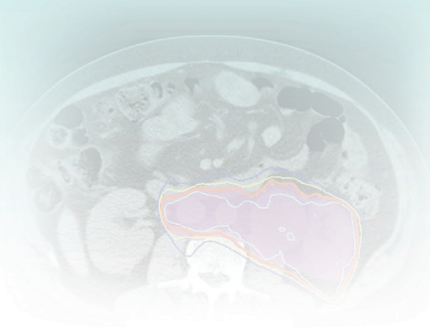
CHAPTER

55 Testicular Cancer



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INCIDENCE

In men 15 to 35 years of age, testicular cancer represents the most frequently diagnosed malignancy but overall only 1% of all malignant tumors. In 2008, 52,000 new cases and 9000 deaths were estimated worldwide from this disease

BIOLOGIC CHARACTERISTICS

Isochromosome 12p is present in more than 80% of cases.

STAGING EVALUATION

After a history and physical examination is undertaken, serum tumor markers, including alpha-fetoprotein (AFP), β-human chorionic gonadotropin (β-HCG), and lactate dehydrogenase (LDH) is important for further assessment.

Imaging should include chest radiography and computed tomography (CT) scan of the abdomen and pelvis. CT scan of the thorax may be omitted in patients with seminoma with normal abdominopelvic CT but is otherwise usually included. Other imaging modalities such as magnetic resonance (MR) and positron emission tomography (PET) scans are not routinely included for staging patients.

PRIMARY AND ADJUVANT THERAPY

Radical inguinal orchiectomy allows pathological subtyping, enables appropriate management, and is also the initial treatment for testicular cancer.

Seminoma

Stage I seminoma has overall survival (OS) rate of almost 100%. There are three main management options with resultant differing relapse rates. Surveillance is the preferred option, with a 15% relapse rate, whereas adjuvant therapy, with either retroperitoneal irradiation or carboplatin chemotherapy, has a 5% relapse rate. Similarly, stage II seminoma has a 5-year OS of 97%. Radiation therapy (RT) for stage IIA or IIB disease, with a 10% relapse rate, and cisplatin-based chemotherapy for stage IIC disease, with a <5% relapse rate are commonly employed as treatment options. For stage III seminoma, the 5-year OS is approximately 85% and cisplatin-based chemotherapy is the preferred treatment option.

Non-Seminoma

Stage I non-seminoma has a 99% 5-year OS. The main treatment options include surveillance with a 30% relapse rate, retroperitoneal lymph node dissection (RPLND) with a 10% relapse rate, and adjuvant chemotherapy (most often given only for high-risk patients) with a 1% relapse rate.

For stage II non-seminoma, the 5-year OS is ~98%. Stage IIA disease is managed with cisplatin-based chemotherapy alone or RPLND plus chemotherapy (both <5% relapse rate), and stage IIB or IIC disease is managed with cisplatin-based chemotherapy, with a 5% relapse rate. Stage III disease is managed with chemotherapy.

Patients with metastatic germ-cell tumors have been divided into good-prognosis, intermediate-prognosis, and poor-prognosis groups based on anatomic spread and elevated level of serum tumor markers. The *good-prognosis group* (60% of cases) has an approximately 86% OS. These patients have a primary tumor of the testis or retroperitoneum, no visceral metastases (except for pulmonary metastases), and low tumor marker levels (AFP, <1000; β-HCG, <5000; and LDH, <1.5 ULN). The *intermediate-prognosis group* (26% of cases) has an approximately 80% OS. These patients have a primary tumor of the testis or retroperitoneum, no visceral metastases (except pulmonary metastases), and AFP levels of 1000 to 10,000, or β-HCG levels of 5000 to 50,000, or LDH levels of 1.5 to 10 ULN. In the *poor-prognosis group* (14% of cases), the OS is around 50%. A primary tumor of the mediastinum is present, or nonpulmonary visceral metastases are found, or tumor marker levels are high (AFP >10,000; β-HCG >50,000; LDH >10 ULN).

Testicular cancers are uncommon in the general population but are one of the most common and important malignant tumors in young men. Worldwide, 52,000 new cases and 9000 deaths were estimated for this disease in 2008.[1] More than 95% of testicular cancers are primary germ cell tumors (GCTs); the others include lymphomas and sarcomas. The incidence of GCTs has doubled in the past 30 years. Although the majority (70% to 80%) present with early-stage and at the same time highly curable disease, the continued rise in incidence of these tumors presents a challenge in these relatively young men most of whom are in the prime of their lives. As with most cancers, specific management is based in part on histologic subtype but more importantly on disease extent. Advances in chemotherapy, imaging, and adoption of multidisciplinary care have led to continued improvements from a potentially deadly disease to the paradigm of the curable cancer over the past three decades. In this chapter, we will discuss the management principles for patients with primary GCTs of the testis, malignant extragonadal GCTs, and other rare testicular tumors.

ETIOLOGY AND EPIDEMIOLOGY

Testicular cancer accounts for only 1% to 2 % of all cancers in men in most populations across the world.[2] Germ cell testicular tumors are the most common solid malignant tumors in men between 20 and 35 years of age, projections for the United States for 2015 were that 8430 new cases would occur with 380 deaths.[3] The cumulative lifetime risk of developing a GCT for a white man in the United States is 0.2%.[4] Although the disease

is rare, the observed rising incidence is a concern. Between 1973 and 2003 the incidence of GCTs rose by 61% in the United States, with the major rise occurring in seminomas rather than non-seminomas.[5]

The age distribution of testicular cancer is similar in all populations of European origin. There is a small peak in early childhood at around 2 years of age, with rates then remaining low until 15 years of age. There is a second peak in young adults at around 25 to 40 years of age, and the rate then declines, with a small peak again between 65 and 75 years of age. Testicular cancers occurring in childhood and in the young adult years are usually GCTs, whereas those occurring after age 65 years are principally nongerm cell malignant tumors, mainly lymphomas. Nonseminomatous tumors are more common in childhood and in young men between 15 and 30 years of age, whereas seminomas present on average 1 decade later (at 25 to 40 years of age).

Risk factors for testicular germ cell cancer (TGCC) include a family history of cancer, the presence of an undescended testis or gonadal dysgenesis, subfertility, and testicular microlithiasis. Men with a history of cryptorchidism have an approximately sixfold increased chance of developing testicular cancer.[6] Orchiopexy before puberty appears to lower the risk of developing a subsequent tumor and may help preserve Leydig cell function and enhance fertility.[7,8] Although most testicular cancers in men with a history of maldescent occur on the ipsilateral side, approximately 5% to 20% develop in the contralateral testicle.[6] The mechanism by which cryptorchidism increases the risk of developing GCTs is unknown, but the effects of maldescent on the testis (e.g., increased temperature or increased risk of trauma if the testis is in the inguinal region) have been suggested as possible factors. The increase in the incidence of tumors in the contralateral testicle, however, suggests that maldescent and testicular cancer may result from the same prenatal etiologic process. Other genitourinary abnormalities associated with testicular cancers include hydrocele and hypospadias.[9]

There is considerable geographic and ethnic variation in the incidence of testicular tumors, with the highest incidence being reported from Denmark (8.4 per 100,000 men per year) and Switzerland (6.2 to 8.8 per 100,000 men per year).[2] The incidence of testicular cancer is lower in non-Europeans as compared with Europeans. In the United States, white men (6.36 per 100,000 per year) are five to six times more likely to develop testicular cancers than black men (1.30 per 100,000 per year); low incidence rates are seen in other ethnic groups, such as Americans of Chinese and Japanese descent.[5] A high incidence of testicular cancer is seen in some nonwhite populations such as the Maoris in New Zealand and Native Americans.[10]

Prior testicular cancer is a major risk factor for the development of a contralateral malignant tumor. In a large population-based follow-up study of 29,515 patients with unilateral testicular cancer, the cumulative risk (at 15 years after diagnosis of the primary tumor) of developing a contralateral malignant tumor was 1.9%.[11]

Heritability of Testicular Germ Cell Cancer

The racial disparities in persons who develop GCTs and the association with other urogenital abnormalities strongly suggest a genetic susceptibility to this disease. In support of this hypothesis, GCTs are among the most heritable of all cancers. Several studies estimate the risk to brothers and fathers of patients with TGCC to be 4 to 6 times increased and 8 to 10 times increased, respectively. This is far greater than the twofold elevated risk of first-degree relatives in other cancers, such as cancers of the breast or colon or melanoma. The relative risk is much greater in monozygotic and dizygotic twins. In addition, brothers and fathers of patients with bilateral tumors have a risk 3.9 and 4.7 times greater, respectively, than relatives of patients with monozygotic tumors.

Given the strong familial association of TGCC, extended pedigrees with this disease are curiously rare. Most families with TGCC have two affected members, most commonly sibling pairs. The International Testicular Germ Cell Linkage Consortium has carried out two large-scale genome scans, neither of which provided convincing or replicable evidence for susceptibility gene(s).[12] Candidate association studies have demonstrated that rare gr/gr deletions of the Y chromosome predispose to TGCC, but such deletions cannot explain more than a fraction of heritable cases of this disease.

More recently, two groups carried out association studies, based on genome-wide, single-nucleotide polymorphisms (SNPs), of patients with TGCC and controls.[13,14] Both research groups identified strong evidence for two susceptibility loci for seminoma and non-seminoma; one locus is on chromosome 12p22, within the *KITLG* gene, encoding the ligand for the receptor tyrosine kinase KIT, and the second locus is on chromosome 5q31.3 near the *SPRY4* gene, encoding sprouty 4, an inhibitor of the MAP kinase pathway. A third locus on chromosome 6 was identified by only one of the research groups and is not associated with a known gene. The relative risk was approximately 3 for the *KITLG* locus and about 1.4 for the other two loci. Both the *KITLG* gene and the *SPTY4* gene are biologically feasible candidates because their products lie in the same signal transduction pathway. Moreover, activating mutations of the *KIT* gene have been identified in a subset of seminomas, while paradoxically, deletions of the *KIT* gene predispose to germ cell cancer in the SV/129 mouse strain. Of note, cases in the association studies included patients with and patients without a family history of TGCC, but none of these loci were enriched in the familial cases and neither were they associated with other abnormalities such as an undescended testis.

As mentioned previously, the SV/129 mouse strain is particularly susceptible to the development of germ cell cancer, and this system has been exploited by Nadeau et al[15] to map several genes predisposing to the disease. Curiously, none of the corresponding loci in humans appear to have any role in TGCC development.

In summary, TGCC is a highly heritable disease, and at least two loci may contribute to its risk in the general population. Despite almost two decades of studies, however, no gene has yet been identified in families with this disease, suggesting that the genetic underpinnings of TGCC may be highly heterogeneous or novel, or both.

Environmental Factors and Testicular Germ Cell Cancer

Other factors linked to the development of TGCCs include a history of testicular trauma, an increased body mass index, immunosuppression following organ transplantation, and human immunodeficiency virus (HIV) infection.[2,16-18] There is no evidence to suggest a causal relationship between testicular trauma and the development of a tumor, and the likely explanation is that testicular trauma leads to examination of the testes. Because of the age distribution of testicular cancer, exposure must occur early in life if there is an environmental contribution to the etiology of these tumors. Prenatal factors linked to the later development of testicular cancers include threatened miscarriage, excessive maternal nausea, and birth by caesarean delivery.[2] To explain these associations it has been suggested that exposure of the germinal epithelium in utero to an elevated level of free unbound maternal estrogen

could give rise to subsequent cryptorchidism and an elevated risk of developing a testicular tumor; the prenatal estrogen theory remains unproven, however.[2]

PREVENTION AND EARLY DETECTION

The identification of carcinoma in situ (CIS) or testicular intraepithelial neoplasia (TIN) as a precursor of testicular GCTs has raised the possibility that the development of invasive testicular cancer could be prevented by treating CIS. In adults, CIS is found adjacent to GCTs in virtually 100% of cases, and it is thought that, with the exception of spermatocytic seminoma, CIS precedes the development of all invasive tumors.[19] The natural history of testicular CIS is unknown, but the Danish experience suggests that all cases of adult CIS will ultimately progress to invasive cancer.[19]

The diagnosis of testicular CIS can only be made by testicular biopsy. Because the incidence of CIS in the general population is low (at most, 0.7%), screening biopsies are currently not recommended. They should be considered in high-risk patients, however, including those with presumed extragonadal germ cell cancer, intersex individuals, and select patients with contralateral GCT (age <40 years and testicular volumes of <12 mL).[20]

The management of patients with testicular CIS is controversial. Orchiectomy has been suggested for unilateral disease, and in cases diagnosed after orchiectomy for GCT, three options can be considered and discussed with the patient: orchiectomy, low-dose RT, or surveillance.[20] Although both orchiectomy and RT offer definitive treatment for testicular CIS, they both destroy any residual fertility. Surveillance, with careful follow-up of the affected testis, is a reasonable option, especially given the excellent prognosis for metachronous testicular cancers.[21]

Testicular self-examination has been advocated for the early detection of invasive tumors, but its usefulness is unproven. There is no evidence to indicate that a population-based screening program would be of benefit; however, there is a need for education about the early signs and symptoms of testicular cancer to reduce delay at diagnosis. The optimal follow-up schedule for patients with unilateral testicular GCTs and those with cryptorchidism, both of whom have a risk of approximately 2% to 5% of developing a future testicular cancer, is unclear, but a yearly testicular ultrasound examination from age 15 years would seem reasonable.

