Management of Germ Cell Tumors

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5.1 Introduction

Germ cell tumors are one of the few solid tumors in which long-term cure has been achieved in an overwhelming proportion of patients, even when the initial presenting occurs with widespread metastasis. Testicular germ cell tumors form the bulk of all germ cell tumors with 95 % of tumors originating in the testis being germ cell tumors. Fewer than 10 % of germ cell tumors arise from extra-gonadal primary sites with the most common sites being mediastinum and retroperitoneum in both males and females. In females, additionally ovarian-based germ cell tumors are observed. In 2015, the estimated new cases in the USA of by far the most common type of germ cell tumor, testicular germ cell tumors, were 8430 with an estimated death of 380 cases [1]. Over the past four decades, the cure rates for this cancer have dramatically increased from 65 % during the 1970s [2] to greater than 95 % 5-year disease-free survival [3] by using either single or integrating combined modality treatments which include surgery, radiation, and/or chemotherapy. This makes testicular germ cell tumors a role model tumor type to follow. The two outstanding reasons for this success have been the availability of effective treatment interventions and the value of integrating highly sensitive and specific tumor markers in the diagnosis, staging, monitoring, and management of germ cell tumors. This chapter will summarize the management of germ cell tumors, with an overwhelming emphasis on the management of testicular germ cell tumors since it is clinically the most frequent observed and treated type of germ cell tumor.

5.2 Clinical Presentations of Testicular Germ Cell Tumors

The initial presentation of most testicular germ cell tumors is with a nodule or swelling of one testicle accompanied with heaviness and discomfort with or without a dragging sensation in the lower abdomen. The median age for testicular germ cell tumors is between 15 and 35 years of age. Occasionally patients may also present with symptoms of orchitis or epididymo-orchitis which are accompanied with acute and abrupt episode of pain with or without accompanied swelling. Symptoms of metastatic disease on initial presentation can include a growing lump in

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F.F. Nogales, R.E. Jimenez (eds.), *Pathology and Biology of Human Germ Cell Tumors*,
DOI 10.1007/978-3-662-53775-6_5

the left neck region, cough and shortness of breathing, loss of weight and appetite, neurological symptoms similar to stroke or peripheral neuropathies, recent onset of breast tenderness and gynecomastia, or bone pains [4]. Examinations of a testicular swelling with these symptoms raise the suspicion of testicular cancer prompting appropriate further work-up.

General physical examination of suspicious testicular no-fluid-filled swelling followed by diagnostic scrotal ultrasound evaluation can diagnose with a high degree of accuracy malignant from nonmalignant testicular tumors. Ultrasonography-based findings for seminomas may include hypoechoic masses without cystic areas, while non-seminoma ultrasound findings can include inhomogeneous masses with cystic areas, calcifications, and masses with indistinct margins. Such findings are followed by measuring blood-based germ cell tumor-specific markers including alpha-fetoprotein (AFP), beta-human chorionic gonadotropin (β-hCG), and imaging scans including a high-resolution computed tomography (CT) scan of the abdomen and pelvis [3]. Based on test results that suggest a germ cell tumor, a unilateral radical inguinal orchiectomy should be entertained, as an orchiectomy provides histological confirmation, accurate pathological subtyping, and staging of tumor apart from local control and riddance of potential sanctuary sites.

5.3 Pathology of Testicular Germ Cell Tumor

The orchiectomy specimen provides the histological classification and immunohistochemistry characteristics based on which testicular germ cell tumors are divided into seminoma and non-seminoma. Seminomas are further classified as seminoma and seminoma with syncytiotrophoblastic cells. Spermatocytic tumor is a rare category of GCT [5] that typically present in the seventh decade of life in males and are typically treated with surgical resection alone. Rarely spermatocytic tumors can present with sarcoma as well on initial presentations which carries a poorer prognosis.

Non-seminomatous testicular germ cell tumors include embryonal carcinoma, teratoma, trophoblastic (choriocarcinoma), yolk sac tumors, and mixed germ cell tumors. Both seminoma and non-seminoma represent nearly 50 % each of all testicular germ cell tumors at initial presentation, but with the non-seminomas which are generally faster-growing tumors than seminoma, it is more likely that initial presentations occur in more advanced stages compared to seminomas which present more frequently with localized stage disease. In fact 80 % of all seminomas present in the localized stages, while greater than 50 % of non-seminomas present with advanced stage disease.

