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REVIEW ARTICLE

Testicular germ cell tumors

N. Diamantopoulos[1], A. Kortsaris[2]

[1]Department of Medical Oncology, Papageorgiou General Hospital, Thessaloniki; [2]Department of Biochemistry, Medical Faculty, Democritus University of Thrace, Alexandroupolis, Greece

Summary

Testicular cancer is the most frequent solid tumor in young male adults and a disease with elusive pathogenesis. Germ cell tumors represent 95% of all testicular cancers. There was an increasing incidence of testicular germ cell tumors during the second half of the 20th century. Despite their increased incidence, mortality is lower than 10% and the cure rate has reached 95%. Epidemiology of the disease shows remarkable geographic and racial variation. Known risk factors and the increased incidence during the last 50 years have led to the development of the two prevalent theories for the pathogenesis of the disease, Henderson theory and Rajpert-de Meyts and Skakkebaek theory.

Appropriate diagnosis and staging of the disease are crucial for successful management. Testicular ultrasound, CT scans, histological examination and serum tumor markers should be utilized in order to stratify the patient correctly. Treatment strategy is chosen according to the patient stage and prognostic group stratification. "Fine tuning" is needed in order to find the balance between treatment, cure and toxicity. Despite progress in therapeutic management, cure rates for poor risk patients do not exceed 50%. These patients should be encouraged to participate in clinical trials.

Long-term toxicity of testicular germ cell tumors' treatment is also another issue that should be kept in mind during follow-up of these patients. This disease became the model of "curable" cancer and gave hope for cure of metastatic malignant diseases in general, as only 400 patients die from this disease in USA annually. More progress will be made only through well-designed clinical trials.

Key words: diagnosis, germ cell tumors, pathogenesis, risk factors, testicular cancer, treatment

Introduction

Testicular cancer is a relatively rare neoplasm, representing 1-1.5% of all malignant male tumors and 5% of all urological tumors. Despite its low incidence testicular cancer is the most common diagnosis of solid tumor in men between the ages of 15 and 35 [1]. Germ cell tumors represent 95% of all testicular cancers. During the last 50 years their incidence has doubled in industrialized countries, attributed to a birth cohort effect and early environmental exposure to yet unidentified carcinogens [2]. Great advances have been made in the treatment of testicular cancer and the cure rate is now above 90%, reaching 80% for metastatic disease [3].

Epidemiology

The risk of developing testicular cancer shows remarkable geographic and racial variation. Scandinavia (with the exception of Finland), Germany, Switzerland and New Zealand are the countries with the highest incidence of testicular germ cell tumors (Figure 1). Whites have the highest incidence and blacks have the lowest, with other races having values between those two (Figure 2).

As SEER data shows, there was a remarkable increase in the incidence of testicular cancer between the years 1950-2000. The risk of developing testicular cancer quadrupled from 1950 to 1990 and increased by 44% from 1973-1978 to 1994-1998. The increase was greater for seminomas than for non-seminomatous germ cell tumors (NSGCTs) (62% and 24%, respectively). There is also a trend for stabilization of the incidence during the last decade (Figure 3). Scant data for Greece show that the annual incidence of testicular germ cell tumors is 5-6 per 100,000 men, at the same level as other countries of the region [4-7].

Correspondence to: Nikolaos Diamantopoulos, MD. Department of Medical Oncology, Papageorgiou General Hospital, Periferiaki Odos, 564 03 Nea Eukarpia, Thessaloniki, Greece. Tel: +30 2310 693141, Fax: +30 2310 960431, E-mail: ndiamantopoulos@yahoo.com

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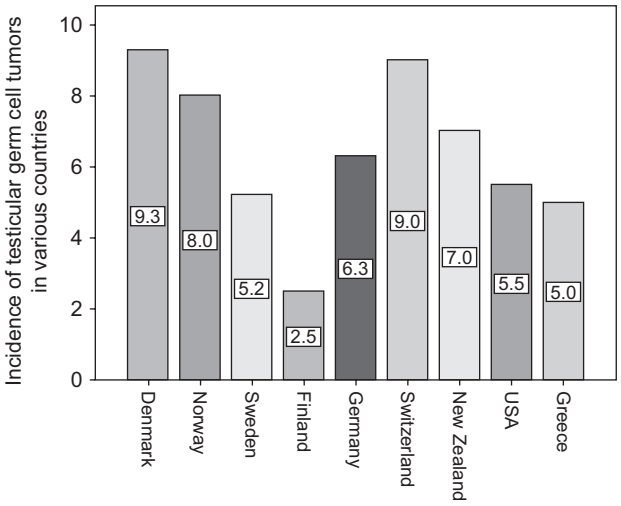

Figure 1. Incidence of testicular germ cell tumors in various countries (patients per 100,000 men annually).