BIOLOGIC CHARACTERISTICS AND MOLECULAR BIOLOGY

GCTs have a distinctive capacity for totipotential differentiation as demonstrated by the frequent finding of combinations of choriocarcinoma, embryonal carcinoma, and seminoma in a single tumor. They also can retain their ability to differentiate as displayed by the not infrequent identification of mature teratoma in residual posttreatment retroperitoneal masses. Cytogenetic analysis of GCTs has shown that chromosome numbers are more homogenous in seminomas than in non-seminomas.[22-24] Triploid and tetraploid chromosomal patterns are common in seminomas, and hyperdiploid to hypertriploid counts are common in non-seminomas. A characteristic chromosome anomaly in GCTs of all histologic types is the presence of an isochromosome of the short arm of chromosome 12.[25] This isochromosome, first reported by Atkin and Baker in 1982,[22] consists essentially of two chromosome 12 short arms. It is present in more than 80% of cases, and GCTs without a 12p isochromosome have extra copies of 12p segments incorporated into other chromosomes. The 12p isochromosome is also found in testicular CIS.[25] Isochromosome copies tend to be more numerous in non-seminomas than in seminomas.

The study of the genetics and molecular biology of GCTs has enhanced our understanding of these tumors.[23,26,27] To date, however, cytogenetics has had little impact in the clinic, with the possible exception of the use of various markers for the identification of non-TGCCs located elsewhere in the body.[28-30]

PATHOLOGY AND PATHWAYS OF SPREAD

Pathology

Testicular cancers can arise from intratesticular and paratesticular cells (Box 55-1). The vast majority is of germ cell origin, and three major classification schemes have been in use worldwide[31-33] (Table 55-1). The Dixon and Moore classification as modified by Mostofi has been adopted by the World Health Organization (WHO) and is the classification scheme most widely used in North America.[34]

For clinical purposes, GCTs are classified into two major groups: seminomas and non-seminomas (NSGCTs). It should be noted that patients with pure seminoma may have relapse with pure NSGCT, and vice versa. Approximately 60% of GCTs are pure seminomas, 30% are NSGCTs, and 10% are mixed tumors (both seminomatous and NSGCT elements are present).[35] Patients with mixed tumors are clinically considered to have NSGCT, the only exception being tumors with syncytiotrophoblastic cells in cases of seminoma.

Carcinoma in Situ

Intratubular germ cell neoplasia, or CIS, is felt to precede the development of all cases of seminoma and NSGCT in adults (with the exception of spermatocytic seminoma).[36] On light microscopy, CIS cells closely resemble seminoma cells and in most cases are found within the seminiferous tubules. Cytologically, there is no difference between the CIS cells that develop into seminomas and those that develop into NSGCTs. In the general population, the incidence of CIS is low (0.2%),

BOX 55-1 Histologic Classification of Testicular Neoplasms

Germ cell tumors (demonstrating one or more of the following components)
- Seminoma
- Embryonal carcinoma
- Teratoma
- Choriocarcinoma
- Yolk sac tumor (endodermal sinus tumor: embryonal adenocarcinoma of the prepubertal testis)

Sex cord stromal tumors (gonadal stromal tumors)
- Leydig cell tumor
- Sertoli cell tumor
- Granulosa cell tumor (adult and juvenile types)

Tumor with both germ cell and gonadal stromal elements
- Gonadoblastoma

Adnexal and paratesticular tumors
- Mesothelioma
- Tumors of soft tissue origin (e.g., sarcomas)
- Adnexal tumor (e.g., adenocarcinoma) of the rete testis

Miscellaneous neoplasms
- Carcinoid
- Lymphoma
- Cyst

Metastatic neoplasms

It is not known how these chromosomal changes contribute to the development of the neoplastic phenotype. The frequent finding of the 12p isochromosome in both CIS and invasive tumors, however, indicates that this chromosome plays an important role in the biology of these tumors. The possibility of amplification of normal or modified genes, such as the *DDX1* gene on the 12p isochromosome, is currently being investigated.[26] Proto-oncogenes present on the short arm of chromosome 12 could be activated by point mutations, deletions, or translocations to become oncogenes, which could then act in a dominant manner.[27] The *KRAS* gene is located on the short arm of chromosome 12, and amplification or enhanced expression of this gene has been reported to occur in testicular tumors and derived cell lines. Other candidate genes being studied include the *c*-KIT oncogene and its ligand KITGL or SCF, the *c*-MOS oncogene, and the *CCND2* gene. In addition to chromosome 12, 17q is overrepresented in 50% of cases of GCT; this area contains a number of genes of interest, including the *GRB7* gene and the plakoglobin gene.[23]

TABLE 55-1 Three Classifications of Germ Cell Tumors

Dixon and Moore, 1953[30]	WHO Classification[33]	Pugh, 1976[32]
Group I	Seminoma	Seminoma
Seminoma	Spermatocytic seminoma	Spermatocytic seminoma
Spermatocytic seminoma	Embryonal carcinoma, adult-type	Malignant teratoma, undifferentiated
Group II	Teratoma	Teratoma, differentiated
Embryonal carcinoma	Mature	Malignant teratoma, intermediate
Group III	Immature	Yolk sac tumor; orchioblastoma
Teratoma, pure	Teratoma with malignant areas other than seminoma, embryonal carcinoma, or choriocarcinoma	
Group IV	Embryonal carcinoma and teratoma (teratocarcinoma)	
Teratoma with carcinoma or sarcoma	Infantile embryonal carcinoma	
Group V	Polyembryoma	
Teratoma with embryonal carcinoma or choriocarcinoma		

but it is somewhat higher in men with impaired fertility (0.5%) and in those with cryptorchid testes (2% to 4%).[19]

Seminomas

Seminoma, the most common type of testicular GCT, is most often seen in the fourth decade of life. On gross examination, the tumors are usually well demarcated from the residual testicular tissue and rarely have foci of necrosis or hemorrhage. On microscopic examination, the classical or typical seminoma type is made up of large cells with abundant cytoplasm divided by connective tissue septae into sheets or cords.[37] These cells typically have round, hyperchromatic or vesicular nuclei with prominent nucleoli. Frequently, there is a lymphocytic infiltrate, and macrophages, plasma cells, and multinucleated giant cells are often present. Syncytiotrophoblasts are present in 15% to 20% of cases, and their presence does not appear to alter the prognosis.

On immunohistochemical testing, virtually all seminomas express placental leukocyte alkaline phosphatase (PLAP) and do not express low-molecular-weight keratins, blood group antigens, or vimentin. Several histologic variants of seminoma have been identified, including anaplastic seminoma and spermatocytic seminoma. Anaplastic seminoma is diagnosed when there are three or more mitoses seen per high-power field.[37] Spermatocytic seminoma is a rare subtype mainly seen in older men and is not associated with CIS or bilateral disease.[36] Also, these tumors do not stain for PLAP on immunohistochemical testing and rarely, if ever, metastasize. An atypical variant of seminoma with some features similar to those of NSGCT on immunohistochemical examination has been reported, although its morphologic appearance is similar to that of classical seminoma.[38] Usually, there is little or no lymphocytic infiltrate and the tumor cells have less cytoplasm than classical seminoma cells. In terms of prognosis, this atypical variant appears to have the same prognosis as classical seminoma.

Nonseminomatous Germ Cell Tumors

Nonseminomatous tumors make up 40% of TGCCs and occur most commonly in the third decade of life. In the WHO classification system, NSGCTs include embryonal carcinoma, teratoma (mature, immature, or with malignant differentiation), choriocarcinoma, yolk sac tumor, and mixed GCTs. Most tumors are mixed, with two or more cell types present. Although some tumors have a component of seminoma, the association of seminoma within a histologically confirmed NSGCT has no major impact on the clinical outcome.[39]

Patients with combined tumors present at an age (median, 33 years) intermediate between those with seminoma (median, 36 years) and those with non-seminoma (median, 27 years).[39]

On gross examination, there is usually a soft irregular mass poorly demarcated from the surrounding testicular tissue, and a considerable amount of necrosis and hemorrhage is often present. Immunohistochemical studies usually demonstrate cytoplasmic expression of low-molecular-weight keratins in embryonal carcinomas, and yolk sac elements, low-molecular-weight keratin, or vimentin expression in mature teratomas.

Pathways of Spread

Direct extension of tumor into the epididymis, through the tunica vaginalis, into the spermatic cord (T3), and rarely into the scrotum (T4) may occur. Locally extensive tumors are rare, however.

Lymphatic spread is the most common route of metastatic spread. The lymphatic drainage of the testis is directly to the paraaortic lymph nodes. There are differences in the distribution of metastases from left or right testicular tumors. The left testicular vein drains to the left renal vein, and the lymphatic drainage is primarily to the lymph nodes in the paraaortic area, directly below the left renal hilum. On the right side, the testicular vein drains directly to the inferior vena cava below the level of the renal vein, and, therefore, paracaval and interaortocaval nodes are the first ones to be involved in right-sided tumors. Figure 55-1, *A* and *B*, shows the distribution of retroperitoneal lymph node metastases in NSGCT and seminoma.[40,41] Contralateral nodal involvement occurs in approximately 15% of cases and is rarely found in the absence of ipsilateral involvement. Supradiaphragmatic spread can occur through the thoracic duct, and although left supraclavicular nodal disease is infrequent at presentation, it is often seen at the time of relapse.

Pelvic and inguinal lymph node involvement is rare (<3%). Factors predisposing to inguinal lymph node involvement include prior scrotal or inguinal surgery, scrotal orchiectomy with incision of the tunica albuginea, tumor invasion of the tunica vaginalis or lower third of the epididymis, and cryptorchid testis.[42,43] Disruption of lymphatic vessels in the spermatic cord during inguinal surgery has been shown to induce anastomoses between the testicular lymphatic vessels and the regional lymphatics destined for inguinal or pelvic lymph nodes. In an occasional patient, a connection with the contralateral inguinal lymph nodes may be established, but this is uncommon. In a small proportion of patients with inguinal relapse, no predisposing factors may be apparent.[42]

In patients with NSGCTs, hematogenous spread occurs early in the course of the disease. The lung parenchyma is the commonest site of hematogenous spread, but liver, bone, brain, kidney, and gastrointestinal metastases are also seen. In a review of over 5000 patients with metastatic GCT,

Teratomas are tumors composed of cells derived from two or more of the germ cell layers (ectoderm, mesoderm, or endoderm). When one of the component tissues in any of the types of teratoma exhibits the histologic appearance of another malignant tumor, such as sarcoma or carcinoma, the term *teratoma with malignant transformation* is used.

Choriocarcinomas are tumors composed of both multinucleated syncytiotrophoblasts and mononuclear cytotrophoblast cells. Pure choriocarcinoma is rare and is usually associated with widespread metastases, high levels of β-HCG, and a poor prognosis. Elements of choriocarcinoma are found in up to 10% of NSGCTs and do not appear to affect the prognosis.

Yolk sac tumor, also known as endodermal sinus tumor, is composed of cells that usually produce AFP and resemble those seen in the yolk sac in an embryo. Pure yolk sac tumors are rare but are the most common variant of childhood GCT. Elements of yolk sac tumor are found in up to 50% of NSGCTs.

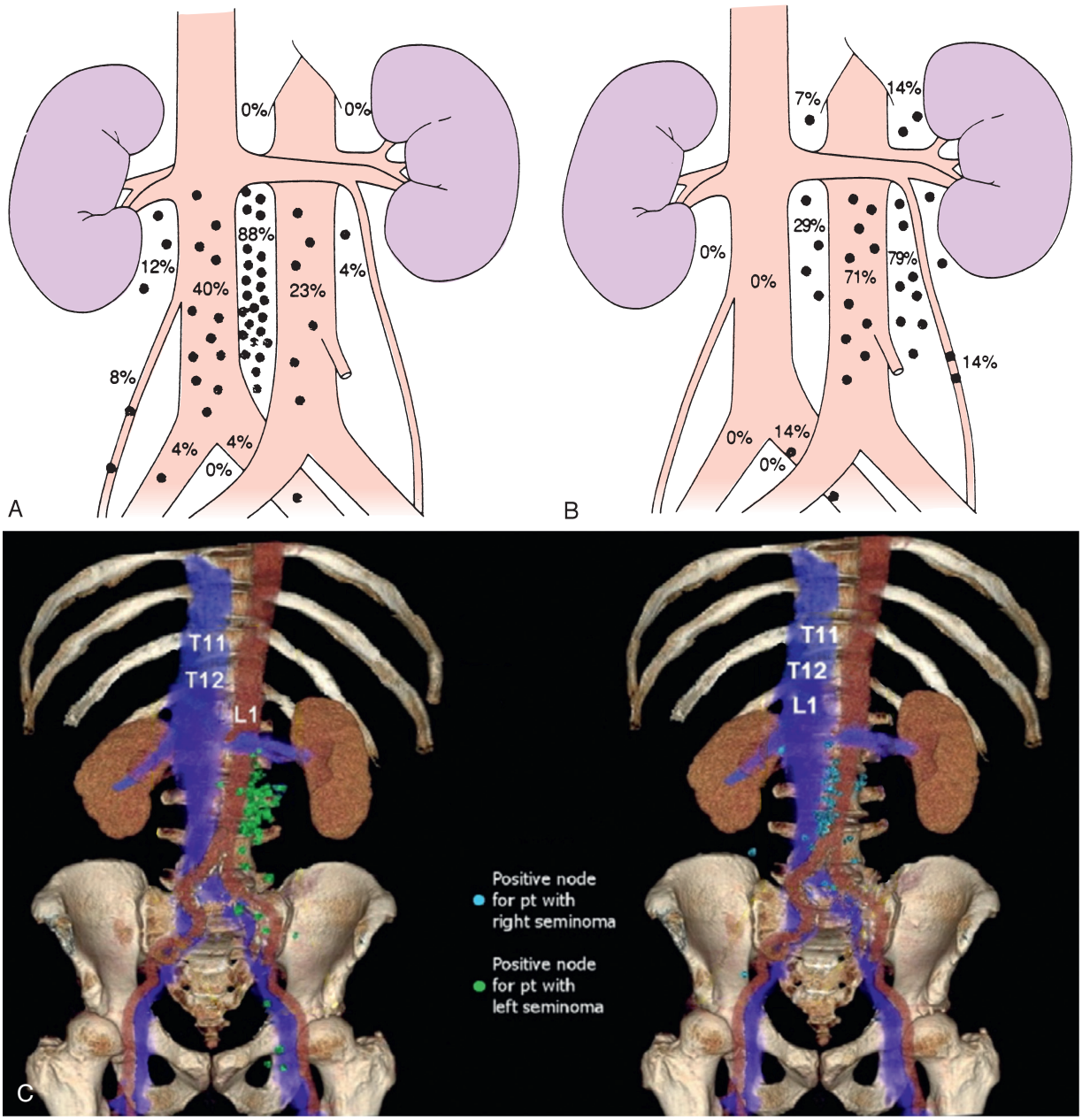

Figure 55-1 Distribution of retroperitoneal lymph node metastases in early-stage testicular non-seminoma germ cell tumor. **A,** Right testis primary tumor. **B,** Left testis primary tumor. **C,** Distribution of retroperitoneal lymph node metastases in early-stage testicular seminoma germ cell tumor. *From Paly J, Efstathoiu J, Hedgire S, et al: Mapping patterns of nodal metastases in seminoma: Rethinking radiotherapy fields. Radiother Oncol 106:64–68, 2013. Copyright © Elsevier.*

