

Testicular Cancer (male germ cell tumors)

Recommendations from the society for diagnosis and therapy of haematological and oncological diseases

Publisher

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Table of contents

1 Summary	2
2 Basics	2
2.1 Definition and basic information	2
2.2 Epidemiology	2
2.3 Pathogenesis	2
2.4 Risk factors	2
3 Prophylaxis	2
4 Clinical characteristics	2
4.1 Symptoms	2
5 Diagnosis	2
5.1 Diagnostic procedures	2
5.1.1 Initial diagnosis	2
5.1.1.1 Role of miRNA as a tumor marker	2
5.2 Classification	2
5.2.1 Histological subtypes	2
5.2.2 Stages and staging	2
6 Cryopreservation	2
7 Therapy	2
7.1 Treatment structure	2
7.1.1 Primary therapy	2
7.1.1.1 Orchiectomy	2
7.1.1.2 Contralateral GCNIS	2
7.1.2 Stage I	2
7.1.2.1 Seminoma	2
7.1.2.2 Non-seminoma	2
7.1.3 Stage IIA/B	2
7.1.3.1 Seminoma	2
7.1.3.2 Non-seminoma	2
7.1.4 Advanced tumors (stages \geq IIC)	2
7.1.4.1 Standard chemotherapy	2
7.1.4.2 Importance of dose-intensified procedures and primary high-dose chemotherapy in patients with advanced tumors	2
7.1.4.3 Antithrombotic prophylaxis	2
7.1.5 Residual tumor resection (RTR)	2
7.1.5.1 Seminoma	2
7.1.5.2 Non-seminoma	2
7.1.6 Relapse and refractory disease	2

7.1.6.1 Treatment structure	2
7.1.6.2 Prognostic factors	3
7.1.6.3 Salvage chemotherapy	3
7.1.6.3.1 Conventional chemotherapy (CDCT).....	3
7.1.6.3.2 High-dose chemotherapy (HDCT)	3
7.1.6.4 Residual tumor resection (RTR) for non-seminomas in the salvage setting	3
7.2 Special settings.....	3
7.2.1 Late recurrence.....	3
7.2.2 Brain metastases	3
7.2.3 Malignant somatic transformation (MST)	3
7.2.4 Growing Teratoma.....	3
7.3 Palliative therapy	3
7.3.1 Chemotherapy	3
7.3.1.1 Substances for systemic tumor therapy (alphabetical order)	3
7.3.1.1.1 Bleomycin	3
7.3.1.1.2 Carboplatin	3
7.3.1.1.3 Cisplatin.....	3
7.3.1.1.4 Etoposide	3
7.3.1.1.5 Gemcitabine	3
7.3.1.1.6 Ifosfamide	3
7.3.1.1.7 Oxaliplatin.....	3
7.3.1.1.8 Paclitaxel.....	3
7.3.1.1.9 Vinblastine	3
7.3.2 Immunotherapy and tyrosine kinase inhibitors.....	3
7.3.3 Radiotherapy	3
7.3.4 Desperation surgery	3
8 New treatment strategies for relapses after HDCT	3
9 Monitoring and follow-up	3
9.1 Follow-up	3
10 References	3
11 Studies	3
15 Links	3
16 Authors' Affiliations	3
17 Disclosure of Potential Conflicts of Interest	3

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1 Summary

In Germany, each year around 4000 men are currently diagnosed with germ cell tumors, and around 180 patients die from the disease. In Austria and Switzerland, around 400 men are diagnosed with germ cell tumors every year. Men aged between 15 and 45 years are mainly affected.

A cure rate of around 95% can be achieved across all tumor stages through the consistent application of stage-adjusted treatment concepts. The use of chemotherapy, surgery and radiotherapy, the selection of appropriate tumor treatment and the type and duration of their use are precisely defined by national and international consensus recommendations and guidelines [58]. These are based on the histology, the individual tumor stage and the presence of known and well-studied risk factors. These guidelines are intended to ensure that the best chance of cure is achieved for each patient with the least burdensome therapy.

Treatment decisions for patients with advanced disease and an unfavorable prognosis, relapses after primary chemotherapy and certain special forms such as late relapses, central nervous system involvement or transformed relapses pose a particular challenge.

Disregarding accepted therapy standards in the treatment of patients with germ cell cancer leads to a higher rate of treatment failure in both primary and second-line therapy and special forms, with the need for subsequent therapies or even a fatal outcome. Therefore, patients with this malignancy, especially in the metastatic, "intermediate" and "poor prognosis" situation, when relapses occur or in the presence of rare disease scenarios, should always be presented to expert centers (contact via: <http://www.hodenkrebs.de>). It is also possible to obtain an internet-based second opinion from urological and oncological experts before making any treatment decisions (<https://www.e-konsil.org>).