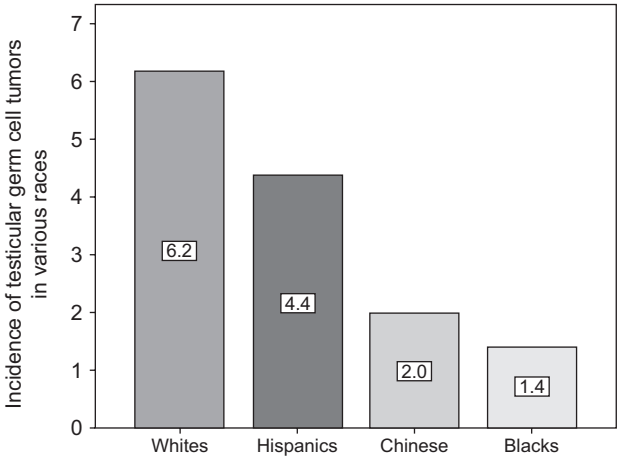

Figure 2. Incidence of testicular germ cell tumors in various races (patients per 100,000 men annually).

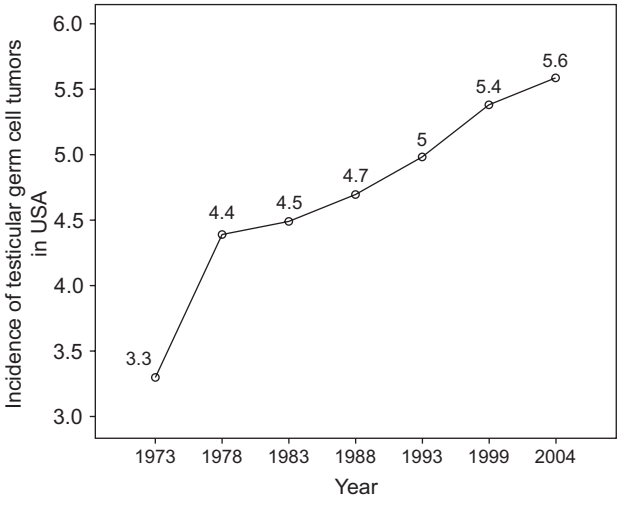

Figure 3. Incidence of testicular germ cell tumors in USA per 100,000 men (1973-2004).

The incidence of testicular germ cell tumors shows 3 age peaks. The first peak is between 0-4 years, when teratomas and yolk sac tumors are increased, the second between 25-40, when classic germ cell tumors develop and the third after the age of 60, when there is an increase of lymphomas and spermatocytic seminomas. It must be emphasized that pediatric germ cell tumors and spermatocytic seminomas have different pathogenesis and treatment than classic adult germ cell tumors [8-10].

The ratio of seminoma and NSGCTs is equal and there is a small prevalence of right testicular tumors, where 55% of tumors develop. The median age at diagnosis of seminomas is 37 years and of NSGCTs is 27 years. It should also be mentioned that extragonadal germ cell tumors comprise 5% of the total, with an annual incidence of 0.2-0.3 per 100,000 population [11].

Risk factors

There is a variety of risk factors for developing germ cell tumors (Table 1). Most of these risk factors have been established through epidemiologic research and their exact mechanism of action still remains elusive. Intratubular germ cell neoplasia unclassified (ITGCNU) is the precursor lesion of all testicular germ cell tumors except spermatocytic seminoma and pre-adolescent tumors. The existence of ITGCNU has been proven in all the high risk groups and has a central role in the pathogenesis of these tumors. It must be mentioned that the term "carcinoma *in situ*", which is usually used instead of ITGCNU, is not suitable as this is not an epithelial lesion. The incidence of ITGCNU is the same as the incidence of germ cell tumors, 1% in general population, 2-5% in patients with an invasive germ cell tumor at the other testicle, 8% or more in men with cryptorchidism and increased respectively in all other high risk groups. At 5 years 50% of ITGCNU will evolve

Table 1. Risk factors for testicular germ cell tumors' development

Intratubular germ cell neoplasia unclassified (ITGCNU)
Cryptorchidism
History of contralateral testicular germ cell tumor
History of extragonadal germ cell tumor
Family history
HIV infection
Testicular microlithiasis
Androgen insensitivity syndrome
Disorders of sex development
Subfertility and testicular atrophy
Fetal exposure to steroid hormones
Ethnicity and race
Dietary and environmental factors
Other factors

into invasive tumors and 70% will do so after 7 years. Treatment of ITGCNU is controversial and usually low dose radiation therapy is used [12,13].

The most frequent risk factor for developing a testicular germ cell tumor is cryptorchidism, as 10% of the patients have a history of this disorder. The risk of developing a testicular tumor in men with a history of cryptorchidism is increased between 3-14 times. This depends on the site of the disorder, as intra-abdominal cryptorchidism carries a much greater risk than inguinal. Also, the risk is lower if orchiopexy is performed before the age of 5. It should be mentioned that germ cell tumors also develop at the healthy testicle of these men; 25% of the tumors will develop in the contralateral testis. There is an increasing incidence of testicular tumors in men with various urological birth defects, such as hypospadias, inguinal hernia and renal defects, which can lead to the hypothesis of the existence of a common environmental or genetic factor that leads to these defects and to the development of ITGCNU [14,15].