pulmonary metastases were present in 44% of cases and liver metastases in 6% of cases, with all other areas of hematogenous spread present in 1% or less of cases.[44] Mediastinal and neck node involvement was present in 11% to 12% of cases.

CLINICAL PRESENTATION, PATIENT EVALUATION, AND STAGING

Clinical Presentation

Testicular cancer most commonly present with a painless mass but up to 45% of patients may have testicular pain, where up to 25% have signs and symptoms suggestive of acute epididymitis. Symptoms and signs suggestive of metastatic disease such as back pain, dyspnea, and gynecomastia (from malignant tumors that produce HCG) is a much less common presentation. Patients with high HCG levels (up to 3.5% of patients) may have hyperthyroidism as a result of stimulation of the thyroid by the alpha subunit of HCG, which behaves identically to thyroid-stimulating hormone (TSH).[45] Various benign conditions including torsion, hydrocele, varicocele, spermatocele, and epididymitis should be considered in the differential diagnosis of a testicular mass (in addition to tumor). Transillumination of the testis on examination does not rule out a diagnosis of malignancy as a small percentage of tumors are associated with a hydrocele.

Patient Evaluation

A solid mass is detected on physical examination or by ultrasonography should prompt a diagnostic and therapeutic radical orchiectomy when there is no obvious evidence of metastasis. Preoperative measurement of serum tumor markers, including AFP, β-HCG, and LDH should be done to allow monitoring of decay with treatment. Staging investigations are usually performed after the histologic diagnosis is confirmed, except for some patients who present with life-threatening advanced metastatic disease where systemic therapy may be instituted based on a clinical diagnosis and unequivocal abnormality of AFP and β-HCG levels. In such cases, pathology may be obtained via needle biopsy or held until orchiectomy, after chemotherapy has been completed.

Staging investigations include chest x-ray, CT scans of the chest, abdomen, and pelvis, and tumor markers. For patients with seminoma and absence of retroperitoneal lymph node involvement, thoracic CT scans add little value. Bipedal lymphography for staging is of historical interest only; however, magnetic resonance imaging (MRI) with lymphotrophic nanoparticles has shown some promise but further data is required to be able to evaluate its role in routine clinical practice.[46] In stage II and III seminomas, especially in patients with bulky retroperitoneal disease, a bone scan may be performed. Abnormal serum marker levels should be monitored to document postorchiectomy decay according to their respective half-lives. Patients with extensive metastatic disease, nonpulmonary visceral metastases (NPVMs), or high tumor marker levels (especially HCG) are at risk for brain metastases, and CT or MRI (preferably) of the brain should be performed.[47] Baseline pulmonary and renal functions are assessed in patients who require chemotherapy.

Tumor Markers

Measurements of AFP, β-HCG, and LDH are essential in the diagnosis and management of patients with GCTs.[48] HCG is a glycoprotein with a molecular weight of 45,000 daltons, composed of two subunits, of which the α-subunit is identical to that of luteinizing hormone (LH), follicle-stimulating hormone (FSH), and thyroid-stimulating hormone (TSH), and a distinct β-subunit. HCG is normally produced by the placenta. About 15% of patients with seminoma have elevated β-HCG levels. Low levels of β-HCG may be found in other neoplasms, including prostate, bladder, and renal tumors. The use of marijuana derivatives also may lead to elevated levels. Because of the possible cross-reactivity with LH, and in cases where an elevated HCG level is thought to be the result of this cross-reactivity, consideration should be given to having levels remeasured after treatment with testosterone.[49] The half-life of β-HCG in blood is approximately 22 hours. In the subset of patients with GCT with elevated HCG, the level of HCG reaches a plateau after the fourth cycle of chemotherapy and is considerably greater than normal. Such persistent HCG levels may not be an indication for salvage therapy because of the possibility of tissue binding of HCG, which slows the decay of serum levels.[47]

AFP is the major serum protein of fetal life. It is a glycoprotein of molecular weight 70,000 daltons. In addition to being elevated in nonseminomatous GCTs, it is elevated in hepatocellular carcinoma, cirrhosis, and hepatitis and during pregnancy. The half-life of AFP is approximately 5 days. AFP is not found in pure seminoma; its elevation in this setting implies the presence of nonseminomatous tumor elements and in those patients is considered to have non-seminoma regardless of the pathologic subtyping seen in the tissue. Liver disease should be considered in the differential diagnosis in patients whose disease appears to be responding and in whom the AFP level fails to fall appropriately or is found to be increasing.

One or both of these markers are elevated in 85% of patients with nonseminomatous GCTs. However, normal markers do not exclude the presence of clinically occult disease.[50]

LDH is another important marker in patients with GCTs. It is elevated in up to 60% of patients with non-seminomas and also in a high proportion of patients with advanced seminomas, but it is the least specific of the three recognized tumor markers in GCTs.[44,51]

Both AFP and β-HCG levels are useful in the diagnosis of malignancy when measured before orchiectomy with the rate of decline (after orchiectomy) indicating the likelihood of residual tumor. Tumor marker levels may be used to assess response to treatment, to predict the likelihood of achieving complete remission, and in regular follow-up to indicate relapse, this is often in the absence of symptoms, physical findings, or abnormal imaging studies.

PLAP is an isoenzyme of alkaline phosphatase and is normally expressed by placental syncytiotrophoblasts. It is also expressed by testicular tissue and has been investigated as a tumor marker in seminoma. Although PLAP levels are often elevated in patients with seminoma, this factor has proven to be of little practical value.[52]

Staging

The 2009 American Joint Committee on Cancer/International Union Against Cancer (AJCC/UICC) TNM classification (Table 55-2) is the recommended staging system. In stage I disease, one of the most important determinants of outcome is the presence of vascular invasion in the primary tumor (particularly in non-seminoma), and this differentiates a pT1 tumor from a pT2 tumor.[53] Tumors with invasion of the spermatic cord are staged as pT3 cancers, and the rare tumors with scrotal invasion are classified as pT4 lesions.

In stage II disease, the extent of retroperitoneal adenopathy and serum tumor marker level determines treatment and outcome. Patients with retroperitoneal lymph nodes less than 5 cm in diameter (N1/N2 disease) are often successfully treated with regional therapy, either RPLND in NSGCTs or external beam radiation therapy (EBRT) in seminomas; however, those with nodal disease greater than 5 cm in diameter have a high risk of distant failure following regional therapy and are usually treated with systemic chemotherapy.

With the current use of cisplatin-based chemotherapy, the survival rate of patients with metastatic testicular tumors is excellent, although a minority of patients still die of testicular cancer despite treatment.

The International Germ Cell Cancer Collaborative Group (IGCCCG) analyzed data from 5168 patients with advanced disease.[44] Independent prognostic variables identified by the IGCCCG were included: histologic type (non-seminoma versus seminoma), site of the primary tumor (testis, retroperitoneal site, or other), presence or absence of nonpulmonary visceral metastases (NPVMs), for example, brain, bone, or liver, and degree of marker elevation (AFP, β-HCG, and LDH). Based on the results of multivariate analysis, the IGCCCG recommended prognostic groupings for patients with metastatic disease. For nonseminomatous cancers, the 5-year OS for the good-prognosis group was 92%, for the intermediate-prognosis group, 80%, and for the poor-prognosis group, 48%. For seminoma, a good-prognosis group without NPVMs had a 5-year OS of 86% and an intermediate-prognosis group with NPVMs with a 5-year OS of 72%. This classification system has been validated by van Dijk et al[51] using Cox regression analysis and recursive partitioning in a cohort of 3048 patients with NSGCT.

TABLE 55-2 Staging of Testis Tumors by the American Joint Committee on Cancer (AJCC)

Primary Tumor	
(The extent of primary tumor is classified after radical orchiectomy)	
pTX	Primary tumor cannot be assessed. (If no radical orchiectomy has been performed, TX is used.)
pT0	No evidence of primary tumor (e.g., histologic scar in testis)
pTis	Intratubular germ cell neoplasia (carcinoma in situ)
pT1	Tumor limited to the testis and epididymis without vascular/lymphatic invasion. Tumor may invade into the tunica albuginea but not the tunica vaginalis
pT2	Tumor limited to the testis and epididymis with vascular/lymphatic invasion, or tumor extending through the tunica albuginea with involvement of the tunica vaginalis
pT3	Tumor invades the spermatic cord with or without vascular/lymphatic invasion
pT4	Tumor invades the scrotum with or without vascular/lymphatic invasion
Regional Lymph Nodes (N) Clinical	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis with a lymph node mass 2 cm or less in greatest dimension; or multiple lymph nodes, none more than 2 cm in greatest dimension
N2	Metastasis with a lymph node mass, more than 2 cm but not more than 5 cm in greatest dimension; or multiple lymph nodes, any one mass greater than 2 cm but not more than 5 cm in greatest dimension
N3	Metastasis with a lymph node mass more than 5 cm in greatest dimension
Pathologic Lymph Nodes (pN)	
pNX	Regional lymph nodes cannot be assessed
pN0	No regional lymph node metastasis
pN1	Metastasis with a lymph node mass 2 cm or less in greatest dimension and five or fewer nodes positive, none more than 2 cm in greatest dimension
pN2	Metastasis with a lymph node mass more than 2 cm but not more than 5 cm in greatest dimension; or more than five nodes positive, none more than 5 cm; or evidence of extranodal extension of tumor
pN3	Metastasis with a lymph node mass more than 5 cm in greatest dimension

Distant Metastasis (M)	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis
M1a	Nonregional nodal or pulmonary metastasis
M1b	Nonpulmonary visceral metastasis
Serum Tumor Markers (S)	
SX	Marker studies not available or not performed
S0	Marker study levels within normal limits
S1	LDH <1.5 × N *and* HCG (mIU/mL) <5000 *and* AFP (ng/mL) <1000
S2	LDH 1.5-10 × N *or* HCG (mIU/mL) 5000-50,000 *or* AFP (ng/mL) 1000-10,000
S3	LDH >10 × N *or* HCG (mIU/mL) >50,000 *or* AFP (ng/mL) >10,000
	N indicates the upper limit of normal for the LDH assay

Stage Grouping				
Stage 0	pTis	N0	M0	S0
Stage I	pT1-4	N0	M0	SX
Stage IA	pT1	N0	M0	S0
Stage IB	pT2	N0	M0	S0
	pT3	N0	M0	S0
	pT4	N0	M0	S0
Stage IS	Any T	N0	M0	S1-3
Stage II	Any T	N1-3	M0	SX
Stage IIA	Any T	N1	M0	S0-1
Stage IIB	Any T	N2	M0	S0-1
Stage IIC	Any T	N3	M0	S1
	Any T	Any N	M1	SX
Stage III	Any T	Any N	M1a	S0
Stage IIIA	Any T	Any N	M1a	S1
	Any T	N1	M0	S2
Stage IIIB	Any T	Any N	M1a	S2
	Any T	N1-3	M0	S3
Stage IIIC	Any T	Any N	M1a	S3
	Any T	Any N	M1B	Any S

From Edge SB, Byrd DR, Compton CC, et al, editors: AJCC Cancer Staging Handbook, ed 7, New York, 2010, Springer.
AFP, *α-fetoprotein;* HCG, *human chorionic gonadotropin;* LDH, *lactate dehydrogenase;* mIU, *milli-international unit;* mL, *milliliter;* ng, *nanogram.*

PRIMARY THERAPY

The initial management involves a radical inguinal orchiectomy in almost all cases except for the uncommon life-threatening presentation in which systemic treatment is urgently needed. Postorchiectomy management is based on the histologic type and extent of disease. The management policies for both seminomatous and nonseminomatous tumors have evolved separately but mirror each other quite closely, with the exception of the use of EBRT in early-stage seminoma and RPLND in non-seminoma. Sperm testing and banking should be considered before treatment with chemotherapy, RPLND, and EBRT because of potential effects on fertility.