2 Basics

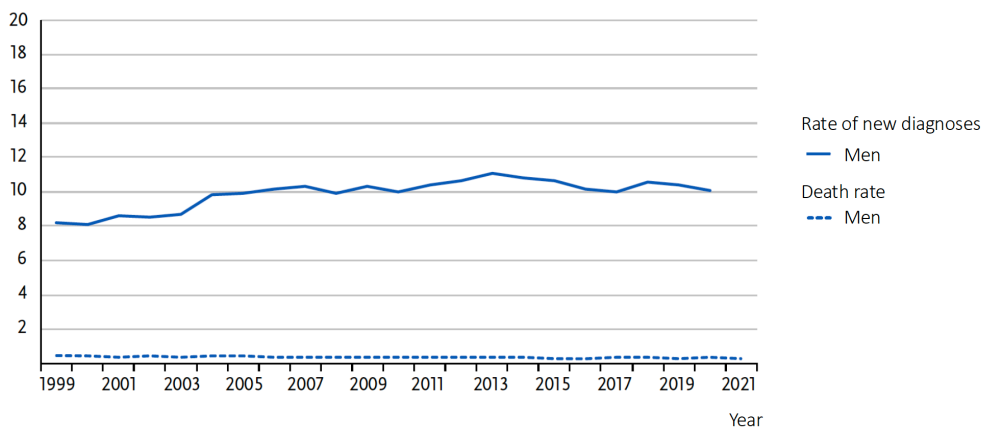
2.1 Definition and basic information

Germ cell tumors are the most common malignancies in young men [76]. There is an increasing incidence in western industrialized nations, the cause of which is unclear. Histologically, a distinction is made between seminomatous germ cell tumors (seminoma) and non-seminomatous germ cell tumors (non-seminoma). In about 3-5% of cases, the tumors primarily affect extragonadal sites. Therefore, in all men with an unclear primary tumor (e.g., retroperitoneal, mediastinal), the diagnosis of testicular cancer or extragonadal germ cell tumor must be included in the differential diagnosis.

2.2 Epidemiology

Around 98.5% of all testicular cancers recorded in cancer registries with specific histological diagnosis are germ cell tumors; conversely, almost 98% of all germ cell tumors in men affect the testicles. The proportion of male germ cell tumors in all cancers is approximately 0.8%. In recent years, the incidence has been rising internationally at up to 10 in 100,000 men, but has remained stable in Germany since 2005 (Figure 1). Bilateral disease is present in 1-2% of affected patients. Around 180 patients die of the disease in Germany every year (Figure 2). The mean age at onset is 37 years [59].

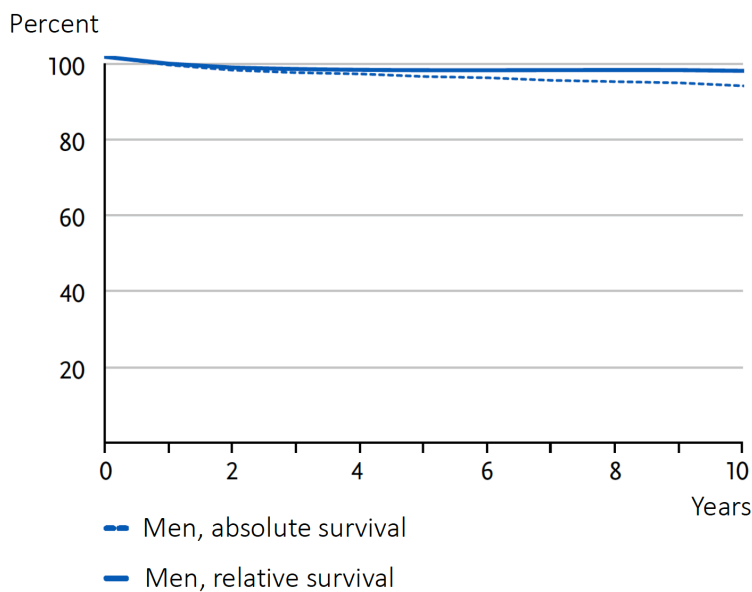
Figure 1: Age-standardized rates of new cases and deaths, ICD-10 C62, Germany 1999 - 2020/2021 (per 100,000, old European standard)



Legend:

Source: https://www.krebsdaten.de/krebs/de/content/publikationen/krebs_in_deutschland/kid_2023/kid_2023_c62_hoden

Figure 2: Absolute and relative survival rates up to 10 years after initial diagnosis, ICD-10 C62, Germany 2019-2020



Legend:

Source: https://www.krebsdaten.de/krebs/de/content/publikationen/krebs_in_deutschland/kid_2023/kid_2023_c62_hoden

2.3 Pathogenesis

Studies have shown that the development of a germ cell tumour begins with a defective maturation of the primordial germ cell into pre-spermatogonia and the associated polyploidization. This defective, transformed germ cell represents the *in situ* germ cell neoplasia (GCNIS). This remains dormant until puberty, only then does the formation of seminomas and non-seminomas occur. This tumor progression is caused by the gain or loss of chromosomal regions (e.g., overexpression of *p53*, excess copies of the isochromosome *i(12p)*, loss of *c-Kit* expression and deregulation of the cell cycle at the G1/S checkpoint). Germ cell tumors without GCNIS characterize prepubertal tumors and spermatocytic seminoma, which is more common in older men.