Another established risk factor is the existence of germ cell tumor in the other testicle. These patients bear a risk of developing germ cell tumor between 2 and 5%, which shows the same geographic and racial variation. The risk at 25 years of follow- up is 5.2% in Denmark and only 1.9% in USA. The majority of these patients have developed ITGCNU in the healthy testicle, so in Denmark most surgeons perform biopsy of the healthy testicle during orchiectomy. There is also an increase in testicular germ cell tumors for patients diagnosed with extragonadal primaries. Ten-year risk of developing a testicular tumor is 14.3% for non-seminomatous extragonadal tumors, 14.2% if the primary is retroperitoneal, 6.2% if the primary is mediastinal and only 1.4% for pure extragonadal seminomas [16,17].

Family history also increases the risk 4-10 times. The risk is higher if the brother had the disease and lower if the father was the patient. There are some families with increased incidence of testicular germ cell tumors and although no particular gene has been linked to the disease there is a positive correlation with Xq27 region. The small number of patients with familial disease (only 1% of the total) makes investigation for discovery of a specific genetic locus difficult. The tumors seem also to develop at an earlier age in successive generations, according to the rules of genetic anticipation [18,19].

Other high risk factors for developing testicular cancer are the androgen insensitivity syndrome and other disorders of sex development, HIV infection (which increases the risk only for seminoma development), Down and Marfan syndromes, ichthyosis and dysplastic nevus syndrome. Also there seems to be a relatively slightly increased risk for men with subfertility and testicular atrophy. Increased testicular temperature (due to occupational reasons), testicular injuries and orchitis (due to mumps virus), have been often mentioned as probable risk factors for testicular tumor development but without substantial evidence. Also microlithiasis, a common finding at testicular ultrasound, has been correlated with germ cell tumor development, but without significant proof [20-26].

Klinefelter syndrome increases 70 times the risk of developing mediastinal germ cell tumors. Peutz-Jeghers syndrome and Carney syndrome have also been linked with non germ cell testicular tumors, especially with Sertoli and Leydig tumors. Estrogen use during the first trimester of pregnancy increases 2-3 times the risk of testicular germ cell tumors. Vasectomy, which was correlated with increased risk for testicular tumors, does not seem to be a predisposing factor according to new epidemiological data. Various perinatal risk factors for germ cell tumor development, such as low birth weight and height, have been linked to these tumors. Also without significant proof, diet rich in animal fat, dairy products and sedentary lifestyle have been correlated with increased incidence of germ cell tumors. Finally, infectious agents, such as retroviruses, have not been sufficiently ruled out as cofactors in testicular germ cell tumors development [27-33].

Pathogenesis

ITGCNU develops during the 8-12 week of fetal development. This was proved from gene expression of this disorder, where c-Kit, placental-like alkaline phosphatase (PLAP) and transcriptional factors such as OCT-3, OCT-4 and AP-2γ show increased expression. These genes are normally expressed during the first trimester fetuses. Also, the notion that ITGCNU forms during the 8-12 week of fetal life is proved by the fact that genomic imprinting has not occurred when this disorder develops. It is proposed that the non-methylating CpG status of 5'-region of XIST gene can be used as molecular marker of the disease [34-36].

All these lesions are usually polyploid. Pure seminomas and the cells of ITGCNU are sometimes hypertriploid. In contrast, NSGCTs are more frequently hypotriploid or hyperdiploid. Generally, regions of chromosomes 11, 13, 18 and Y are under-represented, while regions from chromosomes 7, 8, 12, 21 and X are over-represented. Isochromosome 12p [i(12p)] seems to be the most common abnormality. No specific gene of this chromosome has been correlated with testicular tumors, although CCDN2 gene which codes for cyclin D2 is mentioned frequently. Other candidate genes are SOX5,

JAW1, K-ras, NANOG, DPPA3 and GDF3. The c-Kit gene is also mutated in 10-20% of seminomas, with exon 17 mutation being more common [37-41].

Telomerase activity is increased in these tumors, especially in embryonal carcinomas. Mature teratomas have the lowest telomerase activity, which correlates with their low mitotic index. Mutation of p53 gene is not a frequent event in these tumors and it has been linked with chemotherapy resistance. In prepubertal males, teratomas and yolk sac tumors are almost exclusively the only tumors encountered. Teratomas are usually benign in this age group without any chromosomal abnormality and yolk sac tumors have different chromosomal abnormalities than the adult type of tumor, usually 1q and 3 chromosome gains. ITGCNU does not occur in these patients. Finally, spermatocytic seminomas develop in older adults. These tumors do not have ITGCNU regions and loss of imprinting, are PLAP-negative and only rarely express c-Kit. They have different pathogenesis from classic seminomas and the only chromosomal abnormality found is gain of chromosome 9 [42-44].

All the above seem to give substantial proof to the theories of Henderson in 1983 and Rajpert-de Meyts and Skakkebaek in 1993 about the pathogenesis of these tumors. According to these theories, during the first trimester of fetal development there is a crucial time for the migration and differentiation of primordial germ cells, which are coming from the inner part of the blastocyst. Fetal exposure during this time to some environmental factors, especially to steroid hormones like estrogens, will lead to ITGCNU development. Later, during adolescence and because of the changing hormone environment of teenagers, like the increasing gonadotropin (FSH and LH) levels, ITGCNU evolves to an invasive tumor. The probability of this event increases with the coexistence of lower levels of testosterone. ITGCNU can evolve either to seminoma or to embryonal carcinoma, which will differentiate to the other more mature non-seminomatous histological types [45,46].

