 7) e daí progridem cranialmente, em direção ao mediastino, e caudalmente, em direção aos vasos ilíacos<sup>52</sup>. Por isto, a linfadenectomia deve incluir, sempre e principalmente, os linfonodos localizados ao nível dos pedículos renais; 2) as metástases abdominais acometem os linfonodos que envolvem o grande vaso homolateral ao tumor. Nos tumores do lado direito as metástases retroperitoneais localizam-se principalmente em linfonodos pré-cava e inter-cava-aorta e nos tumores do testículo esquerdo as metástases situam-se em região pré-aórtica ou lateral à aorta. Ademais, em 0% a 5% dos tumores do testículo direito e em 4% a 13% dos tumores do lado esquerdo, existem metástases no hilo renal contralateral<sup>14</sup>. Por este motivo a linfadenectomia deve incluir os linfonodos situados junto ao hilo renal contralateral.

A linfadenectomia retroperitoneal é realizada comumente por 2 técnicas, a transabdominal transperitoneal<sup>11,39</sup> e a tóraco-abdominal extraperitoneal<sup>8,23</sup>. A via transabdominal tem a vantagem de permitir melhor dissecação bilateral do retroperitônio, mas tem o inconveniente de limitar a retirada dos linfonodos supra-hilares. A técnica tóraco-abdominal extraperitoneal constitui uma forma mais trabalhosa de abordagem cirúrgica, mas tem as vantagens de permitir melhor dissecação supra-hilar e de se acompanhar de menor índice de morbidade pós-operatória, já que a integridade do envelope peritoneal é preservada. Os resultados em termos de controle local da doença parecem ser semelhantes com ambas as técnicas.



**Figura 7** — Via de progressão das metástases em tumores germinativos do testículo.

Mais importante que o tipo de incisão é a maneira com que devem ser removidos os linfonodos retroperitoneais. Até recentemente a maioria dos cirurgiões realizava dissecação bilateral, com retirada de todos os gânglios situados em torno da veia cava e da aorta<sup>11,61</sup>. O inconveniente desta técnica é que cerca de 90% destes pacientes tornavam-se estéreis por aspermia decorrente de lesão das cadeias ganglionares simpáticas paravertebrais<sup>34</sup>. Numa tentativa de atenuar este problema passou-se a preconizar a realização de linfadenectomia unilateral modificada (Figs. 8 e 9), que impli-

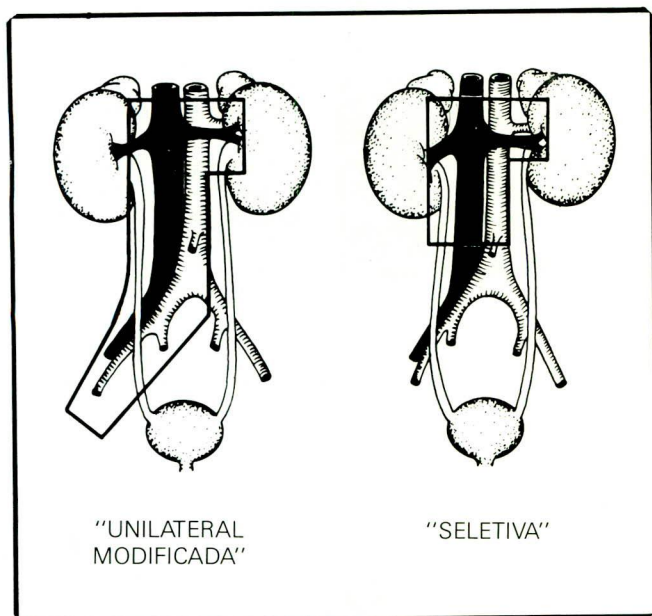


Figura 8 — Limites de dissecação das técnicas de linfadenectomia retroperitoneal.

cava na não-dissecação das estruturas situadas lateralmente ao grande vaso contralateral, de modo a se preservar a cadeia simpática no lado oposto ao do tumor<sup>23,49</sup>. Mesmo assim, cerca de metade dos pacientes ainda desenvolvia aspermia, por lesão do plexo hipogástrico, localizado logo abaixo da bifurcação da aorta. Por este motivo temos empregado atualmente uma técnica mais limitada de dissecação (Fig. 8), que envolve a retirada dos linfonodos situados na frente, atrás e entre os grandes vasos, iniciando-se a dissecação ao nível dos vasos renais e estendendo-a inferiormente até o nível da artéria mesentérica inferior (Fig. 10). Desta forma, as cadeias simpáticas paravertebrais e o plexo hipogástrico são preservados e quase todos os pacientes mantêm a ejaculação. É importante salientar que esta técnica de linfadenectomia seletiva não é tão completa sob o ponto de vista oncológico, pois a remoção dos linfonodos retroperitoneais é apenas parcial. Por isto, nos casos com envolvimento ganglionar comprovado histologicamente, instituímos quimioterapia pós-operatória, de modo a se induzir remissão completa e segura da doença e preservar a fertilidade desses pacientes. Convém enfatizar que a presença de ejaculação não assegura necessariamente fertilidade a estes casos, pois 60% a 70% dos pacientes com neoplasias do testículo têm alterações significativas na análise do fluido seminal antes do início do tratamento, o que por si só justifica quadros de infertilidade<sup>3,6,20</sup>. De qualquer forma, a manutenção da capacidade de ejaculação é relevante, já que contribui para aumentar o bem-estar destes pacientes, melhorando a qualidade de vida dos mesmos. Ademais, as alterações seminais tendem a se reverter com a retirada do tumor e remis-

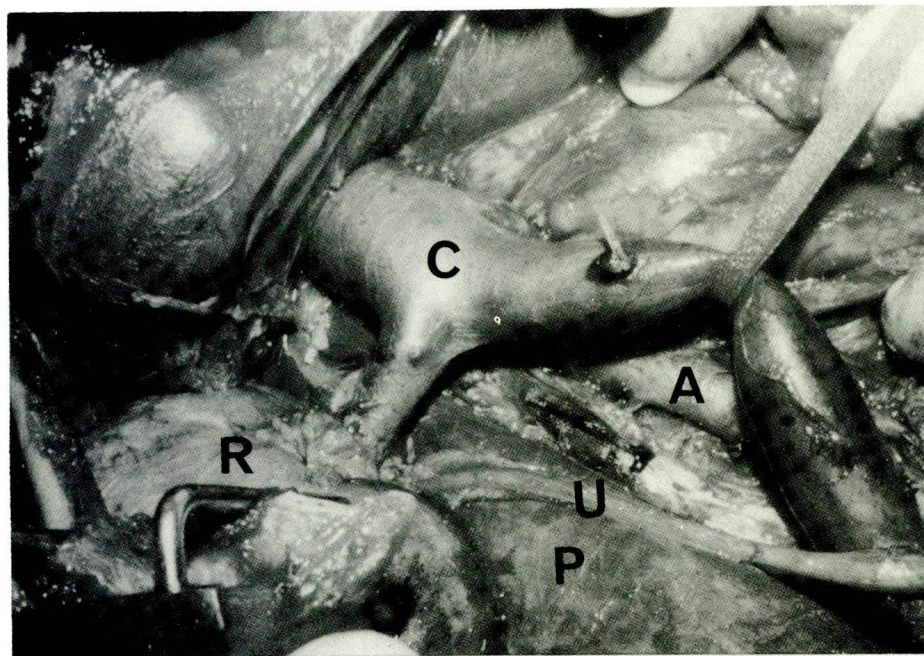
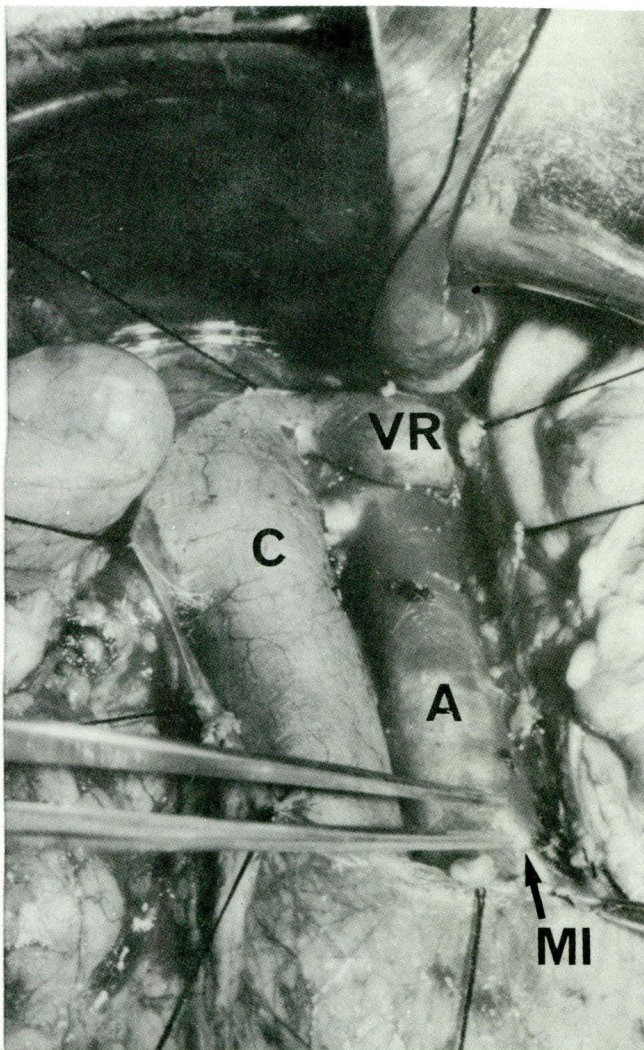