Surgery

Surgery involves a radical inguinal orchiectomy to allow high division of the spermatic cord. Orchiectomy offers cure in a high proportion (60% to 90%) of patients with stage I disease.[20,54] Although not recommended, a transscrotal approach does not appear to compromise the outcome, provided that the scrotal cavity has not been grossly contaminated by tumor during surgery. In patients with life-threatening metastatic disease and a clear-cut diagnosis of germ cell malignancy, initial management is with chemotherapy and surgery is postponed until completion of systemic treatment.[20,54] The role of partial orchiectomy in patients with metachronous or synchronous bilateral tumors will be discussed later.

Seminoma

Most patients present with stage I disease (70% to 80%); stage II disease is found in 15% to 20%; and stage III disease in 5% of cases. Of the predicted 4700 cases of seminoma in the United States in 2013, 3700 were expected to present as stage I disease.

In stage I seminoma, historically, adjuvant retroperitoneal RT was the most widely applied treatment in postorchiectomy management. RT provided excellent long-term results, with local control in the abdomen and pelvis in virtually all patients. However, it is now known that more than 85% of patients are cured with orchiectomy alone and RT has been associated with an increased risk of late gonadal toxicity, development of secondary malignant tumors, and perhaps an increased risk of cardiovascular disease.[55-60] With this knowledge and also the excellent salvage rates with cisplatin-based chemotherapy, the use of adjuvant RT became questionable. Attempts at minimizing RT-associated morbidity included a reduction in radiation dose and treatment volume, surveillance (avoidance of adjuvant therapy and treating only on evidence of relapse), and adjuvant chemotherapy.[61-65] Of these options, surveillance is now the standard approach, minimizing the burden of treatment while maintaining the cure rate at 100%.[66-68]

For stage II disease, retroperitoneal irradiation is effective and is recommended for patients with nonbulky tumor (stage IIA to IIB), whereas chemotherapy is the treatment of choice for patients with more advanced disease. RPLND is usually reserved for rare situations where neither of the other treatments is possible.

In stage III disease, chemotherapy is the treatment of choice.[20,54]

Management of Stage I Seminoma

Surveillance

Mature series of patients managed with surveillance have reported relapse rates of 15% to 24% (Table 55-3) (also see references 62, 67, 68, 71-73). A large experience of surveillance spanning a period of 24 years (1984 to 2007) was from Denmark using cancer registry linked data with median follow up of 15.4 years, the crude relapse rate was 19.5% (355 of 1822 patients).[69] Similarly, in the Princess Margaret Hospital (PMH), Toronto, series of 484 patients, median follow-up was 6.6 years, crude relapse rate was 15%.[68] The other studies with adequate follow-up (>36 months) have reported similar relapse rates. The predominant site of relapse in all studies was the paraaortic lymph nodes (82% in the Danish Testicular Cancer Study Group [DATECA] study and 89% in the PMH series.[67,68] The median time to relapse ranged from 12 to 18 months, but late relapses (>2 years, 4% and >5 years, 1.4%) have been reported.[69,70]

A number of single institution studies reported prognostic factors for relapse, such as age, primary tumor size, and small vessel invasion were predictive of relapse for surveillance patients. Based on these studies an attempt to further refine a prognostic model based on these factors was undertaken by a pooled analysis of four large surveillance data sets.[74] Tumor size and rete testis invasion predicted for relapse on multivariable analysis in 638 patients managed by surveillance. The effect of tumor size on the relapse rate is shown in Figure 55-2, and the hazard ratio for relapse with a tumor size of more than 4 cm was 2 (95% CI, 1.3 to 3.2) relative to baseline (tumor size <4 cm and no rete testis invasion). The high-risk group had up to 35% risk of relapse. The model was not fully validated in an independent dataset analysis of 685 patients, but similar to

TABLE 55-3 Results of Surveillance in Stage I Seminoma

Series	No. Pts	Median FU (mo)	Relapse: No. Pts (%)	CSS (%)
Daugaard[62]	394	60	69 (17.5)	100.0
Germa Lluch[71]	233	33	38 (16)	100.0
Horwich[66]	103	62	17 (16.5)	100.0
Oliver[72]	67	61	16 (24)	97.0
Von der Maase[67]	261	48	49 (18.8)	98.9
Tyldesley[73]	93	33	16 (17.2)	97.8
Leung[68]	484	79	72 (15)	99.8

CSS, *Cause-specific survival* FU, *follow-up;* mo, *months;* No. Pts, *number of patients.*

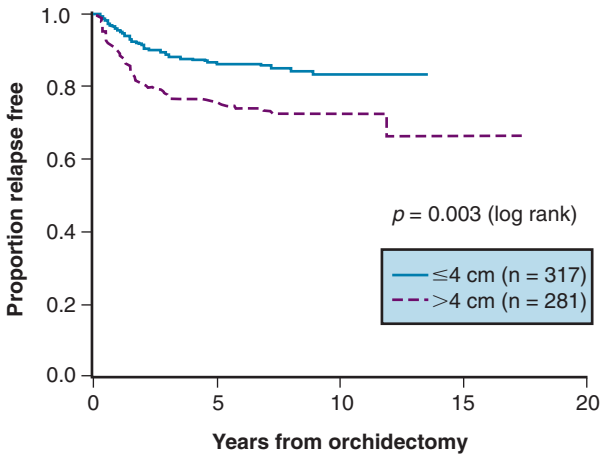

Figure 55-2 Relapse-free rate based on primary tumor size. *From Warde P, Specht L, Horwich A, et al: Prognostic factors for relapse in stage I seminoma managed by surveillance. A pooled analysis. J Clin Oncol 20:4448–4452, 2002. Copyright © American Society of Clinical Oncology.*

TABLE 55-4 Follow-up Protocol for Stage I Seminoma

Years	Month 6	Month 12
1-3	Clinical examination CT of abdomen and pelvis*	Clinical examination Chest radiograph CT of abdomen and pelvis*
4-5		Clinical examination CT of abdomen*
7		Clinical examination CT of abdomen*
9		Clinical examination Chest radiograph CT of abdomen*

CT, *Computed tomography.*
**CT of abdomen and pelvis done only if surveillance or adjuvant carboplatin; may be discontinued after 3 years for carboplatin patients.*

TABLE 55-5 Results of Retroperitoneal Radiation Therapy in Stage I Seminoma

Author	Study Years	No. Pts	Relapse (%)	CSS (%)
Bayens[84]	1975-1985	132	4.5	99.0
Coleman[85]	1980-1995	144	4.2	100.0
Fossa[61,63]	1989-1993	242	3.7	100.0
Hallemeier[91]	1972-2009	199	2	99.0
Hultenschmidt[86]	1978-1992	188	1.0	100.0
Santoni[87]	1970-1999	487	4.3	99.4
Warde[88]	1981-1989	282	5.0	100.0

CSS, *Cause-specific survival;* No. Pts, *number of patients.*

the previous study; larger primary tumors were associated with an increased risk of relapse, whereas median tumor size (>3 cm) was associated with a hazard ratio of 1.87.[75] The more recent analysis of national data from Denmark also confirmed the prognostic value of tumor size but small vessel invasion and HCG elevation >200 IU were also found to be predictive for relapse.[69]

Management options at relapse include irradiation and cisplatin-based chemotherapy. Most patients who relapse while on surveillance are initially treated with retroperitoneal RT and have an associated 10% incidence of second relapse after RT.[76] The likelihood of detecting early progression in the retroperitoneal lymph nodes (nodes <5 cm) and, therefore, suitability of the patient for RT depends on the frequency of follow-up CT scans of the abdomen and pelvis.

The current PMH follow-up policy is shown in Table 55-4. Reducing the frequency of imaging such as chest radiographs and eliminating routine measurement of serum tumor markers has simplified the protocol. There appears to be limited value to routinely including these tests in surveillance protocols because chest radiographs most often were negative in the absence of retroperitoneal nodal relapse and serum tumor markers heralded few relapses in advance of detectable macroscopic disease.[77,78]

One of the concerns regarding the routine use of surveillance was the potential for an increased burden of treatment because of the need for more patients requiring subsequent chemotherapy particularly if first treated with RT in the relapse setting. There seems little to base these fears on as a similar proportion of patients managed with surveillance (4.3%) and adjuvant RT (3.6%) required subsequent chemotherapy as part of their management.[68]

Surveillance does lead to an increased number of imaging studies (most commonly CT scans) during follow up and there are concerns that this might increase the rate of radiation-associated cancers. There is no concrete data available that quantitates the risk of radiation-induced cancer from CT scanning. Estimation of these risks has been derived from long-term follow-up data from survivors of the atomic bombings of Hiroshima and Nagasaki who received low-dose radiation akin to that for medical imaging.[79] The methodologic issues related to these estimations mean that there is doubt as to the accuracy of the data. However, in the pediatric setting there does appear to be some epidemiologic evidence supporting a small increase in the risk of leukemia and brain tumors related to diagnostic radiation.[80] Another epidemiologic study that attempted to estimate radiation-induced cancers in patients with stage I testicular cancer surveillance found no excess cancers in the time period studied but the relatively short follow up in the adult setting may have lead to an underestimation of the risk.[81] The seminoma surveillance population may conceivably be at some risk of radiation-induced cancer, given the young age of many patients and the use of repeated CT scans of the abdomen. Thus, attempts to decrease the frequency of imaging, the use of low-dose CT in surveillance protocols and nonionizing imaging such as MRI to decrease overall exposure is currently under way.[82,83] Currently MRI is not routinely recommended until results of studies become available, although it should be noted that some centers, mainly in Scandinavia, have already adopted this as their standard approach.

Radiation Therapy

OS ranges between 92% and 99% at 5 to 10 years, with the cause-specific survival (CSS) approaching 100%. Although most deaths are the result of intercurrent illness, some premature deaths may be as a result of radiation-induced cancers or possibly cardiac disease.[55,59] Relapse rate after RT has varied from 0.5% to 5%[84-88] (Table 55-5). Wherever local recurrence in-field in suspected, because of its rarity, a biopsy to rule out a nonseminomatous tumor or another malignant tumor is generally recommended. The commonest sites of relapse following adjuvant RT are the mediastinum, lungs, and left supraclavicular fossa. A small proportion of patients, many with predisposing factors, develop relapse in the inguinal nodes. Uncommon sites of isolated metastases such as the brain and tonsils have been noted but are unpredictable.[89,90] For supradiaphragmatic relapse, chemotherapy results in virtually 100% cure rate. Isolated inguinal relapse may be treated successfully with RT alone.[88]

Relapse after adjuvant RT most frequently occurs within the first 2 to 3 years with the occasional relapse beyond this time frame. In the PMH series of 282 patients treated between 1981 and 1999, the median time to relapse was 18 months, with the latest relapse occurring at 6 years. Thus, follow-up policy is concentrated in this early time period and frequency of clinic visits is similar to efforts for patients during surveillance, with the exception that CT of the abdomen and pelvis does not need to be performed because of the exceedingly low risk of local recurrence in the retroperitoneum after adjuvant RT.

Prognostic features that may predict relapse in this group are difficult to ascertain primarily because of the low event rate. The presence of anaplastic seminoma was thought be one possible factor associated with an increased relapse risk,[88] but the WHO criteria for this diagnosis (three or more mitoses per high-power field) are not uniformly used, and contradictory data exist that suggests no difference in relapse between anaplastic and classical histologies.[92] Other features associated with a higher risk of relapse may include tumor invasion of

The more frequent follow up within the first 3 years allows earlier detection of disease relapse in about 90% of those who are destined to relapse. Thereafter only a small proportion of patients will relapse and the frequency of follow up is reduced accordingly. CT thorax is not routinely recommended given the rare instance of chest only relapse but is done to determine extent of disease whenever abdominal relapse occurs.

the tunica albuginea, lymphovascular invasion, invasion of the epididymis, raised preoperative HCG levels, and spermatic cord involvement.[84,88]

Adjuvant Chemotherapy

Seminoma is highly chemosensitive and cures are routinely achieved even in advanced disease settings, thus adjuvant carboplatin has been investigated as an alternative strategy to RT or surveillance in stage I disease. The use of single agent carboplatin after orchiectomy was initially pioneered by Oliver et al[93] in 78 patients, of whom 53 patients had two courses and 25 had one course. Only one patient relapsed with median follow up of 44 months. Relapse rates of 0% to 8.6% have been reported in other Phase II studies with some of the variability in results explained by the method of calculation of the dose of chemotherapy delivered.[94]

In a Phase III noninferiority study design, the United Kingdom Medical Research Council (MRC UK) compared adjuvant RT and a single course of carboplatin (dose calculated with area-under-the-curve [AUC] method) in 1477 patients.[95] The relapse free rates at 5 years were similar, 96% for RT and 94.7% for carboplatin.[96] Relapses in the carboplatin arm occurred largely in the retroperitoneal lymph nodes and similar to adjuvant RT, relapses beyond 3 years was uncommon.[97] A possible benefit of adjuvant carboplatin that was noted was the lower incidence of second primary testicular germ cell tumors, although it is not clear whether the occurrence is eliminated or just delayed.[65] Overall relapse risk may be reduced by higher doses of carboplatin (using the AUC formula) as such patients had lower relapse rates.[98]

Data from other single-institution series indicate that if adjuvant carboplatin is given in this setting, then two courses of treatment may lower the relapse risk further and is consistent with the previous dose-related data.[61,99] Unfortunately, despite the increased dose, small but significant percentage of patients develop relapse in the retroperitoneum, and the usefulness of this approach is uncertain.[61,99] The concept of giving single course, minimally toxic chemotherapy leading to a virtually zero relapse rate allowing patients to be discharged from follow-up with no risk of relapse has not materialized. In addition, the relapse pattern dictates continued surveillance of the retroperitoneal lymph nodes (similar to a surveillance policy albeit with reduced frequency), and although a relative reduction in relapse rates of two thirds is impressive, the absolute reduction of 10% (15% with surveillance and 5% with adjuvant chemotherapy) and small numbers of patients that this affects is less so. Regardless in an adjuvant setting, 85% of patients receive treatment that has no direct benefit, and any long-term toxicity is as yet not fully characterized.[65]

Retroperitoneal Lymph Node Dissection

There is minimal literature about the routine use of RPLND in seminoma. It is a seldom used approach but may be appropriate for patients unwilling to comply with surveillance or unable or unwilling to be treated with RT or carboplatin (e.g., inflammatory bowel disease). RPLND may also be appropriate in patients with a concurrent or previous malignant tumor for whom histologic examination of the lymph nodes is essential to plan treatment.