Many experimental and epidemiological data exist to support these theories. Diethylstilbestrol use during pregnancy doubles the risk of testicular cancer. Excessive vomiting during pregnancy, increase of weight above normal, metrorrhagia, first pregnancy, dizygotic twins and increasing maternal age are events that correlate with increased estrogen levels. The same events have also been correlated with increased testicular cancer risk of male children. Acne and alopecia, which correlate with increased levels of androgens, are rarely encountered in patients with germ cell tumors. Dizygotic twins, which have higher levels of FSH during adolescence than monozygotic, have higher risk of germ cell tumors development. Also, patients with Kallman syndrome, where cryptorchidism coexists with low gonadotropin levels, do not have increased risk of testicular germ cell tumors. Finally, exposure of experimental animals to estrogens during a specific time of their fetal development leads to a substantial increase of germ cell tumors development [47].

Diagnosis-Pathology-Staging

Painless testicular mass is the predominant symptom of testicular cancer. Some patients present with symptoms of epididymitis or orchitis and a trial of antibiotic therapy is often undertaken. If the testicular discomfort continues after 15-30 days, a testicular ultrasound with 7.5 MHz transducer is utilized. About 10% of patients present with symptoms of metastatic disease, most commonly cough, dyspnea and lumbar back pain. Rare presentations include a neck mass, bone pain from metastases, central nervous system symptoms, thrombosis and lower extremity swelling, gastrointestinal symptoms and oliguria due to ureter obstruction. Gynecomastia due to increased levels of β-hCG and rarely hyperthyroidism can occur. Also, paraneoplastic limbic encephalitis with anti-Ma2 antibodies can rarely occur. On ultrasound, testicular tumor is usually intratesticular with one or more hypoechoic masses. A cystic or fluid-filled mass is unlikely to represent malignancy. In comparison, seminomas appear as well-defined hypoechoic lesions without cystic areas, while NSGCTs are typically inhomogeneous with calcifications, cystic areas, and indistinct margins [48,49].

A radical inguinal orchiectomy with ligation of the spermatic cord at the deep inguinal ring is used as both a diagnostic and therapeutic method. Other staging procedures that should be used are abdominal and thoracic CT (alternatively X-ray if no abdominal metastases are detected), combined with serum tumor marker measurement (AFP, β-hCG and LDH), careful pathological examination of the tumor and a comprehensive history and physical examination. Hematological analysis and biochemical blood tests should be undertaken before treatment initiation. Brain MRI, bone scan and other specialized examinations are used only to address specific symptoms or laboratory pathological values. Brain MRI should also be done if the serum β-hCG value is above 5000 mIU/ml. During the imaging studies it should be kept in mind that the usual initial route of metastasis is lymphatic drainage to the retroperitoneal lymph nodes. The primary landing zone for a right testicular tumor lies in the interaortocaval nodes inferior to the renal vessels and the ipsilateral distribution includes the paracaval, preaortic, and right com-

mon iliac lymph nodes. For a left testicular tumor the first groups of lymph nodes that become metastatic are the paraaortic nodes inferior to the left renal vessels and the preaortic and left common iliac nodes. Metastatic disease to other pelvic and inguinal lymph nodes is usually secondary to a large-volume disease, with the exception of previous surgery to the region (hernia, vasectomy) or T4 disease. Contralateral disease can also occur more frequently with right-sided tumors. It is rare for left-sided tumors, except in the presence of extensive disease [50-53]. Testicular germ cell tumors are evenly distributed between pure seminomas and all other histologies (Table 2). Embryonal carcinoma in its pure form accounts for 2% of all testicular tumors, but it is a component of 85% of NSGCTs. Pure yolk sac tumor is rare in adults, but occurs in 40% of mixed NSGCTs. Choriocarcinoma is the rarest and most aggressive type of germ cell tumor in its pure form (less than 1% of all tumors), but it occurs in only 10% of mixed NSGCTs. Is should also be noted that syncytiotrophoblasts may be present in seminomas and in embryonal carcinomas, raising β-hCG value above normal. Teratomas in adults are usually part of mixed NSGCTs and they can metastasize, even the mature ones, in contrast to pediatric teratomas. Teratoma is a tumor with tissue or organ components resembling normal derivatives of all three germ layers, containing respiratory tract, gut, pancreas, thyroid, cartilage, squamous epithelium, and skin adnexal structures. Teratoma is called immature if it contains undifferentiated elements, resembling tissue seen in embryonic stages of development. Rarely a malignant transformation can be seen [54].