Figura 9 — Aspecto operatório de paciente com tumor do testículo direito, submetido a linfadenectomia retroperitoneal extensa (C = veia cava, A = aorta, R = rim direito, U = ureter, P = musc. psoas).



**Figura 10** — Aspecto operatório de paciente submetido a linfadenectomia retroperitoneal limitada, com dissecação circunscrita a área localizada entre os vasos renais e a artéria mesentérica inferior (C = veia cava, A = aorta, VR = veia renal esquerda, MI = art. mesentérica inferior).

são da doença. Nos pacientes com aspermia pós-operatória costumamos aguardar 2 anos e quando o problema persiste, instituímos terapêutica com imipramina (50mg 2 vezes ao dia) ou sulfato de efedrina (50mg 3 vezes ao dia), administrados no período fértil da companheira<sup>43,62</sup>. Isto reverte o quadro de aspermia em 30% a 50% dos casos.

Uma análise crítica do que foi exposto neste trabalho demonstra claramente que, juntamente com os grandes avanços que ocorreram na abordagem e tratamento dos tumores germinativos do testículo, ocorreu também um movimento no sentido de melhorar a qualidade de vida dos pacientes curados. Esta filosofia se fez sentir de forma nítida em relação ao tratamento cirúrgico destes casos, com uma clara tendência de se atenuar o número e a agressividade das intervenções, substituindo-as por uma orientação mais abrangente,

onde se destaca o papel da quimioterapia citotóxica. É auspicioso que se possa atualmente curar a maioria dos pacientes com câncer do testículo e, ao mesmo tempo, oferecer-lhes condições de vida digna e livre de sequelas.

### Summary

*In this study the authors present a critical appraisal of the role of surgery in the strategy of management of patients with germ cell testicular cancer. Special interest is directed to treatment of the primary tumor and the importance of surgery after chemotherapy in patients with advanced disease. Furthermore, a critical discussion on the role of retroperitoneal lymphadenectomy in patients with nonseminomatous tumors is presented.*

**Uniterms:** testicular germinative tumors; orchiectomy

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## BED: Uma Combinação com Etoposide, Bleomicina e Cisplatinum Efetiva em Tumores Germinativos Não-Seminomatosos Disseminados de Testículo

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### Resumo

*Um total de 21 pacientes (pts) com tumor germinativo não-seminomatoso disseminado de testículo foram tratados no período de outubro de 1981 a outubro de 1985, com uma combinação quimioterápica (BED), em que o etoposide (VP16) substituíu a vinblastina (VLB), combinado com bleomicina (BLM) e cisplatinum (DDP), com a finalidade de diminuir a toxicidade e obter melhores resultados. Remissão completa (RC) foi obtida em 15 (71%), e dos seis restantes não foi encontrado tumor viável em quatro, totalizando 19 (90%) de resposta favorável (RF); 14 (67%) permanecem vivos sem doença (SD) após 12 a 48 meses (mediana 26 meses). Nos pts com doença mínima (5) houve 100% de RC sem recidiva. Os pts com doença moderada e avançada apresentaram, respectivamente, RF de 86 e 89%, porém com SD de apenas 57 e 44%. Toxicidade pulmonar ocorreu em 3 pts no grupo com DDP precedendo BLM (16 pts). Não houve nenhum episódio de febre durante leucopenia, ou episódio de mucosite e dor muscular tão freqüentes com o uso de VLB. BED é um esquema menos tóxico, impondo-se, no entanto, a modificação da seqüência, evitando-se que a BLM seja precedida pelo DDP para prevenir novos casos de toxicidade pulmonar. A sua efetividade, semelhante aos esquemas com VLB, BLM e DDP, levam a recomendá-lo nos pts com doença mínima, devendo-se continuar a pesquisar esquemas mais efetivos quando a doença for de pior prognóstico.*

**Unitermos:** tumor de testículo; quimioterapia; etoposide.

### Introdução

Várias combinações de quimioterápicos, tendo como base o Cisplatinum (DDP), são utilizadas atualmente no tratamento de tumores germinativos não-seminomatosos (TG). Taxas elevadas de resposta completa (RC) são alcançadas obtendo-se a cura na maior parte destes pacientes<sup>1-4</sup>.

No entanto, enquanto que em pacientes com pequeno volume de doença, os tratamentos utilizados se aproximam a 100% de resposta, nos casos com massas volumosas retroperitoneais e pulmonares, independente das drogas utilizadas, os sobreviventes de longa duração não atingem 50%<sup>5-7</sup>.

Evidentemente, a questão de toxicidade passa a um papel secundário, frente à necessidade de tratamentos mais eficazes neste grupo de mau prognóstico, enquanto que nos pacientes com doença mínima, a severa mielossupressão, associada com neurotoxicidade e tox-

cidade gastrointestinal produzida por esquemas com vinblastina<sup>8, 9</sup>, deve ser reduzida com a utilização de drogas menos tóxicas e tão ou mais ativas.

Face à evidência de ação do etoposide (VP16) em TG após falha a tratamentos prévios incluindo DDP<sup>10, 11</sup>, a partir de outubro de 1981, iniciamos no Instituto Nacional de Câncer (INCa), a utilização desta droga substituindo a Vinblastina (VLB), combinada com a Bleomicina (BLM) e DDP no esquema denominado BED, com o objetivo de reduzir a toxicidade e avaliar a sua efetividade em pacientes de bom e mau prognóstico. Este trabalho visa apresentar os resultados de vinte e um pacientes tratados em um período de quatro anos.