Overview of Management of Stage I Seminoma

Stage I seminoma is almost universally curable regardless of the approach after orchiectomy. The main advantage of surveillance is the ability to limit further treatment to those who will require it without compromise in survival. The disadvantage is that surveillance requires a commitment to more intense and potentially prolonged follow-up from both patients and clinicians compared to an adjuvant treatment approach. Studies into long-term effects of RT have now documented that patients with seminoma treated with irradiation have an increased risk of second malignant tumors and also the possible risk of developing cardiac disease, and such factors should be considered in management decision making.[55,57,58,100,101]

Patients' role in directing their particular management should likely take precedence and surveillance should be offered as a first choice.[102,103] These preferences may be based on many socioeconomic factors as well as the toxicity associated with adjuvant therapy. Also, the identification of prognostic and molecular factors for occult disease may allow patients and clinicians to adopt a more individualized approach based on a more accurate assessment of risk of relapse.[103,104]

Management of Stage II Seminoma

Stage II disease is usually classified as involvement of paraaortic (and much less frequently pelvic) nodes. These abnormalities are most frequently detected radiologically, and stage II patients are approximately 15% to 20% of patients presenting with seminoma. Patients historically have most often been divided into three groups depending on the transverse diameter of the largest retroperitoneal lymph node mass (≤2 cm, stage IIA; 2.1 cm to 5 cm, stage IIB; and >5 cm, stage IIC), but currently the categories are based on the largest measurement regardless of dimension. Thus, it is possible that over time some of the differences in reported outcomes (i.e., relapse rates), particularly for patients treated with primary RT may have occurred. Approximately 70% of stage II patients have small-bulk retroperitoneal disease at presentation with lymph nodes that are 5 cm or less. Because of the relatively small number of patients in this group, randomized controlled trials have been extremely difficult to accomplish and management has been largely directed by data published from single institutions.

The most important prognostic factor in stage II seminoma (treated with RT) is the bulk of retroperitoneal disease, this as previously mentioned in historic series was often defined by the transverse diameter of the largest lymph node mass visible on CT scanning. It was the only prognostic factor for relapse in a consecutive series of 95 patients with stage II seminoma treated with RT at the PMH between 1981 and 1999.[105] The 5-year relapse-free rate in 79 patients with stage IIA or IIB disease was 91%, compared with 44% in 16 patients with stage IIC disease. Relapse occurred most commonly in mediastinal or supraclavicular lymph nodes, lung, or bone. These results are similar to other series in the literature (Table 55-6) of primary RT in patients with stage IIA or IIB. In a more recent cohort of patients treated at PMH (1995 to 2010), relapse rates have remained at about 10% for patients treated with primary RT.[76] Of 106 patients treated, 49 had stage IIA/B and 57 had retroperitoneal nodal relapse under 5 cm size and the majority (n = 87) were treated with RT with a resultant 5-year relapse rate of 9%. These data support the continued use of RT in this setting.

In stage IIC disease, chemotherapy is recommended. In more recent years, there has been a tendency for larger number of patients even with lower bulk retroperitoneal disease to be treated with chemotherapy.[100,109]

Management decisions, however, should not be based solely on substage of disease; overall tumor bulk, location of disease relative to normal tissue, and anatomic variants must also be considered. Patients with cranial caudal extent of disease in multiple single nodes each smaller than 5 cm may be classified as stage IIB disease, but such a patient should be treated with chemotherapy because of the overall bulk of disease and the possibly higher risk of distant relapse if RT was used. The necessity of irradiating a large volume of

TABLE 55-6 Results of Retroperitoneal Radiation Therapy in Stage IIA or IIB Seminoma

Author	Year	No. Pts	Study Years	Relapse: No. Pts (%)	CSS (%)
Bayens[84]	1992	29	1975-1985	7 (24.0)	93.0
Chung[105]	2004	79	1981-1999	7 (8.8)	97.5
Classen[106]	2003	87	1991-1994	4 (4.6)	100.0
Vallis[107]	1995	48	1974-1989	3 (6.0)	98.0
Zagars[108]	2001	37	1984-1999	5 (13.5)	100.0

CSS, *Cause-specific survival;* No. Pts, *number of patients.*

adjacent renal or hepatic tissue when nodal disease is lateralized or has extensive transverse diameter and other anatomic situations such as a horseshoe, or pelvic kidney usually lead to unacceptable risk of irreversible long-term toxicity. Such circumstances are where chemotherapy would better serve these patients. It should be noted that cisplatin-based chemotherapy may also be associated with toxicity and, in some rare instances, mortality because of unforeseen toxicities such as cardiovascular deaths and not necessarily directly related to the usual expected toxicities of chemotherapy.[110-112] In the unusual situation where the patient has contraindication to both RT and chemotherapy, RPLND may be considered.

The commonest sites of relapse following RT in patients with stage II disease are mediastinal or supraclavicular nodes, lung, and bone. Most relapsing patients are cured with chemotherapy, which emphasizes the importance of regular follow-up with clinical examination and chest x-ray after RT. CT imaging of the abdomen and pelvis is not necessary after complete resolution of abdominal disease.

Carboplatin with RT in stage IIA or IIB seminoma has been used at the Royal Marsden Hospital in 51 patients (of whom 8 had stage I seminoma relapse on surveillance) treated with one course of carboplatin 3 to 6 weeks before RT.[113] The median follow up was 55 months and there had been no relapses, the 95% confidence interval for relapse free survival was 93% to 100%. This approach is interesting and currently under investigation in a Swiss Phase II multiinstitutional study with a smaller volume of RT compared to the Marsden experience.[114]

The technique of irradiation in stage II seminoma is similar to that used in stage I disease and is discussed later in this chapter.

Residual Retroperitoneal Mass

Following treatment, imaging of the abdomen in done until complete resolution of disease is observed. Persistent masses that are stable usually contain fibrotic or necrotic tissue, but occasionally even with pure seminoma primary tumors, a non-seminomatous component within the metastatic disease needs to be considered. However, surgical resection in this setting, often routinely undertaken for non-seminoma, is fraught with technical challenges and also associated morbidity.[115]

Observation of residual masses is an option, particularly if regressing; if disease is suspected, surgical resection may be undertaken or RT may be used to control active disease. PET imaging to help with decision making is controversial in this setting because of false-positive results that may occur, and the decision to treat the residual mass should not be based on a positive PET image alone.[116-118]

There is limited experience of surgical excision in this setting as it occurs with less frequency than residual mass in non-seminoma. Even large experiences may be gathered over a number of years such as that published by the Memorial Sloan Kettering Cancer Center (MSKCC) group where 55 of 104 patients had residual mass following chemotherapy.[119] A substantial minority, 23 (42%), had only intraoperative biopsy because their disease was not resectable; the remaining 32 (58%) did undergo RPLND. Of 27 patients with mass more than 3 cm, 8 (30%) had viable disease (of whom 2 actually had teratoma pathology), whereas no patients with mass smaller than 3 cm had viable tumor. Six of the 8 patients with viable disease remained relapse-free at 47 months of follow-up, the other 2 patients had poorly defined masses on CT scans, died of disease. MSKCC investigators concluded that resection or at least biopsy of masses of 3 cm or larger should be performed. Culine and Droz from the Centre Léon-Bérard in France[120] have recommended an alternative strategy of continued observation as long as the retroperitoneal mass continues to decrease in size after treatment.

Consolidation of treatment with RT localized to the mass was historically used in the postchemotherapy setting. This notion was challenged by Horwich et al[121] who found that the relapse rate was similar whether RT or observation was performed. In addition, the MRC Testicular Tumor Working Party published a retrospective pooled analysis that examined the role of RT for postchemotherapy residual masses among men with seminoma.[122] Of 123 patients with a residual abdominal mass, 56% received consolidative RT. The outcomes reported from this study showed no significant difference regardless of the use of RT, which suggests that routinely applying RT for a postchemotherapy mass should be avoided. Clearly RT in this setting would not be useful for a mass that contains no active tumor or in the setting of distant microscopic disease.

Generally, patients with a residual mass of 3 cm or less may be observed. For those with larger masses, surgery should be a consideration in addition to observation, but should be tailored to the individual situation.

Management of Stage III Seminoma

This uncommon presentation seen in less than 5% of patients with seminoma is usually managed with cisplatin-based regimens (see the section on non-seminoma) and results in high cure rates. Patients with stage III seminoma should be classified according to the IGCCCG system into either the good prognostic group or intermediate prognostic group based on the presence or absence of NPVMs.[44] For patients in the good-prognosis group, three courses of 5-day bleomycin, etoposide, cisplatin (BEP) chemotherapy is considered the standard of care.[100,123] In patients at risk for bleomycin toxicity, four courses of etoposide-cisplatin (EP) is given. For patients with intermediate-prognosis disease, four courses of 5-day BEP is standard.

Non-Seminoma

Since the 1970s, when cisplatin, bleomycin, etoposide, and vinblastine were introduced, non-seminoma has become one of the most curable adult cancers. Before these drugs were available, nonseminomatous tumors were treated with a wide

range of chemotherapeutic agents and there were occasional reports of long-term remissions with the use of single-agent mithramycin and actinomycin D.[124] The modern era in treating advanced disease began at the M. D. Anderson Cancer Center (MDACC) with the use of continuous infusions of bleomycin and vinblastine; at MSKCC with the vincristine plus actinomycin D plus bleomycin (VAB) regimens; and, later, at Indiana University, with the cisplatin plus vinblastine plus bleomycin (PVB) regimen.[125-127] With these regimens, complete responses to treatment became frequent and cures were seen in patients with metastatic disease. The current BEP protocol emerged in the 1990s and is now the standard for first-line chemotherapeutic treatment of metastatic seminoma and non-seminoma.

Management of Stage I Non-Seminoma

The risk of relapse following orchidectomy for Stage I non-seminoma is 25% to 30%. Current treatment options include surveillance with a 30% relapse rate, RPLND with a 10% relapse rate, and adjuvant chemotherapy (most often given only for high-risk patients) with a 1% relapse rate.

The optimal follow-up protocol for nonseminoma surveillance has not been defined. The current National Comprehensive Cancer Network (NCCN) guidelines recommend history and physical examination, tumor marker measurements, and chest x-ray every 2 months, with abdominal and pelvis CT scan every 4 months during year 1 and 4 to 6 months during year 2 for stage IB patients, with less frequent assessments thereafter (see references 53, 62, 125, 126, 129, 131-136).[140] Patients with stage IA disease are also followed on a less intense schedule. It has been suggested that the number of CT scans could be reduced to two, at 3 and 12 months after diagnosis, but this approach has not been widely accepted.[141] There is growing consensus that the optimal CT evaluation schedule may include three to five assessments within the first 2 years of orchiectomy. Given the concern that CT scanning may increase the risk of second malignant tumors, this approach should be explored further. Low-dose CT scanning[83,142] and MRI of the abdomen and pelvis at high-volume imaging centers may be alternatives to reduce cumulative radiation exposure with surveillance imaging.

The OS rate in stage I non-seminoma approaches 100% in most series irrespective of the treatment strategy used.[112] A risk-adapted approach with surveillance for low-risk disease and treatment (either adjuvant chemotherapy or RPLND for patients at a moderate to high risk of occult metastatic disease) has been advocated by some.[147] A surveillance policy, however, is associated with excellent outcomes, and overall, 75% of patients avoid any treatment after orchidectomy.[112,126,148,149] International consensus statements have concluded that all three approaches should be discussed with the patient,[20,54,123] although there is growing support for a universal policy of active surveillance as the preferred approach to reduce the burden of overtreatment.[146] Patients with persistently elevated or rising tumor markers with no radiographic evidence of metastatic disease (Stage IS) are considered IGCCCG good risk and receive treatment with primary chemotherapy with excellent long-term survival.

Management of Clinical Stage II Non-Seminoma

The cure rate for stage II non-seminoma is approximately 98%. Stage IIA disease is managed with cisplatin-based chemotherapy alone or RPLND plus chemotherapy (both <5% relapse rate), and stage IIB or IIC disease is managed with cisplatin-based chemotherapy, with a 5% relapse rate.