Pathological classification of the tumor specimen for lympho-vascular invasion (LVI) is a key initial staging feature that has impact on subsequent management strategies. Accurate initial staging includes work-up based on integrating clinical, pathological, and radiographic features; based on the tumor extent (T), as assessed by pathology, and lymph nodal (N) and metastatic involvement (M), as assessed by CT scan of the abdomen and pelvis and radiography of the chest or other parts of the body; and based on the pre-orchiectomy symptoms and signs in each patient and post orchiectomy serum tumor marker levels. Additional scans such as magnetic resonance imaging (MRI) scans of the testes are performed not routinely but as needed for clarifying the initial work-up. The TNM staging system developed by the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC) applies to all germ cell tumor staging. It is the only staging system in solid tumors which has formally incorporated levels of tumor-specific serum (S) markers into TNM staging. For testicular germ cell tumors, the marker levels are measured *after* an orchiectomy (Table 5.1). The post-orchiectomy level of the serum markers, AFP, β-HCG, and LDH, is graded between S0 and S3 and then taken together with TNM stage to form a final composite tumor stage (Tables 5.1 and 5.2). Assessing the risk for relapse and future prognosis has been extremely well categorized in the past four decades and is also stage dependent. In 1997, a consensus was reached on a uniform and validated prognostic model by the International Germ Cell Cancer Collaborative Group

Table 5.1 Staging for testicular germ cell tumors

Taken from the American Cancer Society Website: http://www.cancer.org/cancer/testicularcancer/detailedguide/testicular-cancer-staging
The TNM staging system
A staging system is a standard way for your cancer care team to sum up the extent of your cancer. Testicular cancer is staged using the TNM system created by the American Joint Committee on Cancer (AJCC). It's based on four key pieces of information:
T refers to how much the main (primary) *tumor* has spread to tissues next to the testicle
N describes how much the cancer has spread to regional (nearby) lymph *nodes*
M indicates whether the cancer has *metastasized* (spread to distant lymph nodes or other organs of the body)
S indicates the *serum* (blood) levels of tumor markers that are made by some testicular cancers
Letters or numbers appear after T, N, M, and S to provide more details about each piece of information. The numbers 0 through 4 indicate increasing severity. The letters "IS" after the T stand for in situ, which means the tumor is contained in one place and has not yet penetrated to a deeper layer of tissue. The letter X after T, N, M, or S means "cannot be assessed" because the information is not known
Primary tumor (T)
TX: The primary tumor cannot be assessed
T0: There is no evidence of primary tumor
Tis: Carcinoma in situ (noninvasive cancer cells)
T1: The tumor has not spread beyond the testicle and epididymis (the tubes next to the testicles where sperm mature). The cancer has not reached nearby blood vessels or lymph vessels. The cancer might have grown through the inner layer surrounding the testicle (tunica albuginea), but it has not reached the outer layer covering the testicle (tunica vaginalis)
T2: Similar to T1 except that the cancer has spread to blood or lymph vessels near the tumor or the tunica vaginalis
T3: The tumor is growing into the spermatic cord (which contains blood vessels, lymph vessels, nerves, and the vas deferens)
T4: The tumor is growing into the skin surrounding the testicles (scrotum)
Regional lymph nodes (N)
NX: Regional (nearby) lymph nodes cannot be assessed
N0: No spread to regional lymph nodes is seen on imaging tests
N1: The cancer has spread to at least one lymph node, but no lymph node is larger than 2 cm (about ¾ inch) across
N2: The cancer has spread to at least one lymph node that is larger than 2 cm but is not bigger than 5 cm (2 inches) across
N3: The cancer has spread to at least one lymph node that is larger than 5 cm across
If the lymph nodes were taken out during surgery, there is a slightly different classification:
pNX: Regional (nearby) lymph nodes cannot be assessed
pN0: Examination of regional lymph nodes removed with surgery reveals no cancer spread
pN1: Examination of regional lymph nodes removed with surgery reveals cancer spread in one to five lymph nodes, but no lymph node is larger than 2 cm (about ¾ inch) across
pN2: Examination of regional lymph nodes removed with surgery reveals cancer spread in at least one lymph node that is bigger than 2 cm but not larger than 5 cm across *or* spread to more than five lymph nodes that aren't bigger than 5 cm, *or* the cancer is growing out the side of a lymph node
pN3: Examination of regional lymph nodes removed with surgery reveals cancer spread in at least one lymph node that is bigger than 5 cm across
Distant metastasis (M)
M0: There is no distant metastasis (no spread to lymph nodes outside the area of the tumor or other organs, such as the lungs)
M1: Distant metastasis is present
M1a: The tumor has metastasized to distant lymph nodes or to the lung
M1b: The tumor has metastasized to other organs, such as the liver, brain, or bone

(continued)

Table 5.1 (continued)