### Material e métodos

Vinte e um pacientes com TG de testículo foram tratados com a combinação BED (Figura 1). Todos os pa-

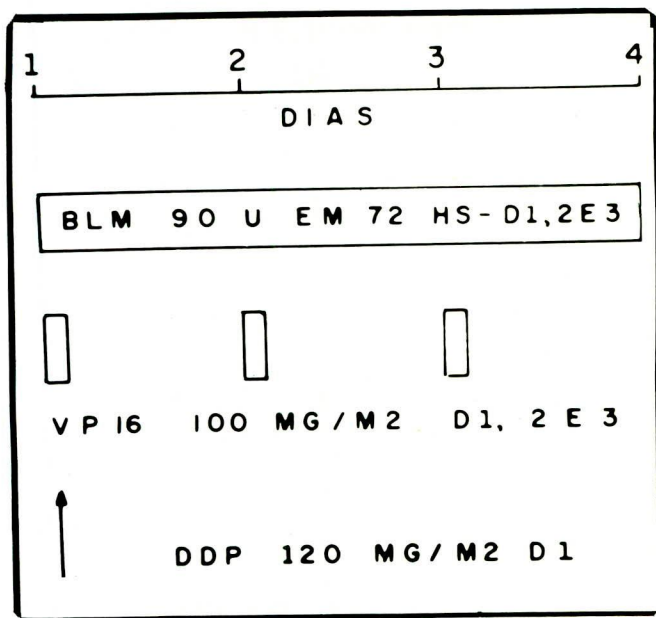


Figura 1 — BED — dose e modo de administração.

cientos receberam a quimioterapia (QT) no Serviço de Oncologia do INCa, de outubro de 1981 a outubro de 1985. Estes pacientes não haviam sido previamente submetidos à QT, e seu diagnóstico histopatológico havia sido confirmado no Serviço de Patologia do INCa. Os subtipos histológicos encontrados nesta população eram constituídos, principalmente, por Carcinoma Embrionário (CE) — 48%, sendo esta a histologia única em oito pacientes. A presença de Tumor do Seio Endodérmico (SE), um subtipo histológico considerado como tendo pior prognóstico<sup>12</sup>, foi encontrada em um terço dos pacientes, sendo associado com Teratocarcinoma (TC) em sete dos pacientes e com CE nos outros dois (Tabela 1). Somente três pacientes com seminoma (S), considerados puros pela patologia no material examinado, mas que apresentavam níveis de alfafetoproteína (AFP) elevados foram incluídos neste grupo de pacientes, face a seu comportamento similar aos TG<sup>13</sup>.

Os níveis dos biomarcadores AFP e subunidade beta da gonodotrofina coriônica humana (HCG) estavam ambos elevados em quatro pacientes, enquanto que a AFP era o único biomarcador em 10 pacientes e a HCG em cinco. Em sete pacientes havia elevação da desidrogenase láctica (DHL).

Todos os pacientes foram avaliados com dosagem de AFP, HCG e DHL. Radiografia em PA e perfil e tomografia linear de tórax, tomografia computadorizada ou ultra-sonografia de abdome e pélvis foram realizadas em todos os pacientes, e caso os exames abdominais fossem normais, linfangiografia bipedal era executada. A partir desta avaliação era feito o estadiamento de acordo com classificação de extensão de doença da Universidade de Indiana<sup>5</sup> (Tabela 2). Nenhum pa-

Tabela 1 — Histologia

Histologia	Pacientes	(%)
Seminoma com AFP elevada (S)	3	14
Carcinoma embrionário (CE) ± S ± SE	10	48
Teratocarcinoma (TC) ± SE	7	33
Teratoma maligno (TM)	1	5
Tumor do seio endodérmico (SE)*	7	33
Total	21	

\*Cinco pacientes com TC e 2 com CE

Tabela 2 — Classificação de Indiana de extensão de doença

#### Mínima

1. HCG e/ou AFP elevados apenas
2. Linfonodos cervicais (± linfonodos retroperitoneais impalpáveis)
3. Doença retroperitoneal irressecável, impalpável
4. Metástases pulmonares mínimas — menos que cinco por campo pulmonar e a maior < 2cm (± doença abdominal impalpável)

#### Moderada

5. Massa abdominal palpável isolada
6. Metástases pulmonares moderadas — cinco a dez por campo pulmonar e a maior < 3cm, ou massa mediastinal < 50% do diâmetro intratorácico, ou metástase pulmonar solitária > 2cm (± doença abdominal impalpável)

#### Avançada

7. Metástases pulmonares avançadas — mais que dez por campo pulmonar, ou múltiplas > 3cm, ou massa mediastinal > 50% do diâmetro intratorácico (± doença abdominal impalpável)
8. Massa abdominal palpável + metástases pulmonares
  - 8.1 — pulmonar mínima
  - 8.2 — pulmonar moderada
  - 8.3 — pulmonar avançada
9. Metástases hepáticas, ósseas, ou SNC

ciente apresentava estádios iniciais com doença ressecável.

Antes do início de cada ciclo de QT era realizada avaliação da função renal, com dosagem da uréia e creatinina e avaliação hematológica, sendo necessárias contagem de granulócitos maior que 2.000/mm<sup>3</sup>, e de plaquetas maior que 100.000/mm<sup>3</sup> para reiniciar a QT.

Nos primeiros 16 pacientes a QT consistiu de DDP 120mg/m<sup>2</sup> de área de superfície corporal, endovenosa, no dia 1 de cada ciclo, VP16 100mg/m<sup>2</sup> EV nos dias 1, 2 e 3, e BLM 30U em infusão contínua, por 24 horas, nos dias 1, 2, e 3 (Figura 1). Os cinco pacientes subsequentes receberam DDP no quarto dia de cada ciclo após a infusão de BLM, face a alta incidência de toxicidade pulmonar observada com a primeira seqüência.

Vigorosa hidratação e diurese forçada por Manitol foi utilizada no dia da administração do DDP. Os ciclos de QT eram repetidos a cada três a quatro semanas, na dependência da recuperação da depressão medular. No mínimo, eram administrados quatro ciclos de QT, sendo dois ciclos após a remissão completa, ou da estabilização da doença com biomarcadores normais, quando os pacientes eram encaminhados à cirurgia.

As respostas ao tratamento foram consideradas como completas (RC), quando houve desaparecimento de toda a evidência de doença incluindo a normalização dos biomarcadores. Os pacientes que apresentaram redução inicial de sua doença com a instituição da QT, com normalização dos biomarcadores e estabilização da resposta com a continuação do tratamento, foram levados à cirurgia, sendo considerados como tendo resposta favorável (RF) o conjunto dos pacientes com RC e os que não apresentaram tumor viável, sendo encontrado teratoma maduro ou fibrose. O achado de tumor viável nos pacientes com 50% ou mais de redução da doença mensurável constituiu resposta parcial (RP).

As sobrevidas global e livre de progressão de doença foram calculadas atuarialmente utilizando o método de Kaplan-Meier<sup>14</sup>. A duração da sobrevida foi calculada a partir do início do tratamento. Comparação das curvas de acordo com a extensão de doença foi baseada no teste estatístico generalizado não-paramétrico de Gehan<sup>15</sup>.

## Resultados

A idade mediana deste grupo de pacientes com TG era 31 anos (variação 16 a 45). O seguimento mediano de todos os grupos e dos sobreviventes foi de 26 meses, sendo o seguimento mínimo dos sobreviventes de 12 meses.

Os resultados produzidos pelo tratamento BED neste grupo de 21 pacientes são mostrados na Tabela 3. Ocorreu remissão completa (RC) em 15 pacientes (71%). Dois pacientes com doença avançada vieram a falecer com insuficiência respiratória após dois e quatro ciclos de quimioterapia. A causa mortis foi, respectivamente, embolia pulmonar e fibrose pulmonar secundária a BLM, não havendo evidência de doença maligna residual em ambos. Estes dois óbitos não foram excluídos da análise de sobrevida, sendo considerados no grupo de RC.

Os seis pacientes restantes apresentaram RP, com negatificação dos biomarcadores e estabilização da doença, sendo então levados à cirurgia. Em somente dois foi encontrado tumor viável constituído de SE. Em dois pacientes foi encontrado apenas tumor necrótico e em dois teratoma maduro. O grupo de pacientes com RC e os quatro sem malignidade nas lesões residuais

**Tabela 3** — Resposta ao tratamento

	Pacientes	(%)
Resposta favorável (RF)	19	90,5
Resposta completa após QT (RC)	15	71,4
Achados cirúrgicos	6	
Tumor necrótico	2	33,3
Teratoma maduro	2	33,3
Tumor viável	2	33,3
Vivos sem doença*	14	66,7
Mortos sem doença	2	09,5
Mortos com doença	5	23,8

\*Um paciente resgatado com alta dose de DDP

foram considerados como tendo RF, que foi obtida, portanto, em 90% dos pacientes.

