New Advances and Directions in Testicular Cancer

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Summary

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

Uniterms: *testicular cancer*

Introduction

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

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

Patients with a history of a cryptorchid (maldescended) testicle are most susceptible to developing testis cancer, with a 10 to 100 fold increased risk. Other factors include a prior history of mumps orchitis, and inguinal hernia. Although some investigators have suggested an association with in utero exposure to DES, the overwhelming body of data suggest that no such association exists. The unilaterally cryptorchid testis itself may be at increased risk of developing a neoplasm, as is the contralaterally, normally descended gonad. Most pediatric urologists now recommend performing an orchiopexy for cryptorchidism at an age less than 2 to help decrease the subsequent testicular cancer risk and improve subsequent fertility potential. The management of adults with an unilaterally cryptorchid testis is controversial. Some advocate exploration and removal of an inguinal cryptorchid testis under the age of 50; in those over 50, the low risk of developing a subsequent testis cancer justifies no surgical intervention[3].

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

Clinical features and diagnosis

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

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

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

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

Pathology

Germ cell cancers of the testis can be conveniently divided into *seminomas* or *nonseminomas,* based upon the histopathology of the orchiectomy specimen. The former must be in pure form; the latter may either be a mixed germ cell cancer with both seminomatous and nonseminomatous components or a pure form of a nonseminoma, such as embryonal cell carcinoma, teratoma, yolk sac cancer, or choriocarcinoma. The term "terato-carcinoma" generally refers to a mixed germ cell, nonseminomatous cancer consisting of teratoma and embryonal cell cancer.

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

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

Biological tumor markers

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

cal half life of hCG is approximately 24 hours.

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

Staging evaluation

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

Pathology results indicate a pure seminoma

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

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

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

Pathology results indicate a nonseminoma

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

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

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

Treatment modalities according to histology and stage (Table 1)

Early seminoma

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

Table 1 — Testis Cancer — General Approach to Management.

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

XRT[1]: Radiation therapy, delivered to subdiaphragmatic lymphatics (3000-3700R)
RPLND[2]: Retroperitoneal lymph node dissection
Chemo[3]: Combination chemotherapy (see Table 2)
XRT[4]: Radiation therapy to residual radiographic abnormalities
TRS[5]: Tumor reductive surgery
Chemo[6]: Additional chemotherapy given if surgical specimen reveals viable cancer
From: Garnick MB — Testicular cancer. In: Braunwald E et al, eds. Harrison's Principles of Internal Medicine. 11th edition. New York, McGraw Hill Book Co., 1987; 1578-1581, with permission.

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

Advanced Seminoma

In the past, these patients with large retroperitoneal masses or mediastinal involvement were often treated with either radiation therapy to fields including subdiaphragmatic lymphatics, whole abdomen, mediastinum and supraclavicular nodes; however, survival rates of only between 40%-70% were achieved. If these patients subsequently relapsed outside of the radiation therapy field, the ability to administer myelosuppressive combination chemotherapy was diminished and was associated with a substantial degree of drug related morbidity. Today, most patients with advanced forms of seminoma should receive initial combination chemotherapy with a cisplatin-containing program. Substantial tumor shrinkage will occur in the majority of patients. However, the proper management for partially regressed retroperitoneal masses following chemotherapy for patients with advanced seminoma remains controversial. Often, patients will receive post-chemotherapy radiation therapy to areas of bulk disease, and, in rare instances, surgical removal of residual tumor masses. However, residual masses following chemotherapy only may actually continue to shrink even after therapy is discontinued. Nonetheless, one treatment strategy allows for cisplatin-combination chemotherapy to be given over a span of 12 to 14 weeks. Patients are then restaged; decisions regarding further chemotherapy, radiation therapy, or surgery are then made.

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

Early (clinical stage I) nonseminoma

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

Early (stage II) nonseminoma

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

Advanced stage (bulk stage II or stage III) nonseminoma[4-8]

Chemotherapy for advanced forms of nonseminomatous germ cell cancer

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

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

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

	PVB	
Vinblastine	0.15mg/kg/D	IV D* 1,2
Bleomycin	30mg	IV D 1,8,15
Cisplatin	20mg/m²/D	IV D 1-5
	Repeat cycles q 21 days x 4 cycles	
	VAP-6	
Induction:	Cyclophosphamide	600mg/m² IV D 1
	Bleomycin	30mg IV D 1, then 20mg/m²/D CIV** D 1-3@
	Actinomycin D	1mg/m² IV D 1
	Vinblastine	4mg/m² IV D 1
	Cisplatin	120mg/m² IV D 4
Maintenance:	Vinblastine	6mg/m² IV D 1
	Actinomycin D	1mg/m² IV D 1

Induction: Repeat cycles q 21-28 days x 3-5 cycles;
D = day;*
***CIV = continuous intravenous infusion;*
@ Bleomycin omitted after cycle 2;
Maintenance: Repeat cycles q 21 days; total duration of "induction and maintenance" is 1 year.