Serum tumor markers (S)				
For staging, serum (blood) levels of tumor markers are measured *after* the testicle containing the cancer has been removed with surgery				
	LDH (U/l)	**HCG (mIU/ml)**		**AFP (ng/ml)**
SX	Marker studies not available or not done			
S0	Normal	Normal		Normal
S1*	<1.5 × Normal	<5000		<1000
S2+	1.5–10 × Normal	5000–50,000		1000–10,000
S3+	>10 × Normal	>50,000		>10,000
Stage grouping				
Once the T, N, M, and S categories have been determined, they are combined in a process called *stage grouping* to assign an overall stage (using Roman numerals and letters)				
Stage	**T**	**N**	**M**	**S**
Stage 0	Tis (in situ)	N0	M0	S0
Stage I	T1–T4	N0	M0	SX
Stage IA	T1	N0	M0	S0
Stage IB	T2–T4	N0	M0	S0
Stage IS	Any T	N0	M0	S1–S3
Stage II	Any T	N1–N3	M0	SX
Stage IIA	Any T	N1	M0	S0–S1
Stage IIB	Any T	N2	M0	S0–S1
Stage IIC	Any T	N3	M0	S0–S1
Stage III	Any T	Any N	M1	SX
Stage IIIA	Any T	Any N	M1a	S0–S1
Stage IIIB	Any T	N1–N3	M0	S2
	Any T	Any N	M1a	S2
Stage IIIC	Any T	N1–N3	M0	S3
	Any T	Any N	M1a	S3
	Any T	Any N	M1b	Any S

Note: Normal values vary among laboratories
LDH lactate dehydrogenase (measured in units per liter [U/l]), *HCG* human chorionic gonadotropin (measured in milli-international units per milliliter [mIU/ml]), *AFP* alpha-fetoprotein (measured in nanograms per milliliter [ng/ml]), < means less than, > means more than, * all the markers must be in the stated range to be considered S1, + only one marker needs to be in the stated range to be considered S2 or S3

(IGCCCG) [6] which is based on this TNM staging and forms the current basis for prognostication (Table 5.3) and also for defining definitive treatment strategies based on prognosis. Table 5.2 highlights the 5-year prognosis of good, intermediate, and poor prognosis categories.

This initial approach sets the stage for further treatment decisions that can range from surveillance to combination treatments in patients presenting with localized stage disease based on prognosis and regardless of pathological subtype.

Apart from using a pathological classification for testicular germ cell tumors, they can also be classified on anatomical location as gonadal and extra-gonadal in origin. The vast majority of germ cell tumors are of gonadal origin. In general, extra-gonadal germ cell tumors carry a poorer prognosis. In order to diagnose suspected extra-gonadal germ cell tumors, it is necessary to perform a biopsy of a presenting mediastinal or retroperitoneal or pelvic area mass for establishing a histological diagnosis and not an orchiectomy. In such presentations, additional serum tumor markers are also evaluated in aiding the initial evaluation of suspected extra-gonadal germ cell tumors.

Table 5.2 Survival rates per clinical staging in Testicular germ cell tumors

The SEER database does not divide survival rates by AJCC TNM stage. Instead, it divides cancers into summary stages: localized, regional, and distant	
Localized means that the cancer is still only in the testicle. This includes most AJCC stage I tumors (stage 0 cancers are not included in these statistics)	
Regional means that the cancer has spread to nearby lymph nodes or tissues. This includes T4 tumors and cancers with lymph node spread (all stage II cancers and some stage IIIB and IIIC cancers)	
Distant means that the cancer has spread to organs or lymph nodes away from the tumor, such as all M1 cancers (which can be stage IIIA, IIIB, or IIIC)	
Stage	**5-year relative survival rate**
Localized	99 %
Regional	96 %
Distant	73 %

Taken from the American Cancer Society Website: http://www.cancer.org/cancer/testicularcancer/detailedguide/testicular-cancer-staging

Table 5.3 IGCCCG prognostic classification of *germ* cell tumors

	Non-seminoma	Seminoma
	Good risk	
Location of primary tumor	Testis/retroperitoneal primary *AND*	Any *AND*
Non-pulmonary visceral mets	No *AND*	No *AND*
AFP (ng/mL)	<1000 *AND*	Normal *AND*
β-hCG (IU/L)	<5000 *AND*	Any *AND*
LDH (N × upper limit of normal)	< 1.5	Any
	Intermediate risk	
Location of primary tumor	Testis/retroperitoneal primary *AND*	Any *AND*
Non-pulmonary visceral mets	No *AND*	Yes *AND*
AFP (ng/mL)	≥ 1000, ≤10,000 *OR*	Normal *AND*
β-hCG (IU/L)	≥ 5000, ≤50,000 *OR*	Any *AND*
LDH (N × upper limit of normal)	≥ 1.5, ≤10	Any
	Poor risk	
Location of primary tumor	Mediastinal primary *OR*	N/A
Non-pulmonary visceral mets	Yes *OR*	
AFP (ng/mL)	>10,000 *OR*	
β-hCG (IU/L)	>50,000 *OR*	
LDH (N × upper limit of normal)	> 10	

5.4 Serum Tumor Markers in Germ Cell Cancers

As mentioned, serum alpha-fetoprotein (AFP), beta-human chorionic gonadotropin (β-hCG), and lactate dehydrogenase (LDH) play an important role in the diagnosis, prognosis, and follow-up assessment of patients in germ cell cancers [7, 8]. The interpretation of tumor marker levels in germ cell cancer management [9] has been refined for clinical application based on the results of multiple randomized clinical trials and will be discussed further in this section.