Três pacientes (20%) com RC recidivaram, sendo que um foi resgatado com altas doses de DDP e VP16, permanecendo sem evidência de doença 18 meses após o segundo tratamento. Os outros dois faleceram de doença, sendo que em um deles a recidiva ocorreu apenas no cérebro, estando controlada a doença fora do sistema nervoso central. Dos pacientes com RP, sem malignidade nas lesões residuais, apenas um, com teratoma maduro, recidivou posteriormente, vindo a falecer com doença. As falhas ocorreram 7, 8, 9 e 11 meses após o início do tratamento.

A resposta máxima ao tratamento ocorreu após dois ciclos de quimioterapia, tendo todos os pacientes recebido pelo menos dois tratamentos depois deste ponto. Apenas um paciente recebeu um quinto ciclo de BED, sem BLM, devido à incerteza quanto a sua estabilização de doença após o segundo ciclo.

A sobrevida global atuarial (SGA) em 48 meses foi de 51% (Figura 2) e a sobrevida livre de progressão de doença (SLP) no mesmo período foi de 61% (Figura 3).

Cinco pacientes apresentavam doença mínima (MN), sete doença moderada (MD) e nove doença avançada (AV). Houve um predomínio da histologia com CE puro (6 pacientes) no grupo com AV (Tabela 4).

Todos os pacientes com MN apresentaram RC, sem nenhuma recidiva posterior. Por outro lado, os com MD e AV apresentaram respostas significativamente piores que os com MN. Um total de 57% dos com MD e 67% dos com AV tiveram RC. Três de cada grupo foram à cirurgia, sendo encontrado SE em um paciente de cada estágio, e teratoma maduro em dois pacientes com MD e tumor necrótico em dois com AV. Portanto, 86% dos pacientes com MD e 89% dos com AV apresentaram RF. Um terço dos pacientes com RF no grupo com MD recidivaram, enquanto que isto ocorreu em 50% nos com AV. Assim, 44% dos pacientes com AV e 57% dos com MD estavam vivos sem reci-

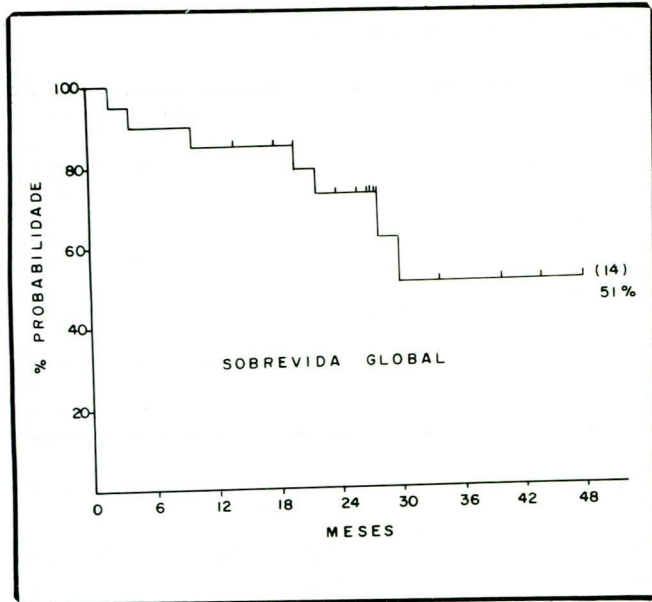


Figura 2 — Sobrevida global atuarial de todos os pacientes.

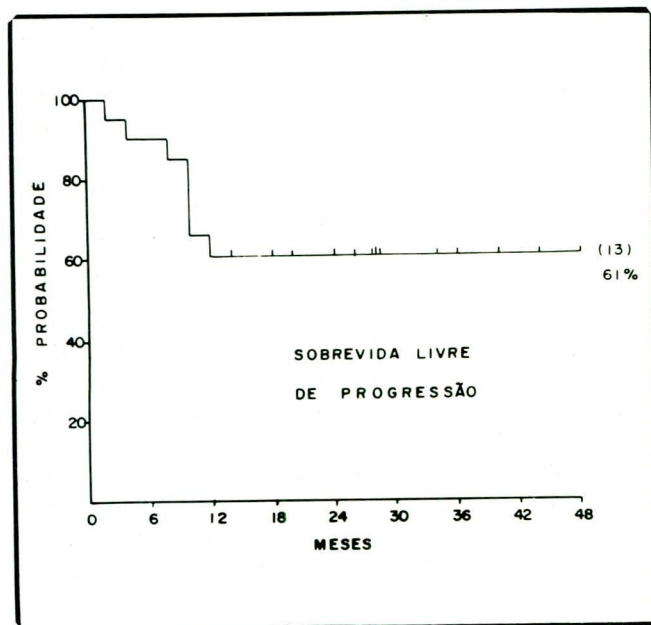


Figura 3 — Sobrevida livre de progressão de todos os pacientes.

diva no momento da análise (Tabela 5). As SGA dos pacientes com MN, MD e AV foram, respectivamente, 100, 42 e 43% (Figura 4) e as SLP foram, respectivamente, 100, 57 e 44% (Figura 5). A diferença entre a SLP dos pacientes com MN comparada com os MD e AV foi estatisticamente significativa ( $p = 0,05$  e  $0,03$ ).

Os pacientes com CE apresentaram 90% de RF, no entanto neste grupo encontravam-se os dois óbitos, o que, acrescido do paciente que recidivou com metástase cerebral, levou a produzir apenas 60% de sobreviventes sem doença. A presença de SE em sete pacientes não levou a piores resultados que no grupo com

TC como um todo, com 71% de respostas favoráveis e de sobreviventes sem recidiva em ambos (Tabela 6).

Todos os pacientes apresentaram leucopenia severa com contagem de granulócitos menor que  $500/\text{mm}^3$  durante a maioria dos ciclos. No entanto, não ocorreu episódio de febre durante granulocitopenia. A contagem de plaquetas não foi menor que  $50000/\text{mm}^3$  em nenhum dos ciclos, não havendo sangramento secundário a trombocitopenia. Não ocorreu estomatite ou toxicidade gastrointestinal como ocorre com o uso da VLB. A náusea e vômito produzidos pelo DDP foram controlados na maioria dos pacientes com o uso de dexametasona e altas doses de metoclopramida ( $2\text{mg}/\text{kg}$ ), porém persistindo náusea e inapetência moderada por cerca de uma semana após a quimioterapia. Quatro pacientes (19%) desenvolveram moderada elevação de creatinina sérica, sendo a mais elevada  $3,2\text{mg}\%$ . Apenas um manteve níveis séricos de creatinina elevada após o término do tratamento. Três des-

Tabela 4 — Extensão de doença por histologia

Histologia	Extensão	Pacientes	(%)
Carcinoma embrionário	Mínima	2	20
	Moderada	2	20
	Avançada	6	60
Teratocarcinoma	Mínima	3	43
	Moderada	3	43
	Avançada	1	14
Seio endodérmico	Mínima	2	28,5
	Moderada	2	28,5
	Avançada	3	43

Tabela 5 — Resposta por volume de doença

Volume de doença	Resposta	Pacientes	(%)
Mínima	RC	5	100
	SP	5	100
Moderada	RC	4	57
	RF	6	86
	SP	4	57
Avançada	RC	6	67
	RF	8	89
	SP	4	44