2.4 Risk factors

There are relatively few proven risk factors for the development of a germ cell tumor. According to current knowledge, lifestyle and environmental factors do not play a role. The confirmed risk factors are summarized in [Table 1](#) [1, 2].

Table 1: Risk factors for the diagnosis of a germ cell tumor

Risk factor	Remark
Non-descended testicles (cryptorchidism)	
History of testicular cancer	Risk factor for contralateral second tumor
Positive family history/genetic disposition	Male first-degree relatives, especially twin brothers
Testicular intraepithelial neoplasia (TIN) (GCNIS, CIS)	
Infertility	
Klinefelter syndrome	

3 Prophylaxis

For early detection, young men should be encouraged to perform regular self-examinations of the testicles from puberty onwards.

4 Clinical characteristics

4.1 Symptoms

In most cases, patients initially notice a painless enlargement, swelling or circumscribed hardening of the testicles. Some patients also complain of testicular or groin pain. Only rarely do patients also exhibit symptoms of advanced disease, such as back pain, dyspnea, weight loss, headaches, gynecomastia or hyperthyroidism.

5 Diagnosis

5.1 Diagnostic procedures

5.1.1 Initial diagnosis

The first step is to confirm the clinically suspected diagnosis by ultrasound of both testicles, routine clinical chemistry (blood count, coagulation, TSH, liver and kidney organ functions for subsequent diagnostics) and tumor markers AFP, HCG and LDH in the serum as well as deter-

mination of total testosterone, FSH and LH and a computed tomography (CT) scan of the thorax, abdomen and pelvis. Cerebral imaging is only recommended if there is evidence of multiple pulmonary metastases, very high tumor marker values (especially HCG) or specific clinical symptoms. The same applies to a bone scintigraphy, which should only be ordered if there are indicative clinical symptoms. A positron emission tomography (PET)-CT scan is not part of the primary staging diagnostics. It is obligatory to inform the patient about the possibility of sperm analysis and cryopreservation in the event that further treatment steps are necessary that restrict fertility. Cryopreservation should be carried out before an orchiectomy (Table 2).

5.1.1.1 Role of miRNA as a tumor marker

The role of microRNA (*miRNA-371a-3p*) in testicular tumors and its significance in routine clinical practice are the subject of intensive research and may provide potentially important implications for diagnosis, prognosis and course of therapy in the future [66, 67, 78]. The usefulness of *miRNA-371a-3p* as a tumor marker in the clinic is the subject of ongoing studies.

Table 2: Diagnostic procedures for suspected gonadal germ cell tumor

Procedure	Remark
Clinical palpation	
Sonography of testicles bilaterally	>7.5 MHz transducer
Determination of the tumor markers HCG, AFP, LDH	
Computed tomography (CT) of the thorax, abdomen and pelvis	Alternatively, thoracic CT and magnetic resonance imaging (MRI) of abdomen/pelvis
Optional MRI head	Mandatory only in the presence of multiple pulmonary metastases, strongly increased tumor markers and/or symptoms
Optional bone scintigram	Only if symptoms are present
Measurement of total testosterone, FSH, LH in plasma	
Sperm analysis and cryopreservation	If further fertility-impairing therapy is planned (e.g., orchiectomy, radio- and/or chemotherapy or therapy of extragonadal tumors)

5.2 Classification

5.2.1 Histological subtypes

The histopathological classification of testicular tumors is based on the World Health Organization (WHO) classification for testicular tumors of 2022 (Table 3). About 95% of cases are seminomatous or non-seminomatous tumors. All mixed tumors and all patients with relevant AFP elevation are considered non-seminomas [86].