For patients with pathologic stage IIA or IIB disease, the risk of relapse with no adjuvant treatment after surgery is 30% to 50%.[123,150] Relapses occur almost exclusively outside the retroperitoneum. Adjuvant chemotherapy with two cycles of BEP in all patients with pathologic stage IIA or IIB disease after RPLND reduces this risk of relapse to 0% to 7%.[151] However, adjuvant chemotherapy represents overtreatment in 50% to 70% of patients with pathologic stage IIA or IIB disease, with resulting treatment-related toxicity and possible late sequelae.

Management of Stage III Disease

Patients with advanced GCTs should always be considered potentially curable. Survival outcomes appear to be better in specialized centers, and this may be related to experience, case selection, volume, or organization of multidisciplinary care. Referral of all patients with advanced GCTs for consultation to a specialized center is strongly recommended

Chemotherapy with or without Retroperitoneal Node Dissection

The standard first-line chemotherapy for all patients is three to four cycles of BEP using a 5-day schedule.[54,123] Modifications in BEP, such as substitution of cisplatin with carboplatin to reduce toxicity or improve convenience, should be avoided because they may reduce efficacy; however, if there is a contraindication to bleomycin, four cycles of EP can be given.

Postchemotherapy radiologic restaging should be performed in all patients 4 to 6 weeks following the final cycle of chemotherapy. If tumor marker decline is seen, as expected, all residual masses should be managed appropriately (see the following section). Only in the case of unequivocal tumor marker rise should salvage chemotherapy be initiated.

Residual Retroperitoneal Mass

In many patients who complete chemotherapy and have normalized tumor markers, residual masses (>1 cm) are seen on imaging. If technically feasible, these masses should be resected 4 to 6 weeks after chemotherapy. On histologic testing, approximately 50% will show necrosis, 35% mature teratoma, and 15% malignant disease.[54] In some centers, RPLND is performed in all cases, even in patients with no residual retroperitoneal disease on imaging. However, there is increasing evidence that observation in patients with complete response after chemotherapy, reserving surgery for those who relapse, gives excellent results and spares many patients unnecessary surgery.[159,160]

Treatment-Related Side Effects

Radiation Therapy Toxicity

RT is generally well tolerated in patients with seminoma partly because of the low doses used in this disease.[111] Nausea and vomiting may occur, but only some patients require regular antiemetics and have fatigue that interferes with activities of daily living. Diarrhea may also occur but usually this is a minority of patients. Severe late radiation complications are unusual but may occur in the patient with underlying medical issues.

Gonadal Toxicity

As the testicular germinal tissue is extremely sensitive to ionizing radiation, it is not surprising that even a small amount of scatter radiation may cause, at minimum, temporary arrest of spermatogenesis. In a series of 451 consecutive patients treated for testicular cancer, RT had a significantly greater deleterious effect on fertility than chemotherapy.[161] Doses between 20 cGy and 50 cGy may produce temporary aspermia, and doses greater than 50 cGy may preclude recovery of spermatogenesis.[162] Scrotal shielding may not eliminate all scatter radiation and thus protection of spermatogenesis is not

The presence of vascular invasion or pure embryonal carcinoma in the primary tumor are associated with a high risk of occult nodal disease. [105,109-111,127-131] Vascular invasion is the most important factor predicting relapse, and the presence or absence of this factor has been used to divide patients into those with high-risk disease (a third of cases), who have an approximately 50% risk of relapse, and those with low-risk disease, who have an approximately 15% to 20% risk of relapse.[53]

In a recent pooled analysis of 1168 patients with clinical stage I non-seminoma managed with active surveillance from six institutions with a median follow-up of 63 months, the overall relapse rate was 22% (256 relapses) with 5-year CSS >99% (six deaths from testicular cancer or treatment).[132] The median time to relapse was 6 months and relapses beyond 2 years from orchidectomy were rarely observed (<5%). Of all relapses, 90% were IGCCCG good risk. At the time of progression, the vast majority of patients were treated with chemotherapy, although RPLND was successfully used in selected cases with small retroperitoneal nodes and negative or low level serum tumor marker elevations. Relapses were more frequently observed in patients who are LVI positive (48% or 117 of 244) compared with patients who are LVI negative (14% or 129 of 903). Relapses occurred earlier (median 5 months versus 8 months) and were more often detected with serum tumor marker elevation ($p < 0.05$) in patients who were LVI positive versus those who were LVI negative. A summary of institutional series of active surveillance for Stage I non-seminoma is provided in eTable 55-1.

RPLND is a recognized alternative to surveillance in clinical stage I disease. A modified unilateral infrahilar RPLND is performed, with nerve-sparing techniques to preserve ejaculation. For right-sided tumors, the interaortocaval nodes and paracaval nodes are removed, with preservation of the left sympathetic chain, and for left-sided tumors, the paraaortic and interaortocaval nodes are removed and the right autonomic chain is preserved. If significant lymphadenopathy is revealed at surgery, a more extensive surgical resection is performed. The relapse rate following surgery is approximately 10% for patients with pathologic stage I disease.[143] Most patients who relapse after RPLND are cured with subsequent chemotherapy.[144]

In some centers, patients with clinical stage I NSGCT at high risk of relapse on surveillance are offered adjuvant chemotherapy with two cycles of BEP or EP chemotherapy.[124] In a recent meta-analysis of one randomized and seven nonrandomized studies of adjuvant chemotherapy, with a total of 873 evaluable patients, 23 relapses (2.6%) were observed.[112] To reduce treatment-related toxicity, a number of studies have tested a single cycle of adjuvant BEP.[145] A recent randomized trial of one versus two cycles of adjuvant BEP chemotherapy for stage I non-seminoma was closed prematurely because of poor accrual.[146] It should be noted that adjuvant chemotherapy does not completely eliminate the need for ongoing clinical and radiological follow-up, although it does reduce the frequency of assessments.

Patients with stage IIA disease with marker elevations (AFP, β-HCG, or LDH) or stage IIB or stage IIC disease regardless of marker status should be treated with chemotherapy according to the algorithms for patients with advanced disease.[54,123] Patients with stage IIA disease with normal or minimally elevated markers have several options. The enlarged nodes may be benign or they may contain teratoma, pure embryonal carcinoma, or mixed tumor elements. In the event of uncertainty about the clinical significant of minimally enlarged nodes, short-term follow-up imaging and tumor marker evaluation to see if the nodes regress without accompanying tumor marker elevation is reasonable. Patients with enlarging nodes or rising markers should receive chemotherapy based on the IGCCG risk classification described in this chapter. Primary RPLND may be considered if there are pathologically enlarged small volume lymph nodes and normal or minimally elevated tumor markers. After RPLND, surveillance or adjuvant chemotherapy may be employed if there are viable germ cell elements.

eTABLE 55-1 Prospective Trials of Surveillance in Stage I Non-Seminoma

Author	No. Pts	Progression Rate (%)	Dead of Disease	Retroperitoneal Progression (%)
Daugaard et al (Copenhagen)[62]	301	29	0	—
Freedman et al (MRC)[129]	259	32	3	55
Freiha et al (Stanford)[133]	23	13	—	67
Jacobsen et al (Denmark)[130]	83	28	—	65
Peckham et al (RMH)[129]	132	27	1	60
Pizzocaro et al (Milan)[134]	85	29	3	66
Raghavan et al (Australia)[135]	49	28	2	38
Read et al (MRC)[53]	396	25	5	61
Sogani et al (MSKCC)[136]	102	25	3	72
Sharir et al (PMH)[137]	170	75	1	65
Thompson et al (New Zealand)[138]	36	33	1 (? + 1)	33
Wishnow et al (MDACC)[139]	82	29	—	—

MDACC, *M.D. Anderson Cancer Center;* MRC, *Medical Research Council;* MSKCC, *Memorial Sloan-Kettering Cancer Center;* No. Pts, *number of patients;* PMH, *Princess Margaret Hospital;* RMH, *Royal Marsden Hospital.*

In patients with IGCCCG good-prognosis disease, three cycles of BEP should be given. If there is a contraindication to bleomycin, four cycles of EP can be given; however, four cycles of EP, however, has been associated with a nonstatistically significant but higher death rate in one randomized clinical trial.[152] Three cycles of BEP with a higher total dose of bleomycin (270 units) and greater dose intensity of etoposide (500 mg/m^2 per cycle) was shown to be superior and less toxic that four cycles of BEP with a lower total dose of bleomycin (120 units) and reduced dose intensity of etoposide (360 mg/m^2 per cycle).[153]

In patients with IGCCCG intermediate- or poor-prognosis disease, four cycles of BEP should be considered the standard therapy.[54,123] The VIP regimen (etoposide, ifosfamide, and cisplatin) has been compared with BEP in this patient population and shows similar outcomes but with more acute toxicity. The VIP regimen represents an alternative to BEP for patients with a contraindication to bleomycin or who develop pulmonary compromise while receiving BEP.[154] The addition of paclitaxel to BEP chemotherapy failed to improved progression-free survival in a randomized clinical trial involving patients with intermediate-risk disease.[155] For patients with intermediate- or poor-prognosis, there is no evidence to date that the use of high-dose chemotherapy with autologous stem cell transplantation is superior to the standard four cycles of BEP.[156,157] A prospective randomized clinical trial has demonstrated that poor-risk patients with unfavorable serum tumor marker decline after 1 cycle of BEP treatment benefitted from dose-intensification of subsequent cycles of treatment compared with standard BEP. However, there was no difference in OS and dose intensification for poor-risk disease is not widely accepted as a standard of care.[158]

Chemotherapy should be given, preferably without dose reductions, even in the setting of a critically ill patient, at 21-day intervals with no delays between cycles. In patients with life-threatening disease, orchiectomy should not delay the initiation of curative therapy and can be performed at the end of therapy. If possible, these patients should be treated in centers with expertise in the management of germ cell tumors. During chemotherapy, assessment of tumor markers before each treatment cycle is essential. As long as tumor markers are declining, a full course of chemotherapy should be completed. If metastases can be seen growing on radiologic examination as tumor marker levels are declining, a diagnosis of growing teratoma syndrome should be considered. In most cases, the full course of chemotherapy should be completed and resection of the residual masses should be done following chemotherapy.

Reduction in fertility appears to have a strong association with testicular cancer as many men who develop testicular cancer may already have a history of subfertility or infertility. However, even with men who have "normal fertility," it is advisable to undertake sperm banking before treatment because there may be a deleterious effect due to therapy and recovery from this may be slow and incomplete. However despite these risks, the majority of men who desired to father children after treatment did so.

universal when using this technique. There has been no evidence to suggest that the incidence of genetic abnormalities in offspring of men previously treated with RT is increased.[163] Although increasing the distance of the testis from the treated volume is expected to reduce scatter dose, this also does not eliminate all dose. However it does appear to have an effect on the length of time to recover normal sperm counts as demonstrated in the MRC randomized trial of paraaortic RT alone versus paraaortic and pelvic RT, where the median time to a normal posttreatment sperm count was 13 months in patients treated to the paraaortic lymph nodes compared to 20 months for patients treated to the paraaortic and pelvic lymph nodes.[63] However, at 3 years, there was no significant difference in sperm counts between the two groups. Testicular shielding is recommended for all patients who wish to retain fertility after treatment.[164]

Cardiovascular Toxicity

Since mediastinal RT has been abandoned, the risk of cardiovascular disease in long-term survivors has decreased. Institutional data from the MDACC and the Royal Marsden Hospital, and population-based data from Norway, however, suggest that long-term survivors of testicular seminoma treated with infradiaphragmatic RT following orchiectomy are at significant excess risk of death as a result of cardiac disease.[55,59,165] Although more recently this notion has been challenged by SEER data that demonstrated no obvious increase in rates in patients treated with RT, the bulk of the published data supports the notion that infradiaphragmatic RT is associated with an increased risk of cardiac mortality.[60] The etiology of the cardiovascular toxicity is currently unclear, but it seems reasonable for patients to be made aware of the data when deciding on whether to undergo adjuvant RT.[166]

Second Malignant Tumor

Second malignant tumors may be induced by RT and a number of studies have been published on this topic. The increased risk is usually expressed more than 10 to 15 years following RT, is often not apparent in series with shorter follow-up times.[167] The largest study of second cancers in long-term survivors of testicular cancer was conducted by Travis et al.[57] This report combined 14 population-based registries including 10,534 patients with seminoma treated with RT. The overall relative risk of a second nontesticular malignant tumor was 2 (95% CI, 1.8 to 2.2). For a 35-year-old man with seminoma, the cumulative 40-year risk of a second malignant tumor was 36%, compared with 23% in the normal population. The increased risk of second malignant tumors after treatment with RT was also shown in a Dutch population-based study of more than 2700 long-term survivors where the risk of a second malignant tumor with subdiaphragmatic RT was 2.6-fold increased as compared with surgery alone.[58] The increased risk associated with irradiation was similar to the increased cancer risk seen with smoking. A recent study from the United Kingdom has confirmed these findings.[101] Limitation of the RT field likely results in a lower risk of second malignant tumors than more extensive fields.