Abreviaturas: RC, resposta completa; RF, resposta favorável; SP, sem progressão

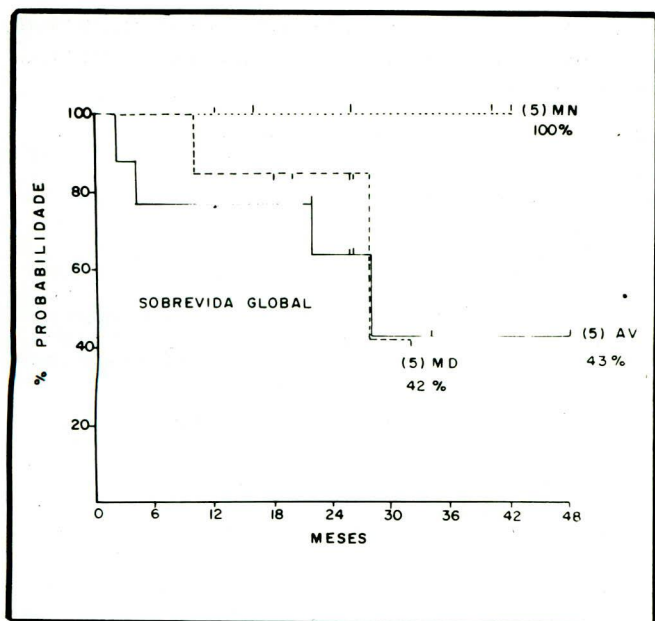


Figura 4 — Sobrevivência global atuarial de acordo com a extensão da doença. Abreviações: MN, doença mínima; MD, doença moderada; AV, doença avançada.

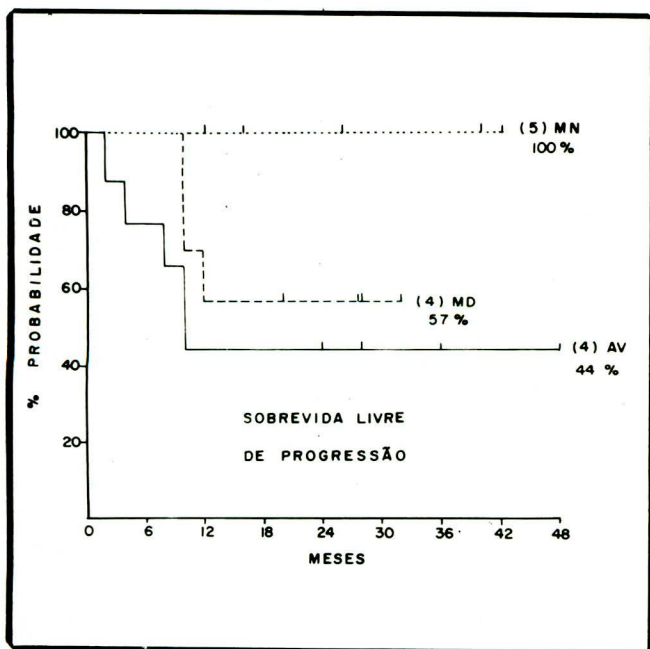


Figura 5 — Sobrevivência livre de progressão de acordo com a extensão da doença. Abreviações: MN, doença mínima; MD, doença moderada; AV, doença avançada.

tes pacientes desenvolveram infiltrado intersticial pulmonar, compatível com toxicidade pulmonar por BLM, com um óbito. Os dois sobreviventes tornaram-se assintomáticos apesar de persistir alteração radiológica pulmonar. A maioria dos pacientes apresentou certo grau de neurotoxicidade pelo DDP, caracterizado por discreta parestesia das mãos e pés, que regrediu após

Tabela 6 — Resposta por histologia

Histologia	Resposta	Pacientes	(%)
Carcinoma embrionário	RF	9	90
	SP	6	60
Teratocarcinoma	RF	5	71
	SP	5	71
Seio endodérmico	RF	5	71
	SP	5	71

Abreviaturas: RF, resposta favorável; SP, sem progressão

alguns meses. Um paciente apresentou ototoxicidade com discreta diminuição persistente da audição.

## Discussão

Desde 1981, quando iniciamos este estudo, vários trabalhos têm surgido na literatura, apresentando modos diversos de redução da toxicidade da quimioterapia nos TG. A redução da dose de VLB para 0,3mg/kg<sup>2</sup>, bem como a substituição do VLB por vincristina (VCR)<sup>4</sup> ou por VP16<sup>3, 16</sup>, foi associada com resultados semelhantes e significativa redução da toxicidade.

Nossos resultados demonstram a grande efetividade da combinação BED nos pacientes com bom prognóstico (MN). A obtenção de 100% de RC sem falhas posteriores e ausência de quadros de febre durante granulocitopenia, a falta de neurotoxicidade e de toxicidade gastrointestinal cumprem, integralmente, os objetivos deste estudo, neste subgrupo de pacientes.

A utilização da classificação da Universidade de Indiana neste grupo apresentou resultado diverso do publicado por Birch<sup>5</sup>, em que os pacientes com MD, tratados com a combinação de VLB, BLM e DDP, apresentaram resultados semelhantes aos com MN. O nosso grupo com MD comportou-se de modo idêntico ao com AV. Não temos justificativa para esta discordância face ao nosso pequeno número de casos, mas que apresentavam, na sua maioria, massas abdominais muito grandes, que em outras classificações, como na de Samuels, seriam consideradas de mau prognóstico<sup>17</sup>.

Os pacientes com doença moderada e avançada, que constituíam 76% do nosso material, apresentaram resposta inferior, pois apesar de uma taxa de 87,5% de RF, somente 50% permaneceram vivos sem recidiva. Como dois pacientes faleceram durante o tratamento em CR, na verdade, apenas quatro pacientes recidivaram. Um destes pacientes foi resgatado com altas doses de DDP, como já descrito<sup>18</sup>, permanecendo sem doença até o momento, e sugerindo a possibilidade do

uso deste recurso como tratamento inicial nos pacientes com mau prognóstico, o que já vem sendo realizado com resultados preliminares promissores<sup>19, 20</sup>.

Foi observada alta taxa de toxicidade pulmonar por BLM. Três pacientes no grupo inicial de 16 (18,7%) apresentaram esta complicação, com um óbito. Houve associação com níveis elevados de uréia e creatinina e, provavelmente, com a utilização do DDP precedendo a BLM, como foi mostrado previamente<sup>21, 22</sup>. Por este motivo, os pacientes subseqüentes receberam DDP no quarto dia do ciclo, após a infusão de BLM, no sentido de evitar-se um aumento de nível sérico de BLM, secundário à diminuição de sua excreção renal por ação tóxica aguda do DDP.

Com base neste estudo, nossos pacientes com doença mínima continuam sendo tratados com BED, de modo a se obter um número maior que confirme este resultado. Os pacientes com MD e AV, de pior prognóstico, estão sendo tratados prospectivamente com altas doses de DDP, associado a VCR, VP16 e BLM, com a intenção de aumentar o índice de cura, e reavaliar a existência de diferenças entre MD e AV.