Table 3: WHO classification 2022 (modified) [86]

1. Germ cell tumors originating from germ cell neoplasia in situ
Non-invasive germ cell neoplasia in situ (GCNIS) Previous intratubular germ cell neoplasia, unclassified (IGCNU)
Seminoma (including cases with syncytiotrophoblasts) Embryonal carcinoma Yolk sac tumor, postpubertal type Chorionic carcinoma Trophoblastic tumor, postpubertal type Cystic trophoblastic tumor Epithelioid trophoblastic tumor Teratoma with malignant components = somatic malignancy Tumors of several histological types (each component to be specified)
2. Germ cell tumors unrelated to germ cell neoplasia in situ
Spermatocytic seminoma Teratoma pre-pubertal Yolk sac tumor pre-pubertal Testicular neuroendocrine tumor pre-pubertal (well-differentiated)
3. Germline/gonadal stromal tumors
<i>Leydig</i> cell tumor Malignant <i>Leydig</i> cell tumor <i>Sertoli</i> cell tumor <ul style="list-style-type: none"> • Large cell calcifying <i>Sertoli</i> cell tumor • Intratubular large hyalinizing <i>Sertoli</i> cell neoplasia • Large cell, calcifying form Malignant <i>Sertoli</i> cell tumor Granulosa cell tumor <ul style="list-style-type: none"> • Adult type • Juvenile type <ul style="list-style-type: none"> Tumors of the fibroma-thecoma group Mixed and unclassified stromal tumors
4. Tumors that contain germ cells and germline components (gonadoblastomas)

5.2.2 Stages and staging

The definition of the extent of the primary tumor and metastasis is based on the Union Internationale Contre le Cancer (UICC)-TNM criteria (Figure 3 and Table 4), the classification of prognostically relevant parameters according to the International Germ Cell Consensus Classification (IGCCCG) score (Table 4).

The IGCCCG score from 1997 [3] was recently validated and supplemented. For this purpose, data of a total of 13,684 patients, all of whom were treated with cisplatin-based standard-of-care regimens for metastatic disease between 1990 and 2013, were collected. 89% of the data (histologically seminomas and non-seminomas) were evaluable with regard to progression-free survival (PFS) and overall survival (OS). The prognostic groups for metastatic seminoma and non-seminoma of the 1997 score (Table 5) were confirmed and further refined. In addition, a nomogram for the individual prediction of PFS was developed. An LDH elevation of >2.5 times the upper limit of normal (ULN) was identified as an unfavorable risk factor in seminoma, and an LDH elevation of >2.5 times the ULN, the presence of pulmonary metastases and age were identified as further risk factors in non-seminoma (<https://www.eortc.org/IGCCCG-Update>) [60, 69].

Figure 3: Schematic display of the Lugano classification, from: [88]

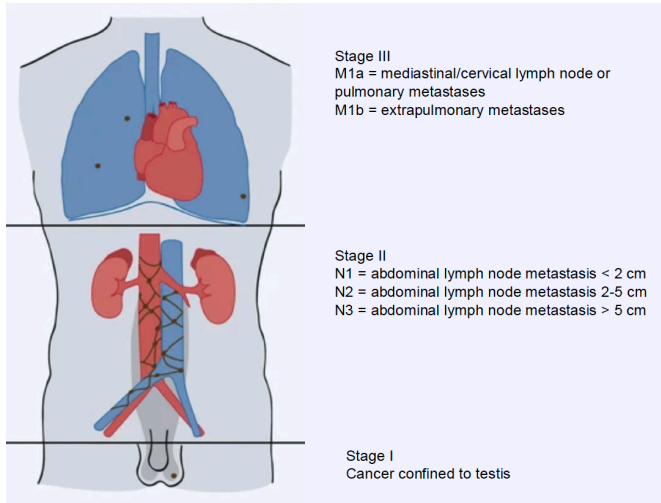


Table 4: Definition of tumor stages (TNM-UICC classification 2017, 8th edition) [87]

T	Primary tumor		
pTis	Intratubular germ cell neoplasia (carcinoma in situ)		
pT1	Tumor limited to the testis (including invasion of the rete testis), without blood/lymph vessel invasion		
pT2	Tumor limited to the testis (including invasion of the rete testis), with blood/lymph vessel invasion or tumor with invasion of the hilar soft tissue, the epididymis or with penetration of the mesothelium over the outer surface of the Tunica albuginea with involvement of the <i>Tunica vaginalis</i>		
pT3	Tumor invades spermatic cord (with/without blood/lymph vessel invasion)		
pT4	Tumor invades scrotum (blood/lymph vessel invasion)		
N	Lymph nodes		
N0/pN0	No regional lymph node metastases		
N1	Metastasis in the form of a lymph node conglomerate or in (solitary or multiple) lymph nodes, each not more than 2 cm in largest extent		
pN1	Metastases in the form of a lymph node conglomerate, 2 cm or less in largest extent, or 5 or fewer positive lymph nodes, none more than 2 cm in largest extent		
N2	Metastasis in the form of a lymph node conglomerate or in multiple lymph nodes, more than 2 cm but not more than 5 cm in largest extent		
pN2	Metastases in the form of a lymph node conglomerate, more than 2 cm but not more than 5 cm in largest extent, or more than 5 positive lymph nodes, none more than 5 cm in largest extent, or extranodal tumor spread		
N3	Metastasis in the form of a lymph node conglomerate, more than 5 cm in largest extent		
pN3	Metastases in the form of a lymph node conglomerate, more than 5 cm in largest extent		
M	Metastases		
M1a	Non-regional lymph nodes or lung metastases		
M1b	Other distant metastases		
S	Serum tumor marker (nadir value <u>after</u> orchiectomy)		
SX	No serum marker analyses performed or available		
S0	Serum tumor marker level normal		
	LDH (U/L) [#]	HCG (mIU/ml)	AFP (ng/ml)
S1	< 1.5 × ULN** and	< 5000 and	< 1000
S2	1. -10 × ULN** or	5000-50000 or	1000-10000
S3	> 10 × ULN** or	> 50000 or	> 10000