Table 2. Classification of testicular tumors

Germ cell tumors
Seminoma (classic, atypical, spermatocytic)
Embryonal carcinoma
Teratoma (mature, immature, malignant transformation)
Choriocarcinoma
Yolk sac tumor
Mixed germ cell tumors
Sex cord-stromal tumors
Sertoli cell tumor
Leydig cell tumor
Granulosa cell tumor
Mixed-unclassified
Mixed germ cell and stromal elements
Gonadoblastoma
Adnexal and paratesticular tumors
Rete testis adenocarcinoma
Mesothelioma
Rhabdomyosarcoma
Miscellaneous
Lymphoma
Carcinoid
Metastases

Immunohistochemistry can also be used to differentiate between the various histologic subtypes. Seminoma is negative for cytokeratins and CD30 immunostains, in contrast to embryonal carcinoma. Seminomas and embryonal carcinomas are also positive for OCT 3/4 and NANOG, in contrast to yolk sac tumors. Sox-2 stains positive only in embryonal carcinomas and c-Kit only in seminomas. AFP stains positive only in yolk sac tumors, but background staining is usually high. Staining for β-hCG supports a diagnosis of choriocarcinoma, but giant syncytiotrophoblastic cells can also be found in seminomas and embryonal carcinomas, so it is the existence of cytotrophoblasts that would verify the diagnosis [55,56].

Three serum tumor markers are used in diagnosis and staging of testicular germ cell tumors: β-hCG, AFP and LDH. Serum concentration of β-hCG is elevated in 40% of patients with NSGCTs and AFP is elevated in 60%. At least one of them is elevated in 80-85% of patients. Serum AFP is elevated in yolk sac tumors and less often in embryonal carcinomas. β-hCG is elevated in choriocarcinomas, in embryonal carcinomas and in 15% of seminomas. Serum half life of β-hCG is 18-36 hours and of AFP is 5-7 days. This is important, when somebody considers the rate of normalization after orchiectomy or after chemotherapy. False-positive results should also be ruled out before the initiation of treatment. Serum LDH concentrations are elevated in 30 to 80% of men with pure seminomas and in 60% of those with non-seminomatous tumors. It is neither a sensitive nor a specific marker, but it may be the only elevated marker in seminomas. Another tumor marker that is more sensitive in seminomas, PLAP, is not used in clinical practice because of lack of specificity. Tumor markers have also prognostic value and they are incorporated in testicular germ cell tumor staging [57,58].

After all the above studies (pathologic examination of orchiectomy specimen, imaging studies and measurement of tumor markers) are completed, staging of the tumor is made using TNM staging system developed by the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC) (Tables 3,4). Metastatic tumors should be classified in a specific prognostic group according to 1997 International Germ Cell Cancer Collaborative Group (IGCCG) consensus (Table 5). Treatment will be decided according to the stage and the prognostic group of the tumor. Before initiating treatment, especially chemotherapy, it would be prudent to have a sperm diagram and semen preservation ordered. It should also be mentioned that sometimes, when disease is too exten-

Table 3. Tumor (T) Node (N) Metastasis (M) and Serum marker (S) staging for testicular cancer

Primary tumor-pathologic (pT) staging. The extent of primary tumor is classified after radical orchiectomy	
pTx	Primary tumor cannot be assessed
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- Clinical staging (N) or pathologic (pN) staging	
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
pN1	Metastasis with a lymph node mass 2 cm or less in greatest dimension and less than or equal to 5 nodes positive, 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
pN2	Metastasis with a lymph node mass more than 2 cm but not more than 5 cm in greatest dimension; or more than 5 nodes positive, none more than 5 cm; or evidence of extranodal extension of tumor
N3	Metastasis with a lymph node mass more than 5 cm in greatest dimension
pN3	Metastasis with a lymph node mass more than 5 cm in greatest dimension
Distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis
M1a	Non-regional nodal or pulmonary metastasis
M1b	Distant metastasis other than to non-regional lymph nodes and lung

Serum tumor markers (S)

	LDH	*HCG, mIU/mL*	*AFP, ng/mL*
S1	<1.5× upper limit of normal value	<5000	<1000
S2	1.5-10× upper limit of normal value	5000-50000	1000-10000
S3	>10× upper limit of normal value	>50000	>10000

sive for orchiectomy to be performed, chemotherapy should begin immediately. This is the case with choriocarcinoma, when very high values of β-hCG coexist with widespread hematogenous metastases [59-61].

Treatment

Stage I

Seminoma

Approximately 80-85% of seminoma patients are classified as stage I disease at initial presentation. High risk features for relapse are considered primary tumor size greater than 4 cm and rete testis invasion. If both of these factors are present (20% of the patients), the risk of relapse can be as high as 40%. If one of these factors is present (40% of the patients), the risk of relapse is about 25% and if no factor is present the risk is only 10-15%. Another important fact about stage I seminomas is that 30% of relapses occur more than 3 years from diagnosis. Also, there is no reliable tumor marker to follow-up these patients.

Taking all these into consideration, there are 3 alternatives for these patients. Intensive follow-up is the less popular option. A second option is adjuvant radiotherapy, using 20 Gy in 10 fractions to paraaortic strip, in order to minimize side effects. The risk of relapse will be less than 5% after radiotherapy, with slightly more pelvic relapses with the paraaortic field than the traditional "hockey stick" field, but with much less side effects. Finally, another option is chemotherapy with 1 cycle of