5.5 Alpha-Fetoprotein (AFP)

AFP is normally produced by the fetal yolk sac and therefore is essentially undetectable in normal adult males (normal levels in males 10–15 μg/l). As a tumor marker in germ cell cancers, it is observed to be elevated in yolk sac testicular tumors and embryonal carcinoma. Seminoma cells do not produce AFP, and therefore by definition, patients with germ cell tumors presenting with elevated AFP levels are treated as non-seminomatous germ cell tumors [9, 10].

In non-seminomas, elevated AFP levels can vary with stage of presentation as it is increased in 10–20 % with stage I disease, 20–40 % with low-volume stage II disease, and 40–60 % with advanced disseminated disease. The half-life of AFP is approximately 5–7 days [9], and, therefore, serum AFP should normalize 25–35 days (five half-lives) following effective treatment for a non-seminoma [9, 11, 12]. Failure to normalize can raise the suspicion of inadequately treated or ineffectively treated disease. There can be misleading false-positive reasons for elevated AFP levels in males. Benign liver conditions such as hepatitis, fatty liver disease, hepatocellular carcinoma, and other gastrointestinal malignancies can produce an elevation in AFP, and these should be kept in mind especially after patients have undergone localized or systemic treatments. In addition, tumor lysis during early chemotherapy could also produce a falsely positive result [9].

5.6 Beta-Human Chorionic Gonadotropin (β-hCG)

β-hCG is a common serum tumor marker for germ cell cancers. The serum concentration of β-hCG is elevated in approximately 15–20 % of patients with advanced pure testicular seminoma. In addition, 10–20 % of stage I, 20–30 % of low-volume stage II, and 40 % of advanced disseminated testicular non-seminomas present with an elevated serum β-hCG [9, 12]. The biologic half-life of β-hCG is approximately 1.5–3 days [9]. Therefore, during monitoring of treatment effect, serum β-hCG should normalize 1–2 weeks following effective treatment for a β-hCG-producing testicular cancer [9].

As with AFP, there can be false-positive reasons for elevated β-hCG levels other than germ cell tumors including in one report with the use of marijuana [13]. Other malignancies including neuroendocrine tumors, non-germ cell genitourinary cancers, lung cancer, and cancers of the female genital tract are also occasionally associated with elevated β-hCG levels. In addition, hypogonadism can also cause increased production of LH and hCG by the pituitary gland via the pituitary–gonadal axis feedback mechanism, thus leading to a falsely elevated serum β-hCG. Of note, this scenario could be observed after primary treatment of testicular cancer such as orchiectomy. Similar to the tumor lysis effect on AFP, β-hCG could also be falsely elevated during the first cycle of chemotherapy [9].

5.7 Lactate Dehydrogenase (LDH)

Approximately 40–60 % of patients with testicular cancer have an elevated serum LDH [8, 9]. As a germ cell marker and specifically testicular germ cell marker, LDH is less sensitive and specific than AFP and β-hCG, in diagnosis, and during monitoring of treatment effect or following the completion of therapy, although sometimes it may be the only positive tumor marker associated with a seminoma presentation.

5.8 Use of Tumor Markers in Testicular Germ Cell Tumors

5.8.1 As Diagnostic Markers

AFP, β-hCG, and LDH checked prior to orchiectomy for all patients with suspected testicular germ cell cancer help in establishing a diagnosis and for proceeding to performing an orchiectomy. These markers should be repeated *after* orchiectomy as the expected outcome postsurgery is for markers to decrease and normalize. Since not all

patients with seminomatous and non-seminomatous germ cell tumors actually present with elevated tumor markers, these markers are not taken alone to determine the need for a diagnostic orchiectomy.

In rare circumstances, when a reproductive age male patient presents with a primary testicular tumor with symptomatic widespread metastases, along with a markedly elevated or rapidly increasing AFP and/or β-hCG, these markers' levels aid in starting chemotherapy empirically in the absence of a diagnostic orchiectomy as it avoids delay of treatments.

5.8.2 As Prognostic Markers

As mentioned before, the International Germ Cell Consensus Classification (IGCCCG) prognostic classification is used universally and is integral in the practice of germ cell tumor management. This was developed in 1997 after a long-term follow-up of 660 patients with pure seminoma and 5202 patients with non-seminoma. The IGCCCG created clinically based prognostic classification system based on post-orchiectomy serum tumor marker levels, the site of primary tumor, and the presence or absence of non-pulmonary visceral metastases (Table 5.1) [6] .

Patients with good-, intermediate-, and poor-risk non-seminomatous germ cell tumors were shown to have 5-year survivals of 92 %, 80 %, and 48 %, respectively. In comparison, patients with good-risk and intermediate-risk seminomatous germ cell tumors had 5-year survivals of 86 % and 72 %, respectively [6].