Legend:

[#] cave: the LDH cut-off values are outdated according to the IGCCCG update analysis

* the extent of the primary tumor is classified according to the radical orchiectomy; only in stages pTis and pT4 is the radical orchiectomy not always necessary for classification; if no radical orchiectomy was performed, the tumor is classified as stage TX.

** ULN denotes the upper normal value in the LDH test (upper limit of normal)

AFP - alpha-1 fetoprotein; HCG - human chorionic gonadotropin; LDH - lactate dehydrogenase

Table 5: Staging according to UICC 2017

Stage 0	pTis	N0	M0	S0, SX
Stage I	pT1-4	N0	M0	SX
Stage IA	pT1	N0	M0	S0
Stage IB	pT2 - pT4	N0	M0	S0
Stage IS	Each pT/TX	N0	M0	S1, S2, S3
Stage II	Each pT/TX	N1, N2, N3	M0	SX
Stage IIA	Each pT/TX	N1	M0	S0, S1
Stage IIB	Each pT/TX	N2	M0	S0, S1
Stage IIC	Each pT/TX	N3	M0	S0, S1
Stage III	Each pT/TX	Each N	M1, M1a	SX
Stage IIIA	Each pT/TX	Each N	M1, M1a	S0, S1
Stage IIIB	Each pT/TX Each pT/TX	N1, N2, N3 Each N	M0 M1, M1a	S2 S2
Stage IIIC	Each pT/TX Each pT/TX Each pT/TX	N1, N2, N3 Each N Each N	M0 M1, M1a M1b	S3 S3 Each S

Table 6: Classification of the International Germ Cell Cancer Collaborative Group* (IGCCCG 1997) and IGCCCG Update 2021 [60, 69]

Favorable risk profile* (approx. 56% of metastatic patients)		Approx. 96% survival rate
	Clinic	Marker constellation
Non-seminomas	Gonadal or retroperitoneal primary tumor	AFP < 1000 ng/ml HCG < 5000 U/l LDH < 1.5 x ULN**
	- <i>and</i> low markers	
	- <i>and</i> no extrapulmonary organ metastases	
Seminomas	Each primary localization	
	- <i>and</i> no extrapulmonary organ metastases	AFP normal, any HCG and LDH**
Intermediate risk profile* (approx. 28% of metastatic patients)		Approx. 89% survival rate
	Clinic	Marker constellation
Non-seminomas	Gonadal or retroperitoneal primary tumor	AFP 1,000-10,000 ng/ml HCG 5,000-50,000 U/l LDH 1.5 - 10 x ULN**
	- <i>and</i> intermediate markers	
	- <i>and</i> no extrapulmonary organ metastases	
Seminomas	Each primary localization	AFP normal, any HCG and LDH**
	- <i>and</i> extrapulmonary organ metastases - <i>or</i> LDH $\geq 2.5 \times$ ULN	
Poor risk profile* (approx. 16% of metastatic patients)		Approx. 67% survival rate
	Clinic	Marker constellation
Non-seminomas	Mediastinal primary tumor	AFP > 10,000 ng/ml HCG > 50,000 U/l LDH > 10 x ULN**
	- <i>or</i> high markers	
	- <i>or</i> extrapulmonary organ metastases (liver, brain, bone, others)	
Seminomas	No patients with this classification	

Legend:

* Classification into the appropriate group directly before the start of chemotherapy

** According to the IGCCCG update analysis, an LDH > 2.5 times the ULN is a risk factor for seminomas and non-seminomas with a favorable risk profile

Abbreviations: AFP - alpha fetoprotein; HCG - human chorionic gonadotropin; LDH - lactate dehydrogenase; IGCCCG - International Germ Cell Cancer Collaborative Group; ULN - upper limit of normal range