Table 4. Stage grouping for testicular cancer

Stage	*TNMS*
0	pTisN0M0S0
IA	pT1N0M0S0
IB	pT2N0M0S0, pT3N0M0S0, pT4N0S0
IC	pTx-4N0M0S1-3 (S as measured after orchiectomy)
IIA	pTx-4N1M0S0, pTx-4N1M0S1
IIB	pTx-4N2M0S0, pTx-4N2M0S1
IIC	pTx-4N3M0S0, pTx-4N3M0S1
IIIA	pTx-4Nx-4M1aS0, pTx-4Nx-4M1aS1
IIIB	pTx-4N1-3M0S2, pTx-4Nx-4M1aS2
IIIC	pTx-4N1-3M0S3, pTx-4Nx-4M1aS3, pTx-4Nx-4M1bS0-3

carboplatin dosed at an area under the concentration x time curve [AUC] of 7, using an EDTA assessment of the glomerular filtration rate. Alternatively, 2 cycles of carboplatin dosed at AUC 6 can be used, something that makes many medical oncologists feel more comfortable. Relapses are similar with chemotherapy and radiotherapy, with less frequent contralateral germ cell tumors in the chemotherapy arm. Also, relapse when radiotherapy is used is more common in the lungs and when chemotherapy is used it is more common in the retroperitoneal lymph nodes [62-68].

NSGCTs

Forty percent of NSGCTs patients present with stage I disease. Most of them are cured with orchiectomy alone, although 30% will relapse. The two most frequently accepted risk factors for relapse are the presence of embryonal carcinoma above 30% and the presence of lymphatic or vascular invasion. If any of these factors is present, the risk of relapse can reach 40-50%, otherwise it is only 10-15%. Also, almost all the relapses occur during the first 3 years and are treatable, something that makes low risk patients ideal for intensive surveillance. For patients with high risk disease (or patients with low risk who deny surveillance), there are two alternatives. Retroperitoneal lymph node dissection (RPLND) is an option only at institutions with large experience in this procedure, with surgeons performing at least 20-30 RPLNDs per year. Patients having pN2 disease after surgery will need additionally 2 cycles of chemotherapy. Two cycles of adjuvant chemotherapy with BEP (bleomycin, etoposide, cisplatin; Table 6) is the treatment used more often for high risk patients, something that lowers the chance of relapse below 3%. After the German prospective multicenter trial, many oncologists feel comfortable with only one cycle of chemotherapy, but this is not yet the standard of care. We should mention that disease in patients with stage IS, which comprise almost one fourth of NSGCTS patients with stage I, is considered micrometastatic and is treated with 3 cycles of BEP chemotherapy [69-73].

Table 5. Prognostic classification of testicular germ cell tumors according to the International Germ Cell Cancer Collaborative Group (IGCCG) consensus

Prognostic group	*Seminoma*	*NSGCTs*
Good	1) Any primary site 2) No non-pulmonary visceral metastases 3) Normal serum AFP 4) Any value for LDH and β-hCG	1) Testicular or retroperitoneal primaries 2) No non-pulmonary visceral metastases 3) AFP <1000 ng/ml 4) β-hCG <5000 mIU/ml 5) LDH <1.5× upper limit of normal value
Intermediate	1) Any primary site 2) Existence of non-pulmonary visceral metastases 3) Normal serum AFP 4) Any value for LDH and β-hCG	1) Testicular or retroperitoneal primaries 2) No non-pulmonary visceral metastases 3) AFP 1000-10000 ng/ml 4) β-hCG 5000-50000 mIU/ml 5) LDH 1.5-10× upper limit of normal value
Poor	Does not exist	At least one of the following: 1) Mediastinal primary site 2) Existence of non-pulmonary visceral metastases 3) AFP >10000 ng/ml 4) β-hCG >50000 mIU/ml 5) LDH >10× upper limit of normal value

Table 6. Chemotherapy regimens for testicular germ cell tumors

First line regimens	
BEP (5-day regimen-every 21 days)	Bleomycin 30 units, days 1,8,15 i.v Etoposide 100 mg/m^2, days 1-5 i.v Cisplatin 20 mg/m^2, days 1-5 i.v
BEP (3-day regimen, every 21 days)	Bleomycin 30 units, days 1,8,15 i.v Etoposide 165 mg/m^2, days 1-3 i.v Cisplatin 35 mg/m^2, days 1-3 i.v
EP (every 21 days)	Etoposide 100 mg/m^2, days 1-5 i.v Cisplatin 20 mg/m^2, days 1-5 i.v
VIP (every 21 days)	Etoposide 75 mg/m^2, days 1-5 i.v Ifosfamide 1.2 g/m^2, days 1-5 i.v (+mesna) Cisplatin 20 mg/m^2, days 1-5 i.v
Second line regimens	
VeIP (every 21 days)	Vinblastine 0.11 mg/kg, days 1-2 i.v Ifosfamide 1.2 g/m^2, days 1-5 i.v (+mesna) Cisplatin 20 mg/m^2, days 1-5 i.v
TIP (every 21 days)	Paclitaxel 250 mg/m^2, day 1 i.v (24h infusion) Ifosfamide 1.5 g/m^2, days 2-5 i.v (+mesna) Cisplatin 25 mg/m^2, days 2-5 i.v
High dose regimen (2 cycles)	Carboplatin 700 mg/m^2, days 1-3 i.v Etoposide 750 mg/m^2, days 1-3 i.v followed by autologous peripheral-blood hematopoietic stem cells infusion
Selected third line regimens	
Paclitaxel+Gemcitabine (every 28 days)	Paclitaxel 110 mg/m^2, days 1,8,15 i.v Gemcitabine 1000 mg/m^2, days 1,8,15 i.v
Gemcitabine+Oxaliplatin (every 21 days)	Gemcitabine 1000 mg/m^2, days 1,8 i.v Oxaliplatin 130 mg/m^2, day 1 i.v
Gemcitabine+Oxaliplatin+ +Paclitaxel (every 21 days)	Gemcitabine 800 mg/m^2, days 1,8 i.v Paclitaxel 80 mg/m^2, days 1,8 i.v Oxaliplatin 130 mg/m^2, day 1 i.v
Epirubicin+Cisplatin (every 21 days)	Epirubicin 90 mg/m^2, day 1 i.v Cisplatin 20 mg/m^2, days 1-5 i.v