5.8.3 For Disease Monitoring and Follow-Up

Serum tumor markers are used to monitor response following surgical resection and radiation therapy, as well as after each cycle of systemic chemotherapy. Tumor marker levels that either do not return to normal range or initially return to baseline but subsequently become elevated indicate residual or relapsed disease. Early detection of relapsed disease allows prompt initiation of salvage therapy.

For patients with stage I and II non-seminoma, post-orchiectomy serum tumor marker levels are crucial in determining the next treatment step. Patients with persistently elevated tumor markers have a high risk of relapse and therefore undergo systemic chemotherapy as their primary treatment [14–16]. For patients with normal post-orchiectomy serum tumor markers, those with stage IIA disease are considered for either systemic chemotherapy or retroperitoneal lymphadenectomy (RPLND). On the other hand, patients with stage IIB disease and normal post-orchiectomy tumor markers are offered chemotherapy followed by RPLND or surveillance if the sites of metastatic disease are not confined to the lymphatic drainage in the retroperitoneum [14].

After stage-specific treatments, tumor markers are also used for assessing the risk of recurrence, which is much higher in the first 2–3 years. Relapsed disease after 5 years is infrequent [17, 18]. Therefore, the National Comprehensive Cancer Network (NCCN) recommends an intensive early surveillance schedule including monitoring tumor markers every 3 months in the first 1–2 years. The frequency of surveillance typically becomes spaced out to every 6–12 months in years 3–5 and annually in years 5–10 [14].

5.9 Principles for the Treatment of Testicular Seminoma and Non-seminomatous Tumors

Following the clinical presentation, radiological and tumor marker evaluation of a testicular mass, the first intervention for a testicular cancer begins with a radical orchiectomy. This provides pathological staging and confirmation of histological subtypes. In rare cases a delayed radical orchiectomy is reserved in those advanced stage patients who are in need of immediate systemic therapy for rapidly growing tumors diagnosed as testicular germ cell tumors based on results of a metastatic site biopsy. Fertility and sperm banking

using cryopreservation prior to initiating any treatment for germ cell tumors are also discussed during the initial treatment planning, as testicular cancers are associated with gonadal dysgenesis and nearly 50 % of men have impaired spermatogenesis [19–21] which increases after orchiectomy or other treatments [22].

In general, seminomatous testicular tumors differ from non-seminomas in several ways. Seminomas are slower growing than non-seminomas and present more often initially in either localized or locoregional stages with only 5 % presenting in advanced stages with spread beyond retroperitoneal lymph nodes. Non-seminomatous germ cell tumors are in comparison faster to grow, and on initial presentation, nearly 33 % of all non-seminomatous testicular tumors present with stages I, II, and III. Seminomas are extremely radiosensitive compared to non-seminomas and therefore radiation therapy is a part of the treatment preamble for seminomas. Seminomas rarely spread hematogenously compared to non-seminomas, which is known to occur more commonly with non-seminomas (pulmonary, liver, brain, and bones), and so advanced stage seminomas are never considered to have poor prognosis as defined by the IGCCCG prognostic stratification system in use. Stage- and pathology-specific treatment guidelines have been well established [23] and are summarized in the following sections.

5.10 Management of Seminomas

5.10.1 Stage I

For stage I testicular seminomas, a radical orchiectomy is usually curative. Afterwards, the preferred management option is to offer a structured schedule of surveillance for at least 5 years. The surveillance schedule suggested includes a history and physical examination along with tumor marker measurements every 3–4 months for 2 years, 6–12 months for years 3–4, and then annually. Additionally imaging scans of the abdomen and pelvis are recommended every 6 months for the first 2 years, every 6–12 months for year 3, and then annually for years 4 and 5 along with a chest X-ray as needed for years 1–5 [23]. In the largest series of 1954 men who underwent a surveillance strategy for stage I seminomas, relapse was observed in 369 (18.9 %) patients after a median time of 13.7 months (range, 2.3–173.6 months) [24]. Of the 369 patients who relapsed, 16 relapsed after a 5-year follow-up. At the time of relapse, over 230 of 369 patients were salvaged with radiation therapy, while 136 underwent systemic chemotherapy, and three underwent surgery for the relapse. The overall survival after 5, 10, and 15 years for this cohort was 98.1 %, 95.5 %, and 91.6 %, respectively, and the disease-specific survival at 5, 10, and 15 years was 99.6 %, 99.4 %, and 99.3 %, respectively.

For men who are unable to comply or refuse surveillance as a management option or may harbor higher-risk features, such as lympho-vascular invasion, post-orchiectomy radiation or systemic chemotherapy with one or two cycles of carboplatin offers similar excellent long-term outcomes [25].