## Summary

*A total of 21 patients (pts) with nonseminomatous germ cell tumors of testis have been treated from October 1981 to October 1983, with a drug combination (BED) using etoposide (VP16) substituted for vinblastine (VLB), in combination with bleomycin (BLM) and cisplatin (DDP), in order to decrease toxicity and get better results. Complete remission (CR) was obtained in 15 (71%), and there was no residual disease at surgery, in 4 of the remaining 6 pts, with a favorable response (FR) in 19 (90%); 14 pts (67%) have remained alive without disease (WD) for 12-48 months (median 26 months). Pts with minimal disease (5) presented 100% of CR without relapse. Pts with moderate and advanced disease presented FR: 86 and 89%, with only 57 and 44% remaining WD, respectively. Three pts presented lung toxicity in the group with DDP preceding BLM (16 pts). There was no episode of leukopenic fever or mucositis and muscle pain so frequent with VLB. BED is less toxic, but change of the sequence, avoiding the use of DDP preceding BLM is necessary, in order to prevent new cases of BLM lung toxicity. Its effectivity, similar to regimens with VLB, BLM and DDP, recommend BED*

*to pts with minimal disease, as well as to evaluate more effective combinations when dealing with poor prognosis disease.*

**Uniterms:** testis tumors; chemotherapy; etoposide

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## Controvérsias no Tratamento dos Estádios I e II dos Tumores de Células Germinativas Não-Seminomatosos do Testículo

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### Introdução

O câncer de testículo é uma doença rara, sendo identificados 5000 casos novos por ano nos Estados Unidos. Apesar de representar somente 1%<sup>1</sup> de todos os tumores masculinos o câncer de testículo tem sido matéria de constante atenção por vários fatores:

1. Ocorre num grupo etário bastante jovem com a maioria dos pacientes apresentando de 15 a 35 anos de idade.
2. É uma das poucas neoplasias produtoras de marcadores séricos de fácil identificação. Estes colaboram não só no estabelecimento do diagnóstico como também na avaliação quantitativa em resposta ao tratamento.
3. É capaz de uma notável transformação biológica. Pode passar de um carcinoma metastático e agressivo, como o carcinoma embrionário, a um tipo não metastático e de crescimento lento como o teratoma.
4. Acima de tudo é um câncer curável na vasta maioria dos casos através de diferentes modalidades de tratamento.

### Patologia

Os tumores malignos de testículo têm origem nas células germinativas em 90% dos casos. Johnson publicou dados obtidos de 2562 pacientes, de diferentes séries, onde em média, 42% dos tumores de testículo

eram seminomas, 26% eram carcinomas embrionários, 26% teratocarcinomas, 5% teratomas e 1% coriocarcinomas<sup>2</sup>. Devido a uma particular sensibilidade dos seminomas à radioterapia, com conseqüências óbvias ao seu manejo, é usual separar-se os tumores de testículo entre seminomas e não-seminomatosos.

Os marcadores séricos produzidos pelos tumores de células germinativas não-seminomatosas (TCGNS) são a alfa-fetoproteína e o beta-HCG. A alfa-fetoproteína é encontrada nos hepatomas e nos tumores de células germinativas não-seminomatosas do testículo. Ali é produzida por células dos seios endodérmicos. É encontrada em 70% dos casos de carcinoma embrionário ou teratocarcinomas. A meia vida da AFP é de aproximadamente 5 dias. Desta forma se uma queda nos níveis séricos de AFP não estiver ocorrendo, de acordo com sua meia vida, no período pós-orquiectomia, doença metastática deve ser contemplada. A alfa-fetoproteína não está jamais aumentada nos casos de seminoma.

O beta-HCG possui subunidades alfa e beta. A subunidade alfa é similar às unidades alfa do LH, FSH e TSH, com possibilidade de reações cruzadas ocorrerem nos testes de radioimunoensaio. A subunidade beta difere daquela encontrada em outros hormônios, sendo sua identificação mais específica ao HCG, oferecendo assim grande utilidade ao manejo dos TCGNST. O beta-HCG é encontrado por sua vez em torno de 40 a 60% dos TCGNST, com uma meia vida de 24h. Assim

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como a AFP, se após orquiectomia os níveis séricos do B-HCG não estiverem diminuindo de acordo com sua meia vida, doença metastática está presente. A AFP e/ou B-HCG estão presentes em 85% dos pacientes com câncer de testículo.

### Estadiamento

Os métodos utilizados para o estadiamento dos tumores de testículo incluem história, exame físico, raio X de tórax, tomografia computadorizada de tórax (TC) e de abdome, AFP,  $\beta$ -HCG e LDH. A linfangiografia de membros inferiores é obtida em alguns casos especiais e não é considerada um teste de rotina no estadiamento desta doença.

O estágio I é a doença limitada ao testículo; o estágio II é a doença presente no abdome. É subdividido em estágio IIa quando a doença é microscópica, detectável somente por marcadores séricos positivos e com TC de abdome e tórax normais. O estágio IIb apresenta nódulos grosseiramente aumentados, identificáveis na TC de abdome, mas o tumor não é palpável. Estádio IIc representa massa abdominal palpável. O estágio III indica a presença de doença acima do diafragma (como metástases pulmonares ou supraclaviculares) assim como metástases ósseas, hepáticas e cerebrais.

### O manejo do estágio I dos TCGNST

Se após a orquiectomia o paciente apresentar raio X de tórax e TC de abdome negativos e marcadores séricos normais, é classificado no estágio I. O tratamento convencional para estágio I dos TCGNST tem sido orquiectomia seguida de dissecação dos linfonodos retroperitoneais (DLNRP). Esta abordagem produz curas em torno de 100% dos casos<sup>3</sup>.

Com o advento dos métodos mais sofisticados para o estadiamento, incluindo marcadores séricos, TC e linfangiogramas, em paralelo à disponibilidade de quimioterapia altamente eficaz, vários investigadores passaram a questionar a necessidade da DLNRP obrigatória após orquiectomia<sup>4,5,6,7</sup>. Nós nos propomos a revisar e criticar os dois métodos de tratamento.

A dissecação dos linfonodos retroperitoneais é um procedimento extenso envolvendo a remoção dos nódulos desde os hilos renais até a bifurcação das artérias ilíacas, podendo ou não também incluir a remoção de linfonodos supra-hilares. O procedimento permite o estadiamento patológico e, de fato, 15 a 35% dos estádios clínicos I tornam-se estádios patológicos II<sup>9</sup>. A cirurgia, quando executada por mãos experientes, é segura, com uma mortalidade praticamente ausente. A maior complicação da DLNRP é a impotência ejaculatória, que afeta 70-100% dos pacientes<sup>8</sup>.

A fim de exemplificar resultados desta cirurgia po-

demos analisar os resultados de um estudo realizado na Universidade de Indiana entre 1973 e 1978. Cento e trinta e seis pacientes nos estádios I e II foram tratados com orquiectomia e DLNRP. Não houve mortes secundárias à cirurgia e o período mínimo de seguimento foi de 2 anos. Sessenta e três pacientes tinham doença no estágio I. Houve 5 recidivas após a DLNRP (7,9%). Todos estes doentes receberam quimioterapia com PVB  $\pm$  Adriamicina, entrando em remissão completa, estando curados. Setenta e três pacientes foram encontrados no estágio patológico II. Tais pacientes receberam terapia pós-operatória de acordo com os padrões da época. Assim 30 pacientes receberam 1 a 2 anos de manutenção com actinomicina D. Treze outros doentes receberam PVB e os 30 doentes restantes não receberam terapia alguma. Houve uma morte por câncer e outra morte por causa diversa. Somente 3 pacientes recidivaram no retroperitônio (2,6%) entre os 116 pacientes operados em Indiana. Dos pacientes com recidiva 80% apresentaram doença mínima (marcadores séricos somente ou pequenas metástases pulmonares)<sup>3,11</sup>.

Impotência ejaculatória secundária à DLNRP apresenta-se como o maior problema nestes pacientes jovens submetidos à cirurgia. Por causa disto os limites do campo cirúrgico têm sido modificados em vários centros médicos, de maneira a limitar a dissecação e evitar o dano aos plexos simpáticos, fator causal da impotência ejaculatória após a cirurgia. A dissecação de linfonodos retroperitoneais modificada é executada em pacientes com nódulos de aparência normal. Pacientes com nódulos grosseiramente aumentados requerem dissecação radical.

DLNRP modificada preserva a ejaculação em 75-90% dos pacientes<sup>12,13</sup>. Wissbach relata 36 pacientes tratados desta maneira com recidiva de 12%, o que não é diferente das recidivas em pacientes tratados por dissecação radical. Ainda neste estudo 75% dos pacientes não apresentaram problemas ejaculatórios<sup>13</sup>.