6 Cryopreservation

Cryopreservation of sperm to ensure fertility after diagnosis of a germ cell tumor is mandatory if fertility-impairing therapies are planned in patients with desire to have children. Ablatio testis of the tumor-bearing testicle also leads to fertility restriction, which is why cryopreservation and ejaculate analysis should ideally be carried out before ablatio testis. In any case, ejaculate analysis and cryopreservation should be recommended before chemotherapy or radiotherapy if there is a desire to have children. In Germany and Switzerland, the costs of sample collection, processing and storage are covered by health insurance for 5 years. In exceptional situations (e.g., indication for immediate start of therapy in the case of a high tumor burden), it may be

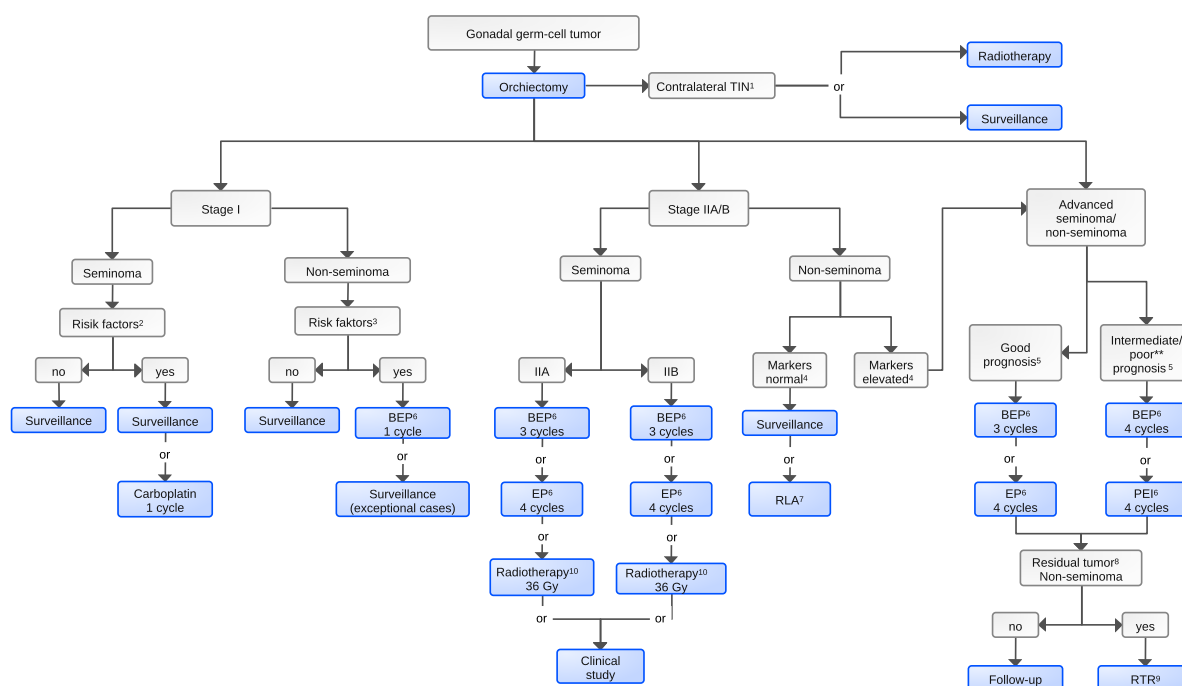
required to refrain from sperm cryopreservation. The patient should then be informed in detail about the consequences of possible infertility after chemotherapy and this should be documented. In some cases, it may also be indicated to surgically obtain sperm from the opposite testicle or epididymis before tumor therapy.

7 Therapy

7.1 Treatment structure

Treatment is adapted to the stage and risk factors. The critical assessment of the differential therapeutic options serves as the basis for the treatment recommendation. Whenever possible, patients should be treated within the framework of clinical trials. A treatment algorithm is shown in Figure 4.

Figure 4: First-line treatment of gonadal germ cell tumors



Legend:

¹ TIN - intraepithelial neoplasia: Contralateral biopsy only indicated in certain risk constellations

² Risk factors for stage I seminoma: tumor size and/or invasion of the rete testis

³ Risk factors in stage I non-seminoma: lymphatic and/or venous vascular invasion (LVI+ or LVI-)

⁴ Markers in non-seminoma: AFP, HCG, LDH

⁵ Classification of the International Germ Cell Cancer Collaborative Group (IGCCCG 1997) [3]; poor prognosis patients: evaluation of dose intensification in case of inadequate marker decline after first cycle of chemotherapy, CNS involvement, primary mediastinal non-seminoma; presentation of patients at a designated center

⁶ Chemotherapy: BEP - etoposide, bleomycin, cisplatin; carboplatin - carboplatin monotherapy; PE - cisplatin, etoposide; PEI - cisplatin, etoposide, ifosfamide

⁷ RLA - retroperitoneal lymphadenectomy

⁸ Residual tumor in non-seminoma: >1cm

⁹ RTR - Residual tumor resection

¹⁰ No longer generally recommended (see text)