The choice to offer an individual patient any of the three options involves balancing the risk–benefit profile for the individual patient [23]. A shared decision with the patient is taken after explaining the pros and cons of each option. Typically, this involves highlighting the risk of overtreatment if systemic chemotherapy or radiation is chosen by way of acute and long-term toxicities over surveillance for stage I seminoma patients, as the vast majority of patients will not need treatments. This is balanced by including in the discussion the risk of relapse for stage I seminoma post-orchiectomy and the excellent salvage options available at the time of relapse.

5.10.2 Stage II

By definition, stage II disease involves lymphadenopathy below the diaphragm. Following orchiectomy and resolution of tumor markers, a radiological evaluation for bulky (>5 cm) versus non-bulky retroperitoneal lymphadenopathy is usually performed for deciding the optimal management of stage II disease. Non-bulky stage II disease patients have excellent long-term

outcomes with radiation therapy alone, which includes radiation fields extended to para-aortic and ipsilateral lymph nodes to a total dose of 30–36 Gy. On the other hand for treating stage II bulky retroperitoneal lymphadenopathy or patients with symptomatic (such as back pain) non-bulky retroperitoneal lymphadenopathy, primary chemotherapy with four cycles of cisplatin and etoposide or three cycles of cisplatin, etoposide, and bleomycin is preferred. Post treatment, patients are again followed every 3 months in year 1 with examination, tumor markers, and biannual CT imaging of the abdomen and pelvis. In years 2–5 follow-up for recurrence is every 6 months and then annually for years 6–10.

5.10.3 Stage III/Advanced Stage

Patients with advanced stage present with either lymphadenopathy above and below the diaphragm or meet the definition of advanced stage disease on the basis of non-pulmonary visceral metastasis or persistently elevated tumor markers. The approach to treatment planning starts with an initial evaluation for prognostic risk based on the IGCCCG risk stratification system (Table 5.3). By definition no seminomas are graded as "poor prognosis" and so stage III disease is either "good" prognosis or "intermediate" prognosis. This relevance for prognostication is important to establish as it has a direct impact on treatment planning. Seminomas with good prognosis receive systemic chemotherapy with either four treatments of cisplatin and etoposide or three of cisplatin, etoposide, and bleomycin, while intermediate-risk seminomas receive four treatments with cisplatin, etoposide, and bleomycin.

Posttreatment management for bulky stage II and advanced stage (III) seminoma treated with systemic chemotherapy is complex and depends on the response to chemotherapy [23]. Immediately following systemic therapy, patients should undergo imaging with CT scans of the chest, abdomen, and pelvis along with tumor markers. If there are no residual masses, or for residual masses less than 3 cm in size and normal tumor marker levels, patients are offered surveillance with exams, tumor markers, and a chest X-ray every 2 months in year 1, every 3 months in year 2, every 6 months in year 3, and then annually. CT of the abdomen and pelvis should be performed 3–6 months in the first 2 years and then as clinically indicated thereafter. If post-chemotherapy residual masses on imaging reveal a size greater than 3 cm and normal markers, a positron emission tomography (PET) scan is obtained, at least 6 weeks following treatments. If results of the scan are positive for uptake (considered to have a standardized uptake value (SUV) of >4.0 units), then a surgical resection of the mass (or lymph-nodal mass) is considered, or second-line systemic chemotherapy may be advocated if resection is considered to be risky. If the PET scan is negative, then patients are followed up as for no residual masses after chemotherapy as most of these masses resolve over time. Finally, if after completing chemotherapy, imaging reveals progressive disease or rising tumor markers, then second-line systemic chemotherapy is considered. The overall 5-year survival with the above management for patients with good-risk stage III seminomas is 92 and 72 % for the intermediate-risk group.

In addition to monitoring for treatment effects, long-term side effects of systemic chemotherapy are also monitored in the follow-up. In particular bleomycin [26, 27] can have long-term side effects in causing pulmonary toxicity and peripheral vascular disease, while cisplatin can increase the risk of nerve damage and renal insufficiency [28]. As mentioned previously, gonadal effects of treatments can lead to infertility in young men, and this potential complication of therapy can be mitigated by offering cryopreservation to men before initiating therapy.

5.11 Management of Non-seminomas

5.11.1 Stage 1

The rate of cure for non-seminoma testicular germ cell tumors like seminoma depends on the stage and prognosis at the time of initial presentation. For stage I disease patients, the 5-year survival exceeds 95 % with appropriate management