Desde sua introdução nos anos 70, quimioterapia com cisplatino é capaz de resgatar e curar 100% daqueles doentes que recidivam com doença mínima<sup>11</sup>. Por causa disto muitos autores têm se sentido seguros em tratar pacientes com estágio I somente com orquiectomia e observá-los cuidadosamente, sem outra terapia<sup>4,5,6,14,15,16,17</sup>. Pizzocaro<sup>7</sup> recentemente compilou dados de várias séries de pacientes tratados sem DLNRP. Tais pacientes eram estadiados com história, exame físico, raio X de tórax, TC de tórax e de abdome, linfangiografia e marcadores séricos. Após a orquiectomia os pacientes eram seguidos mensalmente durante o primeiro ano. A cada visita tinham um raio X de tórax, marcadores séricos e raio X de abdome até o desaparecimento do contraste do linfangiograma, que ocorria em média entre 6 a 12 meses do exame. A partir de então TCs de abdome eram obtidas a cada 2 me-



ses. No segundo ano as visitas eram a cada dois meses e TCs de abdome eram obtidas a cada 3 a 4 meses.

Nos pacientes tratados com orquiectomia e observação as recidivas ocorreram em 16 a 40% dos casos, em sua maioria presentes no retroperitônio. O tempo de recidiva foi em média 4,7 meses após a orquiectomia, sendo 90% dos casos observados nos primeiros 8 meses.

A maior crítica aos trabalhos de observação é feita ao curto período reportado. O período mínimo de observação variou de 2 a 6 meses, que é mais curto que o tempo requerido para o aparecimento de recidiva. Quando o período de observação foi estendido, a incidência de recidiva aumentou para até 40%. Um outro fato importante é que muitas das recidivas ocorreram com doença volumosa no retroperitônio, apesar do seguimento sistemático e correto. E espera-se que alguns destes doentes não sejam curados, o que fica difícil de avaliar, pois vários dos pacientes em recidiva ainda recebiam terapia por ocasião das publicações, não se sabendo do resultado final do tratamento naqueles doentes. Contudo, dentre os pacientes computados naquelas séries, houve somente uma morte por doença progressiva após quimioterapia. Os demais pacientes estavam ou em remissão completa ou em tratamento.

Orquiectomia seguida por observação em pacientes com estágio I é um método potencialmente perigoso se executado de maneira imperfeita. É formalmente contra-indicado nos pacientes que não possam ter entendimento do problema, que venham a ter seguimento incerto, ou que estejam sendo tratados em locais que não tenham fácil e pronta obtenção dos métodos laboratoriais necessários para o seguimento.

Deve ser mais uma vez lembrado que a cura de 100% com quimioterapia é obtida naqueles doentes que recidivam com doença mínima. Pacientes recidivando com doença volumosa, o que não é incomum no grupo tratado sem DLNRP, terão uma maior mortalidade.

Finalmente se enfatiza uma vez mais que os resultados aparentemente não desfavoráveis apresentados nas séries há pouco relatadas foram obtidas em centros médicos especializados, com uso de protocolos rígidos, onde a obtenção de tomografias computadorizadas, linfangiogramas e outros métodos laboratoriais eram facilmente obtidos. Certamente o uso de orquiectomia seguida por observação em práticas privadas e centros menores e menos equipados trará resultados diferentes daqueles apresentados.

A filosofia de tratamento de TCGNS em estágio I na Universidade de Indiana, considerada padrão também em grande parte de outros centros, é de que estes pacientes sejam tratados com orquiectomia seguida de DLNRP, se possível com técnica modificada. Esta abordagem leva a índices de cura sem paralelo no tratamento do câncer, com mortalidade muito pequena e evitar-

do-se terapia sistêmica. Estádio patológico II é prontamente identificável e tratável de maneira adequada com DLNRP, que é curativa na grande maioria dos casos. A esterilidade foi um problema de alta incidência no passado, mas o uso de dissecação modificada faz com que ocorra somente numa minoria dos pacientes sem diminuir os índices de cura. As vantagens de seguir os pacientes mensalmente com raio X de tórax e marcadores séricos incluem a simplificação do método mantendo-o seguro e mais barato, podendo ele ser facilmente executado na comunidade.

### Quimioterapia adjuvante no estágio II e TCGNST

O índice de recidivas após DLNRP é proporcional ao volume inicial de doença no retroperitônio. Em pacientes com estágio IIa (doença microscópica) o índice de recidiva é de 25%; no estágio IIb (mais de 6 metástases microscópicas ou nódulos aumentados entre 2-6cm) é de aproximadamente 40%, e no estágio IIc as recidivas variam entre 75 a 100%<sup>18</sup>. Devido à alta incidência de recidivas o estágio IIc é tratado com quimioterapia, não sendo foco desta discussão.

Em muitos centros médicos os estágios IIa e IIb têm sido tratados com DLNRP seguido de quimioterapia adjuvante. Com a disponibilidade de terapia eficaz e tendo tais pacientes sido submetidos à dissecação retroperitoneal passou-se a questionar a necessidade de quimioterapia adjuvante<sup>19,20</sup>.

Entre 1979 e 1985, 213 pacientes foram tratados no "Intergroup Testicular Study", onde várias instituições colaboraram a fim de comparar quimioterapia adjuvante versus observação com resgate quimioterápico por ocasião da recidiva pós DLNRP, em estágio II. Cento e noventa e cinco pacientes foram considerados para avaliação.

Todos os pacientes foram tratados com orquiectomia seguida de DLNRP. Logo após, os pacientes eram casualmente assinalados a receber quimioterapia com PVB ou VAB, versus observação mensal com quimioterapia, sendo dada somente aos casos apresentando recidiva. O tempo médio de seguimento foi de mais de 4 anos (2,5-5,5).

Noventa e sete pacientes foram designados a receber terapia adjuvante com PVB ou VAB, dependendo da instituição, a cada 4 semanas, por dois cursos. Seis pacientes recidivaram (6%). Destes, 5 nunca chegaram a receber quimioterapia devido à recidiva logo após a cirurgia. O sexto paciente foi tratado com DLNRP modificada apesar de apresentar doença metastática grosseira no retroperitônio, em violação ao protocolo. Ele recebeu PVB, mas posteriormente progrediu e morreu.

Noventa e oito pacientes foram seguidos sem terapia adicional após DLNRP. Quarenta e oito pacientes (49%) recidivaram e, em sua maioria, receberam terapia apropriada. Cinco pacientes morreram neste gru-

po. O primeiro paciente recusou completar o tratamento, dois outros tiveram progressão da doença e os dois restantes morreram de causas não relacionadas ao câncer de testículo. Foram curados 93/98 pacientes.

Neste estudo 189/195 pacientes (97%) estão vivos e sem evidência de doença. Também ficou documentado que dois cursos de quimioterapia adjuvante são altamente efetivos na prevenção de recidivas seguidas a DLNRP, em estádios IIa e IIb de TCGNST. Ao mesmo tempo se observou que, apesar do alto índice de recidiva no grupo da observação, aproximadamente 100% dos doentes são resgatáveis e curados por quimioterapia. Não houve diferença significativa no índice de cura ou mortalidade causada por câncer entre os dois grupos.

Em condições de cirurgia, seguimento e quimioterapia ideais, nós acreditamos que quaisquer das abordagens, quimioterapia adjuvante ou observação com quimioterapia na recidiva são métodos de tratamento efetivos e equivalentes. Em nossa instituição o assunto é discutido em detalhes com o paciente pouco antes de sua alta pós-DLNRP, sendo a escolha do método dada ao doente, dando-se ao mesmo tempo a certeza que a cura é esperada em 100% dos casos.

O câncer de testículo é uma doença fascinante pelas múltiplas maneiras que pode se apresentar, proporcionando um desafio à equipe médica que aborda o problema. A cooperação interdisciplinar, a boa relação médico-paciente com entendimento do processo e o uso apropriado das eficazes táticas de tratamento, permitem que sejam alcançados os altos índices de cura nesta doença, sem par na oncologia.