7.1.1 Primary therapy

7.1.1.1 Orchiectomy

The standard treatment is usually orchiectomy of the affected testicle. The testicles are uncovered via an inguinal or inguinoscrotal approach. If the tumor diagnosis is uncertain, tumor markers are normal and a small isolated tumor (< 30% of the testicular volume) is present,

only organ-preserving enucleation of the tumor should be performed initially and the histological result awaited, as benign findings may be present in many cases (such as benign *Leydig* or *Sertoli* cell tumors). An organ-preserving procedure should also be discussed for malignant, small focal findings in the presence of a single testicle or bilateral tumor disease. Patients with initially advanced (stage III with pulmonary or visceral metastases) or acutely life-threatening disease do not primarily undergo orchiectomy, but immediate chemotherapy, and are only orchiectomized after completion of chemotherapy [4]. The possibility of synchronous implantation of a testicular prosthesis should be discussed before ablatio testis.

7.1.1.2 Contralateral GCNIS

Non-invasive germ cell neoplasia in situ (GCNIS) is found in the opposite testis in around 9% of patients with germ cell tumors. Patients at risk are particularly men under 40 years of age with a testicular volume of less than 12 ml or a history of maldescensus testis. The performance of a contralateral biopsy is optional.

If GCNIS is detected, a definitive treatment option in addition to orchiectomy is radiotherapy with 18-20 Gy. Patients with desire to have children can alternatively be offered a close monitoring strategy using ultrasound checks until family planning is completed, whereby, if the GCNIS is not monitored, an invasive CCT develops in 50% of cases within five years. Radiotherapy of the GCNIS-bearing testicle leads to impaired *Leydig* cell function and thus to hypogonadism in around 40% of cases in the longer term, i.e., treatment of the GCNIS-bearing testicle is primarily dependent on the total testosterone level. In affected patients with an indication for primary chemotherapy, GCNIS is completely eradicated in only about 66% of cases, so that in the case of histologically documented persistence (valid assessment only about 1 year after completion of chemotherapy), radiotherapy of the testis should also be carried out after family planning [5- 7].

7.1.2 Stage I

7.1.2.1 Seminoma

In stage I seminoma, increasing tumor size and/or invasion of the rete testis have been confirmed as risk factors in both retrospective and published prospective studies. According to more recent data, lymphovascular invasion and elevated LDH and HCG are also risk factors in seminoma [85]. However, the risk of recurrence is only around 20% in all stage I patients. In patients without risk factors, it is around 4%, with one risk factor around 12% and in the presence of several risk factors up to a maximum of 32%.

Based on the current data available, in addition to the preferred option of monitoring alone for all patients, a risk-adapted approach is still possible and should be discussed with patients. However, patients without risk factors should undergo surveillance alone. Patients with risk factors can also receive adjuvant chemotherapy with one cycle of carboplatin AUC 7 as an alternative to surveillance in individual cases. This reduces the risk of recurrence to around 4-9% without improving overall survival. Adjuvant radiotherapy is only reserved for rare exceptional cases. The advantages and disadvantages associated with adjuvant therapy should be discussed in detail with the patient (Table 6) [8- 12]. The overall tumor-specific survival rate for patients with stage I seminoma is more than 99%.

7.1.2.2 Non-seminoma

Risk factors for occult metastasis are lymphatic or venous vascular invasion (LVI+ or LVI-). The risk of recurrence in the presence of a risk factor is around 45-50%, without a risk factor around

15%. In principle, all patients in stage CS I can undergo surveillance. However, a risk-adapted approach seems appropriate. Active surveillance is recommended for patients without a vascular invasion risk factor (LVI or so-called "low risk"). For patients with a risk factor of vascular invasion (LVI+ or so-called "high risk"), 1 cycle of adjuvant chemotherapy with bleomycin, etoposide and cisplatin (BEP) is recommended [17]. The adjuvant chemotherapy previously carried out with 2 cycles of PEB is no longer recommended according to current data [13- 17]. Whether 1 cycle of cisplatin and etoposide (EP) is equivalent to 1 cycle of PEB for contraindications to bleomycin has not yet been clarified by clinical studies.

Before the standard of cisplatin chemotherapy was established, primary retroperitoneal lymph node dissection (RLA) has been considered the only effective adjuvant treatment option inducing long-lasting remissions. Currently, it is reserved for individual cases and should only be carried out at centers with a high level of expertise [17].

The overall tumor-specific survival rate for patients with stage I non-seminoma is more than 99%.