[3, 23]. Treatment planning begins following orchiectomy, and after obtaining pathological "T" staging, depending on the presence or absence of lympho-vascular invasion (LVI) for staging T1 versus T2 tumors. The absence of LVI with no radiological evidence of pelvic, abdominal, or distant metastasis (clinical stage IA) carries the most favorable prognosis. Such patients are excellent candidates for a strategy of surveillance as was observed in one large retrospective case series of 1139 clinical stage I (CSI) nonseminoma patients who were offered and followed with active surveillance between 1998 and 2010. Relapse was observed in 221 (19 %) with a median time to relapse of 4 months (range, 2–61 months) for LVI positive (CSIB) and 8 months (range, 2–77 months) for LVI negative (CSIA). The majority of relapses occurred within the first 2–3 years after orchiectomy for CSI nonseminoma (90 %) [29]. Active surveillance involves strict adherence to a structured follow-up schedule that involves repeat examinations with tumor marker measurements every 1–2 months in year one (after orchiectomy), every 2 months in year two, 3 months in year three, 4 months in year four, 6 months in year five, and then annually. Additionally imaging with CT abdomen and pelvis is performed every 3–4 months in year one, 4–6 months in year 2, 6–12 months in years 3–5, and then annually.

For those patients who are either unable to follow this schedule, nerve-sparing retroperitoneal lymphadenopathy (RPLND) for CSI or primary chemotherapy with one to two treatment cycles of cisplatin, etoposide, and bleomycin is offered as an option which produces excellent outcomes. RPLND dissection is both diagnostic to stage microscopic pathological nodal involvement and performed with curative intent. However, these options can have complications such as retrograde ejaculation and infertility with RPLND, or long-term complications of systemic chemotherapy. An individual assessment of risk–benefit ratio has to be made while offering any of the three choices, all of which have excellent long-term survival results.

A specific substage classified in CSI is CSIS, which stands for persistent tumor marker(s) elevation post-orchiectomy. Such patients are best treated with three to four treatment cycles of systemic chemotherapy as they usually harbor disease outside the retroperitoneum.

5.11.2 Stage II

Imaging of retroperitoneal lymph nodes in patients presenting with stage IIA disease is by definition less than 2 cm and between 2 and 5 cm for stage IIB. CSIIA patients with normalized post-orchiectomy tumor markers are best treated with nerve-sparing RPLND which confirms pathological nodal involvement. Following a RPLND adjuvant systemic chemotherapy is typically reserved for men if the pathological nodal involvement is detected to be greater than 2 cm as the relapse risk is highest for this category. For clinical stage IIB and IIC (lymph node size greater than 5 cm), primary systemic chemotherapy with either four treatments of cisplatin and etoposide or three of cisplatin, etoposide, and bleomycin is offered.

For all stage II patients treated with primary systemic chemotherapy, posttreatment tumor markers and imaging are performed 3–4 weeks after the last treatment. Negative markers with resolution of lymph nodal masses are typically followed with surveillance, while if markers have normalized, but imaging reveals remnant nodal masses, a RPLND is offered in such cases. If markers have not normalized, such carry a poor prognosis and are generally offered salvage chemotherapy with ifosfamide- and taxane-based regimens.

5.11.3 Stage III

Advanced or stage III disease is treated with primary systemic chemotherapy following orchiectomy and tumor marker and radiographic imaging. The number of treatments is based on the results of these investigations and the final prognostic category. Good prognosis advanced stage disease is treated with either four treatments of cisplatin and etoposide or

three of cisplatin, etoposide, and bleomycin, while intermediate to poor prognosis is treated with four treatments of cisplatin, etoposide, and bleomycin. Between 20 and 25 % of patients with advanced germ cell tumors present with hepatic, bone, or brain metastases or with mediastinal masses or with extremely high tumor markers. The success of cure in such poor prognosis is low.

After completion of primary systemic chemotherapy for patients with complete response surveillance with examination, tumor marker and radiographic assessments are used to guide further management. Patients with normalized tumor markers who have radiographic residual disease undergo resection. The presence of necrotic debris or teratoma requires no further treatments. However, if viable germ cell tumor is detected pathologically, in order to maximize the rate of cure, additional two cycles of systemic chemotherapy are offered. Further follow-up should include history and examination with tumor markers every 2–3 months for the first 2 years, every 3–6 months in year 3, every 6 months in years 4 and 5, and then annually. Radiography with CT imaging of the abdomen and pelvis with chest X-rays is performed every 6 months in the first 2 years and then annually until year 5 and as clinically indicated after that.

During follow-up after chemotherapy, detection of masses that appear to increase in size in the presence of normal tumor markers should raise the suspicion of a growing teratoma syndrome in such presentations. The treatment for these chemo-insensitive masses is surgical resection without chemotherapy.

5.12 Resistant of Recurrent Disease

For advanced stage patients who recur after primary systemic chemotherapy or who fail to show a complete response to therapy, second-line systemic chemotherapy with combinations of ifosfamide, taxane, and platinum agents or gemcitabine is preferred as it offers a chance of cure in at least 25 % of such cases [30, 31]. High-dose or autologous stem cell rescue is offered to patients who are not cured with the above combinations [32–34].