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**REVISTA BRASILEIRA DE CANCEROLOGIA, 33 (1)**  
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### VII JORNADA DE ONCOLOGIA ONCO-APM 88

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A VII Jornada de Oncologia Onco-APM 88 será realizada na Associação Paulista de Medicina — Avenida

Brigadeiro Luiz Antonio, 278, São Paulo — de 17 de agosto a 16 de novembro/88.

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#### ATUALIZAÇÃO EM CÂNCER GINECOLÓGICO PROGRAMA

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17/8/88 — 4ª-feira: 20h30m:

Presidente da Sessão: Dr. David Chvindelman  
LAPAROSCOPIA NOS TUMORES GENITAIS  
MALIGNOS

Prof. Bernardo Bitelman (F.M.U.S.P.)

TUMORES GENITAIS MALIGNOS DA INFÂNCIA E ADOLESCÊNCIA

Prof. Álvaro da Cunha Bastos (F.M.U.S.P.)

19/10/88 — 4ª-feira: 20h30m:

Presidente da Sessão: Dra. Suely Karaguelian  
Alperovitch

BASES FISIOLÓGICAS DA ANALGOTERAPIA  
EM GINECOLOGIA

Dr. Abraham Hamaoui (Hospital Santa Catarina)

SARCOMAS DO ÚTERO

Prof. Moses Zitron (Hosp. A.C. Camargo e F.M. Itajubá)

21/9/88 — 4ª-feira: 20h30m:

Presidente da Sessão: Prof. David Alperovitch  
CÂNCER DA VAGINA

Prof. José Focchi (Escola Paulista de Medicina)

NEOPLASIAS TROFOBLÁSTICAS GESTACIONAIS

Prof. Caetano Giordano (E.P.M. e F.C.M. Santa Casa — SP)

16/11/88 — 4ª-feira: 20h30m:

Presidente da Sessão: Prof. Paulo Merochmetchenko

TRATAMENTO CIRÚRGICO DO CÂNCER DA MAMA

Dr. Nassif Alexandre Galeb Jr. (Soc. Bras. Mastologia)

HEMOPATIAS MALIGNAS NA GRAVIDEZ

Profa. Nair Sumie Mori

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#### CIRURGIA MAMÁRIA ESTÉTICO-TERAPÊUTICA PROGRAMA

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DATA: 30 de setembro de 1988 — Sexta-feira

10h30m: Sessão I: Moderador: Dr. David Chvindelman

Definição da Mama de Alto Risco — Dr. Fausto F. Baracat

Tratamento Conservador versus Radical com Reconstrução no Câncer Mamário — Dr. João Sampaio Góes Júnior

Abordagem da Mama oposta e Mastectomia Subcutânea — Dr. Orlando Lodovici

Planificação e Correção estética do Tratamento Conservador no Câncer Mamário — Dr. Ewaldo Bolivar Souza Pinto

Seleção e preparo da paciente para a Reconstrução Mamária — Dr. José Marcos Mélega

Reconstrução da Placa aréolo-mamilar — Dr. Juarez Avelar

Discussão.

13h: Almoço

14h: *Sessão II*: Moderador: Dr. Raul Loeb  
Reconstrução Mamária com Próteses e/ou Expansores — Dr. Rolf Gemperli  
Reconstrução Mamária com retalho do músculo Latissimus Dorsi — Dr. Antonio Carlos Abramo  
Reconstrução Mamária com retalho de músculo reto abdominal — Dr. Munir Miguel Curi  
Reconstrução Mamária em casos especiais — Dr. João Carlos Sampaio Goes  
Complicações na Reconstrução Mamária com retalho do músculo reto abdominal — Dr. Edward Merlin Keppke  
Discussão

16h: Café

16h15m: Painel: Como eu faço Reconstrução Mamária  
Moderador: Dr. João Carlos Sampaio Góes

**LOCAL:** Auditório Aché — Ônibus às 8h no Hosp. Santa Catarina

Os médicos sócios da APM, de qualquer especialidade, estão isentos da taxa de inscrição. Para médicos não-sócios da APM a taxa de inscrição é de Cz\$ 1.000,00 e para residentes, estagiários e acadêmicos de medicina é de Cz\$ 500,00.

Serão conferidos certificados aos participantes presentes a 3/4 das reuniões. Maiores informações pelos tels.: 231-0960/231-4363/ com Dra. Suely K. Alperovitch.

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## II CONGRESSO IBERO-AMERICANO DE ONCOLOGIA

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Será realizado no Centro de Convenções da Bahia, de 9 a 14 de outubro de 1988, o II Congresso Ibero-Americano de Oncologia, sob o patrocínio da Sociedade Brasileira de Cancerologia.

O evento, de natureza multidisciplinar, tem o objetivo de reunir oncologistas de língua portuguesa e espanhola — congregando 21 países das três Américas,

da Espanha, de Portugal e Colônias Africanas para possibilitar o intercâmbio de informações e solução de problemas comuns.

Com base em estimativa do I Congresso realizado na Espanha, em 1985, espera-se para este a presença de 1800 participantes.

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## CINQUENTENÁRIO DO INSTITUTO NACIONAL DE CÂNCER

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Em comemoração ao Cinquentenário do Instituto Nacional de Câncer — INCa — será realizado, no período de 27 a 30 de novembro de 1988, no Copacabana Palace Hotel, Rio de Janeiro, RJ, o Simpósio "PERSPECTIVAS EM ONCOLOGIA", que contará com a presença de especialistas brasileiros e estrangeiros ligados às áreas clínica e de pesquisa, abordando os seguintes temas: Biologia Molecular em Câncer: Oncogênese e Retrovírus; Anticorpos Monoclonais: Diagnóstico, Terapêutica; Fatores de Crescimento e Aplicações em Oncologia; Imagem em Oncologia; Imunoterapia: Interleucinas; Câncer Inicial de Mama, Perspectivas; Novos Agentes Quimioterápicos; Cirurgia Reconstructora em Câncer; Tumores Germinativos; Sequelas do Tratamento do Câncer na Infância; Transplante de Medu-

la Óssea; Infecção no Hospedeiro Comprometido; Patologia dos Sarcomas; Dor no Paciente Oncológico; Epidemiologia do Câncer no Brasil; Suporte do Paciente Oncológico; Câncer de Pulmão; Radiobiologia.

Como parte integrante do Cinquentenário serão realizados Cursos, no Centro de Estudos e Ensino do INCa, cuja programação é a que se segue:

### GINECOLOGIA

Tema

EXPERIÊNCIA DO INCa NO TRATAMENTO CIRÚRGICO DO CÂNCER GINECOLÓGICO

Local — INCa

Vagas — 100

Coordenação — Maria Luiza Pessoa Cavalcanti

Data — 26 e 27 de Maio



# INFORMAÇÕES AOS COLABORADORES

A Revista Brasileira de Cancerologia tem por finalidade publicar artigos originais que contribuam para o conhecimento sobre o câncer e ciências afins. Publica também artigos para as seções de Atualização, de Revisão e de Notas e Informações. Aceitam-se também matérias encaminhadas como Cartas ao Editor.

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- . Sumário com Unitermos
- . Texto
- . Agradecimentos
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Ex.: Kroeff M. Câncer e Gravidez. Sarcoma da parede abdominal com várias recidivas ligadas a gestações. Rev. Bras. Cancerol. 1947; 1: 31-41.

Hersh EM, Mavligit GM, Gutterman JU. Immunodeficiency in cancer and the importance of immune evaluation of the cancer patient. Med. Clin. North Am. 1976; 60: 623-639.

– *Livros*

Eisen HN. Immunology: an introduction to molecular and cellular principles of the immune response. 5th ed. New York: Harper and Row, 1974: 406.

– *Capítulo de livro*

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Comunicações pessoais, trabalhos em andamento e inéditos não devem ser incluídos na lista de referências bibliográficas, mas citados em nota de rodapé.

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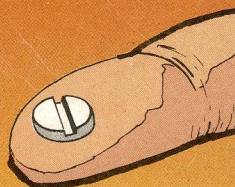
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