PEB	
Etoposide	100mg/m² IV D 1-5
Bleomycin	30mg IV D 1, 8, 15
Cisplatin	20mg/m² D 1-5
Repeat cycles q 21 days x 4 cycles	

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

Following such therapy, patients are then restaged (with physical, radiographic, and biochemical examinations) to assess the response of areas which previously contained disease and to determine the need for additional therapy. Large abdominal masses can undergo astonishing regression. Pulmonary nodules often completely resolve, and biological markers frequently normalize following 12 weeks of intensive combination chemotherapy. If following combination chemotherapy, a residual abdominal or pulmonary mass remains in the setting of normal markers, surgical removal of the mass (es) should be performed. Table 3 outlines current recommendations. Preoperatively, it is difficult to determine the histology of such residual masses. Approximately one-third will contain residual, viable cancer; one-third will be fibrosis, necrosis or hemorrhage, and an additional third will demonstrate the phenomenon of "teratomatous transformation". This latter finding is thought to result from either chemotherapy induced differentiation of the primary mass into a teratoma or from chemotherapy selection of more malignant elements in the mass with residual teratomatous components remaining. If either fibrosis, hemorrhage or teratoma are found following chemotherapy, additional post-surgical chemotherapy is usually not indicated. If, however, viable cancer is demonstrated, additional chemotherapy is generally administered.

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

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

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

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

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

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

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

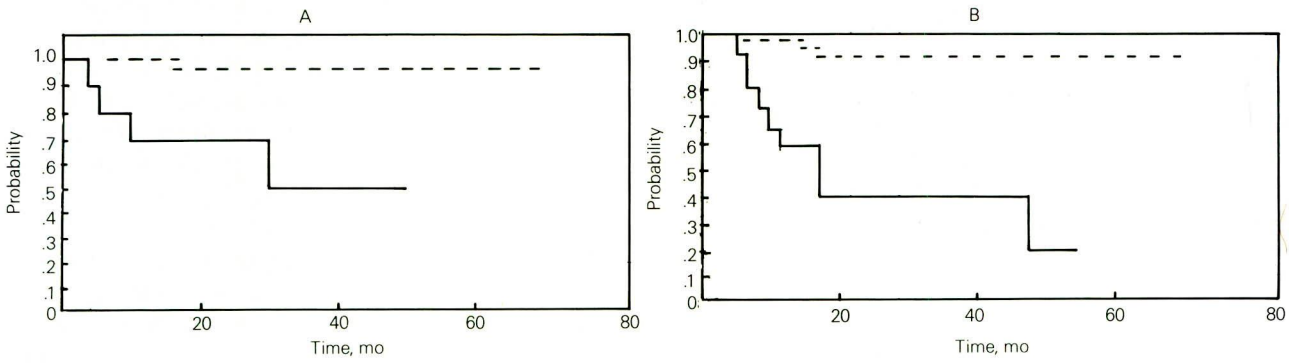

Figure 1 — Kaplan-Meier survival curve for patients with primary gonadal cancer (broken line) and primary extragonadal cancer (solid line) from day 1 of chemotherapy. A, Disease-free (continuous complete remission). B, Overall survival. (From: Reference 8, with permission.)

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

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

Side effects of curative cancer therapy — selected aspects

Radiation therapy and surgery

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

Combination chemotherapy

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

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

Orchiectomy alone for clinical stage I disease[9,10]

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

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

"Second line" treatment programs

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

The extragonadal germ cell syndrome

Patients who present with a large anterior, mediastinal mass, central nervous system abnormalities or retroperitoneal disease, consistent with a germ cell histology in the presence of clinically and ultrasonographically normal testes constitute the extragonadal germ cell cancers. The response to therapy is generally lower when compared to primary testicular cancer, which justifies the need for more intensive therapies. However, a proportion of these patients may be cured when treated with chemotherapy + tumor reductive surgery. In addition, patients with "undifferentiated" cancer of the mediastinum or retroperitoneum may have an unrecognized form of extragonadal germ cell cancer syndrome. Biological markers and immunohistochemical staining for AFP or hCG of the biopsy material may often provide useful clues. If positive, these patients should be treated as if they have potentially curable advanced testicular cancer.

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