Psychological Toxicity

The issue of psychological morbidity associated with the diagnosis of cancer in young men may result in survivors with a higher level of anxiety and a higher prevalence of anxiety disorders than the normal population, and screening using a simple tool such as the Hospital Anxiety and Depression Scale (HADS) should be part of routine follow-up care.[111,168] Appropriate social support should be offered to patients with testicular tumors. Although highly curable, testicular cancer is still a life-threatening condition in young patients with a concomitant threat of infertility and impaired sexual function as a result of the disease or its treatment.[169]

Chemotherapy Complications

The complications of chemotherapy in testicular GCTs are related to the drugs employed.[111] Nausea and vomiting occur with all the drugs used but are controlled effectively in most patients with 5-hydroxytryptamine receptor-3 (5-HT3) antagonists, steroids, and neurokinin receptor 1 (NK1) antagonists. Myelosuppression is frequent. Febrile neutropenia is seen in about 10% to 15% of patients receiving BEP, and prophylactic hematopoietic growth factors may be considered in some patients at increased risk. Nephrotoxicity, primarily a reduction in the glomerular filtration rate, occurs with the use of cisplatin and ifosfamide. Renal tubule function is normal in most patients, but hypomagnesemia is seen in patients after repeated use of cisplatin. Raynaud phenomenon has been reported in 23% to 49% of patients, although resolution of symptoms is common.[170] Chronic peripheral neuropathy (often asymptomatic) is well recognized after treatment with cisplatin, vinblastine, and etoposide. This symptom may require up to 12 months to 18 months to resolve or may be permanent. Cisplatin-induced hearing loss, particularly at higher frequencies, may occur particular with >400 mg/m^2 of cumulative cisplatin doses. Pulmonary toxicity is seen with the use of bleomycin and can be fatal in a small number of cases.[171] Impaired fertility, which may precede the use of chemotherapy, may also continue after its use. Although chemotherapy also produces infertility, recovery of sperm counts at least to levels compatible with fertility has been observed in the majority of patients.[172] Approximately 75% of patients who attempt paternity after chemotherapy are successful with a strong association with treatment intensity.[173] Hypogonadism is observed is 11% to 35% of long-term survivors (often subclinical), related to the duration of follow-up and the cumulative dose of cisplatin.[109] There is an increased risk of late onset atherosclerotic cardiovascular disease, possibly related to early development of metabolic syndrome (obesity, hyperlipidemia, and hypertension) following cisplatin-based chemotherapy.[174]

Nongerm Cell Testicular Tumors

Leydig Cell Tumors

Leydig cell, or interstitial cell tumors account for less than 2% of testicular tumors.[175] Twenty-five percent occur in children and can present with signs of prepubertal virilization. Seventy-five percent are in patients presenting between the age of 20 and 50 years, usually with a painless testicular mass. Most Leydig cell tumors are benign, and there are no definite histologic criteria for malignancy.[175] The regional lymph nodes are the commonest site of metastatic disease, but lung, bone, and liver metastases have also been reported. The initial management is similar to that for GCTs, with a radical inguinal orchiectomy followed by staging assessment with a chest radiograph and CT scanning of the abdomen and pelvis.[176] Testis-sparing surgery can be considered in experienced hands. Urinary and serum steroids should also be assessed. RPLND can be considered in selected cases.[177] There is no role for adjunctive or definitive irradiation or chemotherapy.

Sertoli Cell Tumors

Sertoli cell tumors account for less than 1% of all testicular tumors.[175] They have been classified into three subtypes: classic, large cell calcifying, and sclerosing.[178] Most present with a painless testicular mass, and initial management is with a radical inguinal orchiectomy. Both precocious puberty and feminization have been reported to be associated with Sertoli

cell tumors in children. Most Sertoli cell tumors are benign, and orchiectomy is nearly always curative.

Extragonadal Germ Cell Tumors

Extragonadal germ cell tumors (EGCTs) have histologic findings similar to those of testicular GCTs but are found in other parts of the body, in the absence of a testicular mass. They account for 1% to 5% of all GCTs and like testicular GCTs tend to occur in young men, although the median age of presentation is 5 to 10 years older than with testicular GCTs.[179] In infants, EGCTs are more common than testicular primary tumors (usually, sacrococcygeal teratomas).[179]

Overall, patients with EGCTs (especially NSGCTs) have a worse prognosis than patients with testicular primary tumors.[180] An increased incidence of EGCTs is seen in Klinefelter syndrome. A number of patients present with poorly differentiated carcinomas (predominantly in midline locations), with a cytogenetic pattern similar to those with typical EGCTs, and do respond to cisplatin-based chemotherapy regimens.[29]

EGCTs most commonly arise in three midline sites in the mediastinum, the pineal and suprasellar regions, and the sacrococcyx (usually in infants). There have been rare case reports of tumors arising in the orbit, prostate, vagina, and liver. Tumors arising in the retroperitoneum are usually thought to be associated with an occult testicular primary lesion. Mediastinal GCTs usually occur in the anterior superior region of the mediastinum adjacent to the thymus. Patients may present with cough, dyspnea, and chest pain, and tumor marker levels are frequently abnormal. Local invasion or metastatic disease to the lungs, liver, or bone is common. Biopsy should always be performed because treatment is dependent on the histologic subtype. For mature teratomatous tumors surgery is advised, whereas for NSGCTs or seminomas the preferred approach is cisplatin-based chemotherapy, omitting bleomycin as many patients require extensive thoracic resection after primary chemotherapy.[181] Surgical resection is recommended for residual mass after chemotherapy. However, the precise role of locoregional therapy after primary chemotherapy is unclear.

The results of an international analysis of 635 consecutive patients with EGCT treated in 11 European and U.S. centers have shown that patients with pure seminomatous histologic typing had a long-term cure rate of 89%, irrespective of the primary site (retroperitoneum or mediastinum).[180] In patients with nonseminomatous tumors, however, a mediastinal primary site was an adverse feature, with only 45% of these patients alive at 5 years as compared with 63% of patients with retroperitoneal presentations. Prognostic variables for response and outcome have been identified, and four prognostic risk groups have been identified based on histologic findings, the presence of liver, lung, or central nervous system (CNS) metastases, elevation of β-HCG levels, and number of metastatic sites involved with disease.[182] The best prognostic group has an 89% 5-year OS and encompasses all patients with seminoma. The other groups all have nonseminomatous histologic findings and 5-year OS of 69%, 55%, and 17%, respectively.

The excellent treatment results with chemotherapy alone of mediastinal seminomatous tumors would suggest that there is no routine role for RT in their management. Platinum-based chemotherapy regimens are recommended. Although a 5-year OS of 73% has been reported with the use of cisplatin, vincristine, methotrexate, bleomycin, actinomycin D, cyclophosphamide, and etoposide (POMB/ACE), there is no evidence that this regimen is superior to BEP.[183] POMB/ACE is considerably more toxic, and its routine use cannot be recommended.

Special Treatment Situations

Germ Cell Tumors in Patients with Horseshoe Kidney

Horseshoe kidney (pelvic kidney) occurs in approximately 1 in 400 persons in the general population.[184] There are two main problems in the management of GCTs associated with horseshoe kidney. The first is related to the technical problem of delivery of RT in patients with seminoma. In a number of cases of horseshoe kidney, a large part of the renal parenchyma directly overlies the regional lymph nodes and lies within the standard radiation volume. The delivery of a standard radiation dose would be associated with an unacceptable risk of radiation nephritis. The second problem is related to the possible abnormalities in lymphatic drainage of the testis, and therefore, the possibility of relapse when the standard radiation fields are used. Unusual patterns of relapse have been observed in patients managed by surveillance, confirming concerns regarding abnormal lymphatic pathways.[185] For these reasons, in patients with seminoma and NSGCTs, postorchiectomy surveillance in stage I and chemotherapy in stage II have usually been recommended. RPLND is another option for patients unwilling to follow the surveillance program, but it has to be assumed that the issue of abnormal lymphatic drainage may also result in technical challenges for the surgeon. However, reports in the literature suggest that RPLND was both safe and effective in the selected cases where it was performed.[185]

Testicular Tumors Developing in Patients Who Are Immunosuppressed

It is well established that the risks of developing Kaposi's sarcoma and non-Hodgkin lymphoma are markedly increased in patients with human immunodeficiency virus (HIV) infection.[186] Initial data suggested that men who are infected with HIV have an increased incidence of testicular cancer, but more recent studies have indicated that this may not be true.[18,186] Organ transplant patients may also have an increased incidence of testicular tumors.[187] The clinical course of patients who are immunosuppressed with testicular tumors is similar to that of patients who are immunocompetent, and these patients should be offered standard oncologic therapy. Both chemotherapy and RT reduce the CD4 count even when antiretroviral therapy is used; therefore, wherever possible, surveillance should be used in patients with stage I disease.[18] Caution must be exercised because benign retroperitoneal adenopathy related to acquired immunodeficiency syndrome (AIDS) may be mistaken for metastasis from a testicular primary tumor. For those receiving chemotherapy, consideration should be given to concomitant prophylaxis for opportunistic infection. Most patients can be cured of their tumors, and the outcome of patients with HIV-related GCTs is similar to that of patients who do not have HIV.

Bilateral Testicular Germ Cell Tumors or Tumors Arising in a Single Testicle

Men who have had cancer in one testicle are at increased risk of developing contralateral disease with reported rates of metachronous or synchronous development of 1% to 5%.[187] Bilateral orchiectomy is recommended as standard management, with resulting infertility, lifelong dependence on androgen replacement, and psychological morbidity because of castration at a young age.[188]

To preserve endogenous hormonal function, organ-sparing surgery followed by low-dose RT (16 Gy to 20 Gy in 2-Gy daily fractions using a direct field with electrons) to the remnant testis to eradicate residual CIS and prevent future invasive disease is an option with a high likelihood of cure in selected patients.[20,189] Close observation after surgery may be

undertaken and adjuvant radiation may be postponed if there is a fertility concern for the patient and he is willing to risk the onset of invasive disease during that period.[189] Patients with large tumors (>30% of the testis volume) or clinical evidence of metastatic disease are not suitable for this approach. Because this is an area that requires expertise, organ-sparing approaches should be concentrated in centers with such experience.[20]

Central Nervous System Metastases

Up to 40% of patients who die of progressive disease have brain metastases at autopsy. Thankfully, presentation with brain metastases is uncommon with approximately 2% to 3 % of patients overall. Such patients are potentially curable, with approximately 50% 5-year CSS, but this requires aggressive treatment.[54] The optimal sequence of chemotherapy, RT, and surgery is unknown, although systemic chemotherapy is required in all cases, only in one study did the addition of cranial RT improve overall survival.[190] Whether the addition of RT when a complete response is obtained with chemotherapy is needed is uncertain, as is the need for RT if surgery removes gross disease. When RT is given, a dose of 40 Gy to 45 Gy should be considered for gross disease if using conventional fractionation. It is unclear if the entire brain should be irradiated but when this is done, the intended dose should not exceed 40 Gy because of the risk of neurotoxicity. A stereotactic approach is now being used more frequently and has the advantage of tumoricidal doses and relatively low risk of toxicity to the surrounding brain. Patients presenting with late relapse with CNS metastases should be treated aggressively because long-term disease-free survival times are possible.[191] Patients who develop brain metastases during chemotherapy have a poor prognosis.[191]

Spermatocytic Seminoma

Spermatocytic seminoma is a rare testicular tumor accounting for only 1% to 2% of all seminomas.[192] It usually occurs at age 50 to 60 years but is seen in younger patients.[192] It is distinct in its histologic characteristics, usually having three different cell sizes, spherical nuclei, a lack of cytoplasmic glycogen, and sparse or absent lymphocytic infiltrate when compared with classical seminoma.[193] Unlike classical seminoma, it does not appear to arise from CIS, occurs solely in the testis and has no ovarian equivalent. All patients present with stage I disease, and subsequent metastatic disease is extremely rare. In the past, the treatment approach was similar to seminoma with adjuvant RT. Current recommendations call for surveillance in all patients and the frequency of investigations may also be reduced given the seemingly minimal metastatic risk this histology poses.[194]

IRRADIATION TECHNIQUES AND DOSE

With the advent of successful salvage chemotherapy in metastatic disease, various strategies have been investigated to reduce the long-term complications of RT and in particular adjuvant RT (the standard of care after orchiectomy in stage I disease). This has included the reduction of the volume of tissue irradiated together with a dose reduction strategy. Alternative to RT including adjuvant chemotherapy and surveillance also have become popular, as has the increasing use of cisplatin-based chemotherapy in stage II disease. All of these strategies have been designed to lessen the potential adverse impact of RT.

Radiation Target Volume

The intended clinical target volume for both stage I and stage II seminoma has included the paraaortic lymph nodes and ipsilateral pelvic lymph nodes. In the case of left-sided tumors, the left renal hilum is included to allow for nodes that cluster around the left gonadal vessels. The most frequently used field arrangement is parallel opposed anteroposterior fields, and patients are treated with 10-MV to 18-MV linear accelerator photons. Although almost identical on both sides of the Atlantic, this classical plan was called the "hockey-stick" field in North America and the "dogleg" field in the United Kingdom and Europe. The superior extent is usually at the T10/T11 interspace and the inferior at the inguinal ligament. The penis is moved out of the field and the contralateral testis is placed in a scrotal shield to protect fertility and to a lesser extent future hormone production. In general, scrotal irradiation is avoided except in patients with extensive local disease, incomplete surgery, and gross scrotal contamination before surgery. Of note is that in the case of transscrotal orchiectomy, scrotal irradiation is still not recommended. Mediastinal irradiation is now of historical interest only.