Stage II-III

Seminoma

Only 10-15% of patients with seminoma present with stage II disease. For stage IIA disease radiotherapy is the treatment of choice, consisting of low dose treatment to the paraaortic and ipsilateral pelvic lymph nodes and a boost to the involved nodal area. The total delivered dose to areas of gross adenopathy is 35 Gy. Another option is 3 cycles of chemotherapy with BEP or 4 cycles with EP (etoposide, cisplatin). For stage IIB seminoma most oncologists use 3 cycles of chemotherapy with BEP or 4 cycles with EP. Alternatively, radiotherapy can be used. For stage IIC and the rare patient with stage III disease, chemotherapy with the above regimens is used. For patients with stage III disease who belong to the intermediate IGCCG risk group (less than 1% of patients with testicular seminomas), 4 cycles of BEP should be used. Also, it should be mentioned that seminoma patients with β-hCG levels above 50 IU/L should probably be treated with chemotherapy even for early- stage disease [74-77].

NSGCTs

Patients with stage II-III NSGCTs belonging to the good prognostic group (stages IIA-IIIA and 60% of all the patients with stage II-III disease), should be treated with 3 cycles of chemotherapy with BEP or alternatively 4 cycles of EP, although not all oncologists are confident that bleomycin can be omitted safely. The cure rate for these patients is above 90%. Alternatively, patients with stage IIA disease and normal serum tumor markers

can undergo RPLND at institutions with large experience with the procedure and receive chemotherapy only if substantial disease burden is confirmed pathologically. Patients with intermediate risk disease (stage IIIB patients, comprising 26% of the total) should receive 4 cycles of BEP chemotherapy, with cure rates exceeding 80% [78-82]. Patients with poor risk disease (stage IIIC, 14% of the total) should initially receive 4 cycles of BEP chemotherapy, with cure rates of only 40-50%. Alternatively, these patients should take part into clinical trials. VIP regimen (etoposide, ifosfamide/mesna, cisplatin) has the same efficacy as BEP, but is more toxic and should be used only if there is a significant risk of bleomycin pulmonary toxicity. BEP completed in 3 days instead of 5 has the same efficacy if the same total doses are used, but it is more toxic and should be avoided. High dose chemotherapy, with peripheral blood stem cell support should not be used as first line regimen outside a clinical trial setting, because it has not yet proved its value [83-92].

Post therapy residual lesions

Seminoma

In patients with seminoma, residual masses after treatment represent necrosis or viable seminoma, which can reach 30% for masses larger than 3 cm. Size is not the best indicator of viable tumor and positron emission tomography (PET) scan is now used, with sensitivity above 80%, specificity 100%, positive predictive value 100% and negative predictive value 96%. Treatment decisions are better to be based on PET results than the size of the lesion. If PET is negative, the patient can be safely placed to a follow-up program. If PET is positive, surgery, radiation therapy and second- line chemotherapy are all viable options, with very good long-term results and cure rates above 70% [93-96].

NSGCTs

For NSGCTSs patients with residual lesions and negative tumor markers after 4 cycles of chemotherapy (25% of all patients), resection should be undertaken. Retroperitoneal disease is the most common site of residual disease and full RPLND should be utilized for disease larger than 1 cm. PET is not advisable in these situations, as it cannot discriminate between teratoma and viable tumor. Necrotic and fibrotic tissue is found in 40-50% of the patients, teratoma in 30-40% of patients and viable tumor in 10-20%. If viable tumor is confirmed pathologically, 2 more cycles of chemotherapy are usually utilized. This can probably be avoided if complete resection has been achieved, viable tumor is less than 10% of the total mass and the patient initially belonged in the good prognostic group according to IGCCC classification. Residual lesions at other sites should also be excised. For men with both supradiaphragmatic and retroperitoneal disease, a sequential surgical approach is used more often. If only necrosis is found in the RPLND material, some advocate only surveillance for the supradiaphragmatic (lung and mediastinal) lesions, but there is not a general consensus about this. For liver lesions, resection should be undertaken for any lesion above 1 cm and intensive surveillance for smaller lesions. For brain disease, chemotherapy followed by radiotherapy are frequently used. Resection maybe considered for single brain lesions, if there is no systemic disease. Radical orchiectomy should also be performed, if it was not performed initially, because 10-15% of patients will have viable tumor and 30-40% teratoma elements [97-106].