5.13 Ovarian Germ Cell Tumors

Germ cell tumors may also arise from the ovary accounting for approximately 2–3 % of ovarian malignancies in distinction to the more common epithelial type [35, 36]. Ovarian germ cell tumors most commonly occur in women in their 20s. The WHO histological classification for ovarian germ cell tumors differs from testicular germ cell cancers [37, 38]. Broadly, ovarian germ cell tumors are divided into embryo-like (teratomas and dysgerminomas) or extraembryonic (placenta-like) cell populations or a mixture of both. Teratomas can have several subtypes including benign cystic mature teratoma (dermoid cyst) which is the most common ovarian germ cell tumor and immature teratoma. Mature teratomas can also develop a somatic malignant neoplasm (mature teratoma with malignant degeneration). Dysgerminomas are the female equivalent to seminomas in males. On the other hand, yolk sac tumors are ovarian carcinomas that differentiate toward primitive endodermal structures, while the rare mixed germ cell tumors can have a mixture of all of the above elements. They are clinically treated based on the most aggressive histological component. Among malignant ovarian germ cell tumors, dysgerminomas, yolk sac tumors, and immature teratoma account for greater than 90 % of all cases. Embryonal carcinoma, mixed germ cell tumors, non-gestational choriocarcinoma, and polyembryoma are far more rare in occurrence. For ovarian germ cell tumors based on clinical TNM classification, there are four stages as opposed to testicular cancers, which have three. Overall, although there are a number of similarities between ovarian germ cell tumors and testicular cancers, there are some key differentiating features of both which influence which treatment modalities are used. Both diseases share in common significant chemosensitivity of disease and, therefore, overall favorable prognosis.

Approximately 60–70 % of ovarian germ cell tumors present in stage I when diagnosed, which means that cancer is found in one or both ovaries. Most of these are confined to a single ovary (stage IA disease).

Clinically, the majority of ovarian germ cell tumor patients present with abdominal pain and a palpable mass. Since many ovarian germ cell tumors produce hormones including β-hCG, symptoms of pregnancy can often be mimicked in the initial presentation. Other less common symptoms include abdominal distention, fever, urinary symptoms, and vaginal bleeding. When an ovarian germ cell tumor is suspected, for evaluating these nonspecific symptoms, additional testing with β-hCG and AFP tumor markers is often performed. β-hCG is commonly produced by embryonal carcinomas with trophoblastic component, ovarian carcinomas, mixed germ cell tumors, and some dysgerminomas, while elevated AFP levels are suspected in yolk sac tumors, embryonal carcinoma, mixed germ cell tumors with yolk sac tumor component, and some immature teratomas. As with testicular germ cell tumors, these markers aid in diagnosis and also for monitoring response and recurrence following treatments. Imaging with transvaginal ultrasound or MRI in the initial work-up also plays a key role.

Surgery is typically the first step in treatment for ovarian germ cell tumors, both for diagnosis and therapy [39]. Preoperative elevated levels of β-hCG in children, teens, or young women can indicate specific subtypes of germ cell tumors as mentioned and apart from providing diagnostic clues can also aid in preparing for surgery while preserving fertility. Since most of these tumors are unilateral and occur in young women, fertility preservation is an integral part in treatment planning along with the surgical approach which typically involves offering a unilateral salpingo-oophorectomy with preservation of the uterus if these organs appear normal during surgical resection. For bilateral disease however, a bilateral salpingo-oophorectomy is done, though, in both cases, the uterus is typically not removed.

For patients diagnosed with stage IA dysgerminoma following surgery, surveillance is offered. Surgical principles are heavily dependent on maximal cytoreduction if disease is advanced. The recurrence rate is 15–20 % in early-stage presentations, and adjuvant combination chemotherapy postsurgery or at the time of recurrence offers a high chance of cure. Dysgerminomas are also very radiosensitive like testicular seminoma, though use of adjuvant radiotherapy for stage IA disease has fallen out of favor due to long-term side effects. For patients with dysgerminoma and stage greater than IA, combination adjuvant chemotherapy in the form of bleomycin, etoposide, and cisplatin (BEP) is given usually with three treatment cycles for fully resected disease and four cycles for those with microscopic residual disease [40]. Surveillance post treatment is critical and should include serial history, physical examinations, tumor markers, and radiographical surveillance to be performed for at least 2 years if the tumor markers were not elevated initially. For dysgerminomas late relapses can occur and annual surveillance up to 10 years is a clinical consideration as well.

For patients with non-dysgerminomas, typically combination chemotherapy after resection of disease is offered regardless of final stage. As with dysgerminomas, the most common regimen is BEP. Patients with stage IA, grade 1 immature teratoma which is fully resected can be observed without postoperative chemotherapy especially in the case of a motivated patient. For patients with immature teratoma of similar stage, but grade 2 or 3, there is a higher risk of recurrent disease, and, therefore, postoperative chemotherapy is considered. All patients with non-dysgerminomas should receive active and serial follow-ups on nearly similar schedules as male patients with non-seminomatous germ cell testicular tumors.

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