More conformal radiation techniques such as intensity-modulated radiation therapy (IMRT) have not been pursued in part because the necessity of exposing more normal tissue to the low-dose radiation that is typical for the multiangle beam arrangements used in IMRT, resulting in an increase in the integral dose.[195] Another concern is the possibility that this integral dose may risk an increase in second malignancy rates in this younger population. With the increase in the availability of proton facilities, there has been some interest in exploring the possibility of using proton beams to improve dose conformality as well as minimize the risk of second malignancy.[196]

Reduction in Radiation Treatment Volume

Stage I Seminoma

Recognition of the low risk of pelvic nodal involvement in stage I disease led to the investigation of eliminating pelvic nodal irradiation. Advantages of such an approach would include lower scatter dose to the testes and reduced irradiated volume of normal tissue which in theory might reduce risk of second malignancy. The literature shows excellent results with few pelvic failures.[92,197] This was confirmed in the MRC Testicular Study Group randomized study of 478 patients comparing paraaortic plus pelvic RT and paraaortic RT alone, relapse rates were similar, 4% with paraaortic irradiation and 3.4% relapse rate with paraaortic and pelvic irradiation.[63] The sites of relapse were different, whereas all patients who received paraaortic and pelvic RT relapsed in supradiaphragmatic sites, four patients (1.6%) treated to the para-aortic lymph nodes alone had pelvic relapse. This highlighted the potential need for regular imaging with CT to detect pelvic relapse in these patients. When no imaging of the pelvis is carried out, patients fail with bulky disease (median, 5 cm).[92] It may be reasonable to confine such imaging to the first 3 years after RT as supported by data from the German Testicular Cancer Study Group.[198] Although there are advantages to paraaortic RT alone, its true value in stage I disease remains unclear especially when surveillance is an attractive alternative.

A compromise between traditional irradiation fields and paraaortic irradiation alone is to treat the paraaortic and ipsilateral common iliac lymph nodes by positioning the inferior border of the radiation fields at midpelvis[199] (Figure 55-3). This encompasses the lymph nodes that are typically removed at lymphadenectomy in patients with nonseminomatous tumors and also covers the vast majority of pelvic nodal relapses in patients treated with paraaortic irradiation alone.[197] This treatment volume is also partly supported by the data for stage II disease discussed in this chapter. Similarly a multiinstitutional study that examined nodal relapse sites in 90 patients with

stage I seminoma relapsed surveillance and de novo stage IIA/B found no sites of disease cranial to the L1 vertebral body.[41] This data may therefore support a reduction of the cranial aspect of the traditional RT field to the superior aspect of T12 vertebral body and may allow lower amount of radiation exposure to the heart and upper abdominal structures with the ultimate goal of the minimizing radiation toxicity without sacrificing rates of disease control.[200]

Stage II Seminoma

The RT technique in stage II seminoma is similar to that used in stage I disease. The treatment volume includes the gross tumor as well as the paraaortic and ipsilateral common and external iliac lymph nodes (Figure 55-4, *A*). Previously the dog-leg field was used but data from the German Testicular Cancer Group, although not a randomized study, provide some support for the placement of the inferior extent of the field at the acetabulum.[106] In this study of 87 assessable patients at median follow up of 70 months, only 4 patients relapsed with none distal to the inferior extent of the volume; although this study was small and not designed to test the question of volume reduction it is somewhat reassuring with the low rate of relapse seen. The contralateral iliac lymph nodes may also be treated in cases where lymphadenopathy in the low paraaortic area is deemed to increase the risk of these nodes being involved by tumor. However, such patients often have bulky retroperitoneal lymphadenopathy and are better treated with primary chemotherapy. Adjuvant RT of the supraclavicular lymph nodes in patients with stage II disease has been suggested by some, although it is not justified on a routine basis in view of the low risk of isolated supraclavicular relapse (2 of 79 patients with stage IIA or IIB disease in the PMH series).[108,201]

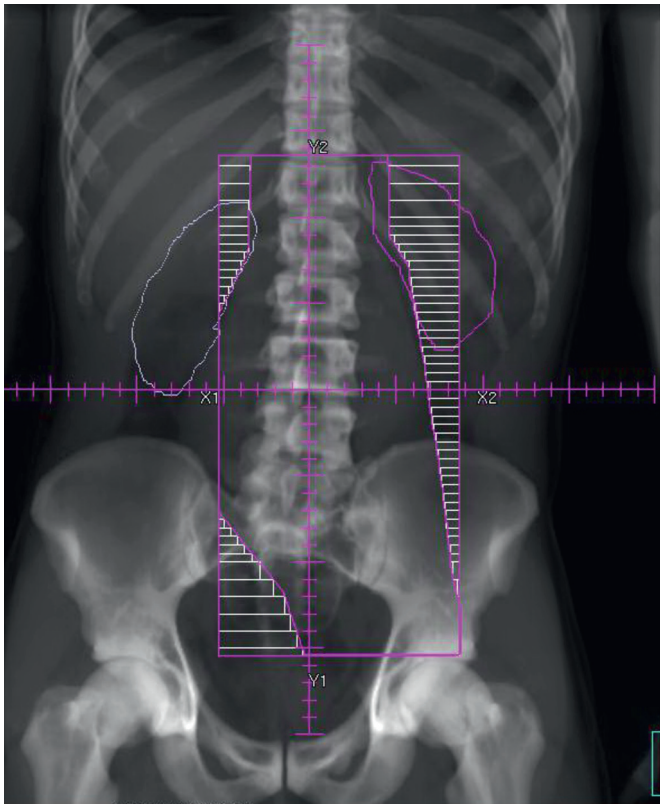

Figure 55-3 Radiation fields, stage I.

Radiation Dose

Stage I Seminoma

Doses of 20 Gy and 25 Gy are more than adequate to eradicate microscopic seminoma. No in-field recurrences have been observed in the series from PMH (Toronto) where 25 Gy is delivered over 20 daily fractions with total duration of 4 weeks.[68] A Phase III study of dose reduction comparing 30 Gy in 15 fractions over 3 weeks and 20 Gy in 10 fractions over 2 weeks in 625 patients was undertaken in the MRC TE18 trial.[64] A total of 10 and 11 relapses, occurred in the 30-Gy and 20-Gy groups (hazard ratio [HR], 1.11; 90% CI, 0.54 to 2.28), respectively, at median follow up of 61 months. The resulting 5-year relapse rates were 3% and 3.6% for the 30-Gy and 20-Gy groups, respectively. Longer follow up data published subsequently have confirmed these findings.[97]

Stage II Seminoma

The radiation dose is typically 25 Gy in 20 daily fractions plus a boost of a further 10 Gy to the gross lymphadenopathy (see Figure 55-4, *B*). At PMH, this boost is given concurrently with the large-field treatment. Some authorities suggest that 30 Gy for small bulk (IIA) gross disease is adequate but no trials have

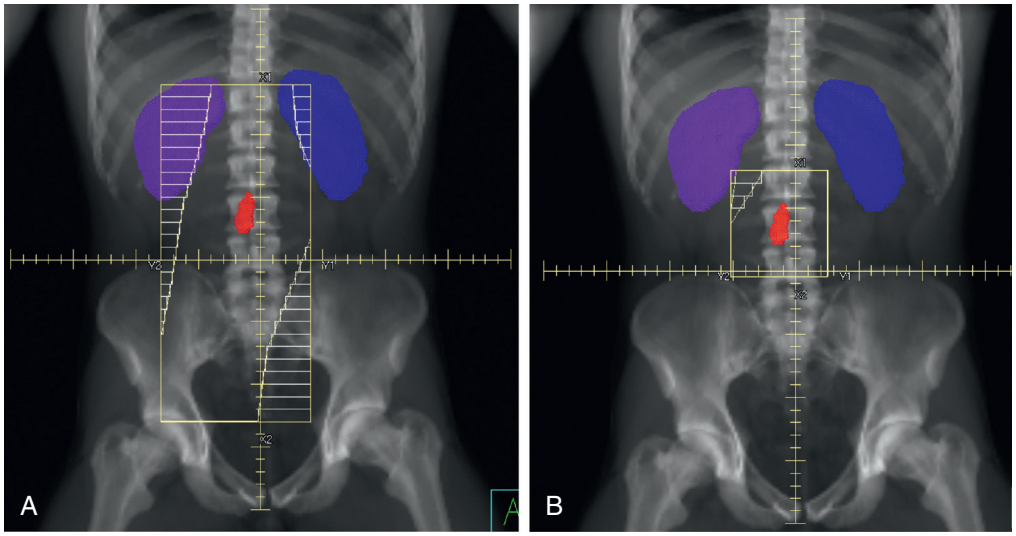

Figure 55-4 Radiation fields, stage II. **A,** Extended field. **B,** Boost field.

been done in this area.[106] One possible mechanism to reduce dose in this setting is the addition of carboplatin in a sequential fashion perhaps allowing even bulky disease to be safely eradicated with lower doses.

TREATMENT ALGORITHMS, CONCLUSIONS, AND FUTURE POSSIBILITIES

The recommended treatment algorithms for seminomas and non-seminomas based on disease extent are outlined in Figures 55-5 and 55-6. Although the overall results are excellent, there are ongoing controversies regarding the optimal management of GCTs.

In seminoma, the major area of controversy involves the management of stage I disease. The mature data from surveillance and adjuvant therapy series suggest that almost 100% of patients with stage I testicular seminoma are cured no matter which approach is chosen as postorchiectomy management. Surveillance should be considered the management option of choice, although the patient should be fully involved in the decision making.[146] Change is adopted slowly and a considerable proportion of urologists and oncologists do not discuss all the options with their patients.[202]

The optimal RT target volume for patients with stage I seminoma is under investigation, and limiting treatment to the paraaortic lymph nodes is now popular. However, if pelvic irradiation is omitted, it does not eliminate the need for ongoing follow up and surveillance of the pelvic lymph nodes; patients thus managed will experience both the morbidity of RT and the ongoing inconvenience of surveillance. Thus, a modified treatment volume to include the common iliac nodes may reduce the need for ongoing surveillance of the pelvis.

The management for patients with NSGCT needs to be further refined and improvements in outcome still remain elusive particularly for patients with the highest risk of death related to disease. In stage I disease, individualized management perhaps based on prognostic factors and patient participation in the decision making should now be routine. For good and intermediate-risk metastatic disease, identification of subgroups that may be adequately treated with reduced toxicity may be a priority area for further research, which may come in the form of less chemotherapy, omission of bleomycin, or even new agents with similar efficacy and less toxicity. In advanced or poor-risk disease, clinical trials are needed to further evaluate high-dose regimens with stem cell support, identify subgroups of patients most likely to benefit from this

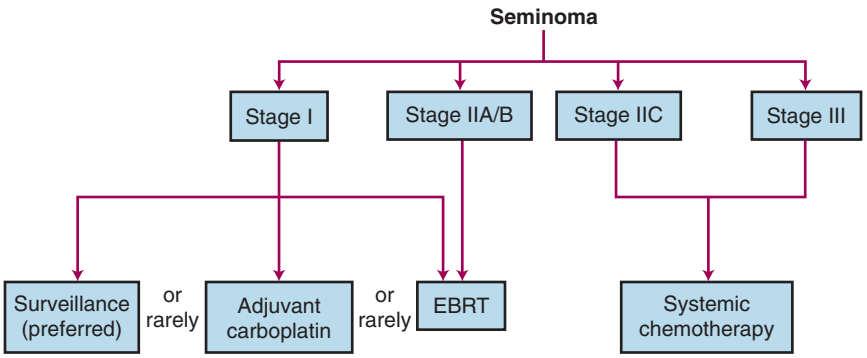

Figure 55-5 Treatment algorithm for testicular seminoma based on TNM groupings.

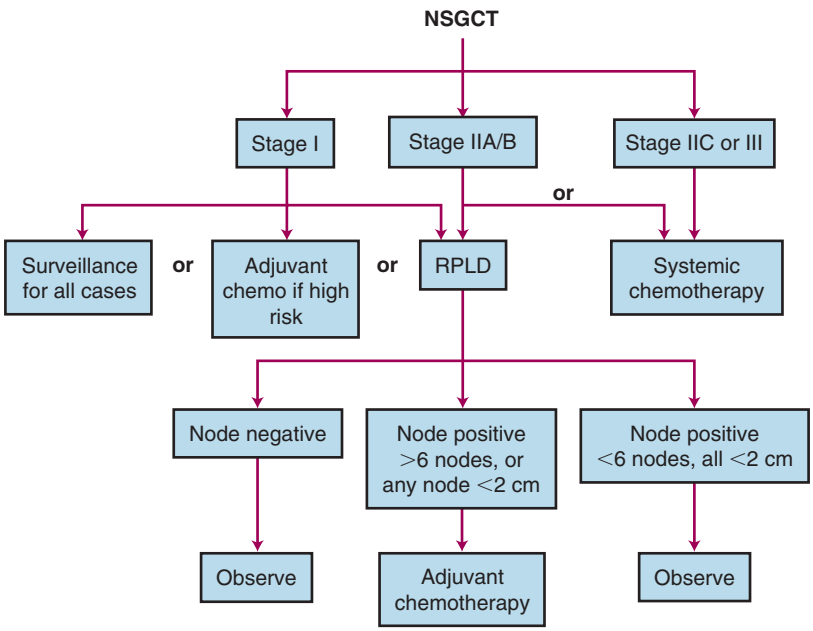

Figure 55-6 Treatment algorithm for testicular nonseminomatous germ cell tumors (NSGCTs) based on clinical TNM groupings.

aggressive approach and identify alternative regimens that reduce toxicity. Finally, new drugs with similar clinical efficacy but less toxicity would be a welcome addition in the treatment of these neoplasms.

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