Residual masses with increased serum tumor markers should be treated with second-line chemotherapy regimens or with participation in a clinical trial and high- dose chemotherapy. It seems that 2 cycles of blood stem cell-supported high-dose chemotherapy achieve better results than one. Surgery may have a place in carefully selected patients [107-109].

Relapsed and refractory disease

Patients with relapsed or refractory disease should be referred to a center with expertise in the treatment of these tumors. Patients who relapsed after surveillance for stage I disease or after radiotherapy for stage I-II seminomas are usually salvaged successfully with standard chemotherapy. For patients who relapsed within the first 2 years after a complete response to chemotherapy, second-line regimens (TIP /paclitaxel, ifosfamide, cisplatin or VeIP / vinblastine, ifosfamide, cisplatin) should be used. Alternatively, high-dose chemotherapy in the context of a clinical trial can be utilized. Patients who progress during or 1 month after the completion of chemotherapy, should take part in clinical trials and aggressive therapy should be utilized in order to increase their chances of long-term survival [110-118].

Late relapse, which is defined as the relapse after 2 years from the completion of chemotherapy, is a separate entity. If the patient was in a surveillance program and had not received chemotherapy, first-line regimens should be used. Seminomas are treated the same way as if they have relapsed early, with excellent results. Patients with NSGCTs who had received chemotherapy, should be treated with an aggressive surgical approach with or without chemotherapy, as surgery is necessary for long- term disease-free survival [119,120].

Follow-up

Seminoma

An appropriate surveillance program for patients with stage I seminoma who wish to undergo surveillance, considering their long-term risk of relapse, should be intensive. It consists of abdominal CT scans every 4 months for 3-4 years, every 6 months for years 4-7 and every 12 months for years 8-10, in order to avoid bulky relapse to the retroperitoneum. Follow-up also includes chest X-ray, history, clinical examination and annual ultrasound of the contralateral testicle. Many physicians omit CT scans after the 5th year, but this not the standard of care. A similar schedule, probably with less often CT scans, is used for patients with seminoma and complete response to treatment. Abdominal CT scan can safely be replaced by MRI [121,122].

NSGCTs

Patients with low-risk stage I NSGCTs are ideal candidates for a surveillance program, as 95% of relapses take place during the first 3 years of follow-up. An appropriate surveillance program consists of physical examination, chest X-ray, and serum tumor marker levels every 2 months for the first 2 years, every 4 months in the 3rd year, every 6 months in the 4th year, and annually thereafter. Abdominal CT should be used every 4 months for the first 2 years, and less often thereafter. Surveillance is necessary for 5 years following orchiectomy, although 10 years is safer. If tumor markers are elevated before orchiectomy, weekly measurements should be undertaken in order to document the appropriate decline and normalization of their values [123-125].

Following RPLND for stage I-IIA NSGCTs, an appropriate schedule of surveillance consists of tumor markers and chest X-ray every 2 months for the first 2 years and CT of the abdomen and pelvis at one year, tumor markers and chest X-ray every 4 months for the 3rd year and annually for 3 more years. A similar schedule should be used after complete response of advanced disease to chemotherapy. More intensive surveillance may be utilized for poor-risk disease (stage IIIC) patients and after finding viable tumor in the RPLND material. National Comprehensive Cancer Network (NCCN) recommends a more aggressive schedule with tumor markers and chest X-ray monthly for the first 12 months, every 2 months for the 2nd year, every 3 months for the 3rd year, every 4 months in the 4th year, every 6 months in the 5th year and annually thereafter. They also recommend imaging of the abdomen and pelvis every 3 months for the first 2 years, every 4 months for the 3rd year, every 6 months for the 4th year, and annually thereafter. In all these studies abdominal CT can safely be replaced by MRI [126,127].

During surveillance, long-term toxicities of treatment should be kept in mind. Pulmonary toxicity from bleomycin, neurotoxicity, ototoxicity and renal disorders from cisplatin are well known toxicities. Azoospermia, after exceeding 400 mg/m^2 total cisplatin dose, may be irreversible. Long-term cardiovascular toxicity is also a well known side effect of chemotherapy regimens used for germ cell tumors. The risk of developing a solid tumor is also increased by a factor of 2-3 after chemotherapy or radiotherapy. Also, the risk of leukemia increases significantly if the total etoposide dose exceeds 2000 mg/m^2. Finally, non-cancer mortality seems to increase in the long-term by 6%. Taking all the above into consideration, surveillance of these patients should include a thorough assessment of their general health status and not only confined to their oncologic issues [128-137].

Conclusions

After cisplatin-based combination chemotherapy regimens have entered germ cell tumors' therapeutics in mid-1970s, the disease became highly curable and the cure rate increased from 25% to above 90%. This disease became the model of "curable" cancer and gave hope for cure of metastatic malignant diseases in general. Despite the above success, a minority of patients with poor-risk disease (14% of all patients with NSGCTs), still have cure rates below 50%. Long-term toxicity of treatment remains also significant, so we still need better and less toxic regimens for this disease. Finally, better prognostic and predictive factors are needed, in order to achieve "fine tuning" of germ cell tumors' treatment and to find the best balance between treatment, cure and toxicity.

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