Table 7: Treatment options in stage I seminoma and non-seminoma

Seminoma	Active Surveillance (preferred)*
	One adjuvant cycle of carboplatin AUC 7
	Adjuvant diaphragmatic paraaortic radiotherapy (exception)
Non-seminoma	Active Surveillance* (preferred, especially for low risk without vascular invasion)
	One adjuvant cycle of PEB in high-risk patients
	Primary retroperitoneal lymphadenectomy (exception)

Legend:

* For the procedure for active surveillance, see chapter 9.1

7.1.3 Stage IIA/B

7.1.3.1 Seminoma

Seminomas with an isolated retroperitoneal lymph node up to 2 cm and without a clear marker elevation (questionable stage IIA) should first receive a renewed imaging staging after about 8 weeks, before a final treatment decision is made, in order to clarify whether the lymph node enlargement is likely to be reactive or indicate a second malignancy, for example. Alternatively, the diagnosis can also be confirmed by a CT-guided puncture. If this is not technically possible and the findings remain unclear despite further imaging, a minimally invasive histological diagnosis and treatment using laparoscopic or robot-assisted unilateral RLA can also be discussed. This should be carried out in a designated center. If the histological confirmation shows an isolated seminoma metastasis, adjuvant therapy can be waived. Systemic therapy and/or radiotherapy should not be started without reliable evidence of stage IIA.

In stage IIA and B, the so-called involved field irradiation with 30 Gy (IIA) or 36 Gy (IIB) with an infradiaphragmatic, paraaortic radiation field including the ipsilateral iliac region (so-called field hockey stick field) [18, 19, 20], which is still mentioned in guidelines [58], is no longer recommended as standard. Patients should be informed about alternative treatment options. These include, especially in stage IIA, combined radiochemotherapy analogous to the SAKK 01/10 study [82]. Patients are treated with 1 cycle of carboplatin AUC 7 and consecutive involved node radiotherapy (INRT) with 30 Gy (IIA) or 36 Gy (IIB). In the SAKK 01/18 follow-up study, which is now fully recruited, the radiation dose was reduced again to 24 Gy (stage IIA) and 30

Gy (stage IIB). In stage IIB, however, the chemotherapy intensity was increased from 1 cycle of carboplatin AUC 7 to 1 cycle of cisplatin/etoposide (PE). No data from this study have been published to date.

Chemotherapy with 3 cycles of cisplatin/etoposide/bleomycin (PEB) or 4 cycles of EP (etoposide/cisplatin) should also be evaluated as a treatment option, particularly in stage IIB (axial CT diameter of the singular metastasis 2-5 cm) and/or in the case of multinodal, unilateral involvement with a maximum axial CT diameter of 5 cm.

In the meantime, data on solely surgical treatment in patients with stage IIA and B using minimally invasive, laparoscopic or robot-assisted RLA without adjuvant therapy (in designated centers) have been published [65, 71, 72, 73]. In selected patients, this option can also be discussed with patients in designated centers, especially in stage IIA, or patients should currently be included in the follow-up study PRIMETEST II [NCT06144736] in Germany (*Chapter 11*).

In the event of a relapse after combined chemo-radiotherapy or surgery without adjuvant therapy, patients should be treated with chemotherapy (3 x BEP/4 x EP) according to stage.

The overall long-term tumor-specific survival rate for patients with stage IIA/IIB seminoma is approximately 99%.

7.1.3.2 Non-seminoma

Patients with increased tumor markers are treated according to their IGCCCG classification in line with the therapy algorithm for advanced tumor stages. It should be noted that due to the long half-life of AFP after orchiectomy, it can sometimes take several weeks for the tumor markers to normalize. The decision to use chemotherapy should therefore only be made if tumor markers are clearly persistently increased or rising.

Patients with a normal tumor marker constellation and morphologically suspicious retroperitoneal lymph nodes represent a special subpopulation. In these patients, a short-term follow-up by CT (or MRI) after 6 weeks with close simultaneous marker monitoring is recommended. Alternatively, a (minimally invasive) RLA can be discussed in these patients in designated centers to definitively confirm the diagnosis. Histologically, most of these cases are teratomas, less frequently marker-negative embryonal cell carcinomas or non-tumor-involved lymph nodes. Patients who had evidence of 100% teratoma in the orchiectomy specimen and have a marker-negative metastasis should be treated with RLA. In 5-32% of these patients, retrograde ejaculation occurs despite the nerve-sparing approach, so RLA should always be performed at an designated center by an experienced surgeon [21, 22]. If vital tumor cells are detected, adjuvant treatment with 2 cycles of PE may be recommended depending on the histology (e.g., embryonal carcinoma) and the percentage of vital tumor or the number of affected lymph nodes. Alternatively, close surveillance alone is also possible.

All patients with increasing tumor markers and/or rapidly progressing tumors on imaging require immediate initiation of chemotherapy in accordance with the IGCCCG risk stratification for metastatic tumors.

The tumor-specific survival rate for stage II A and II B non-seminoma is around 98%.

7.1.4 Advanced tumors (stages \geq IIC)

7.1.4.1 Standard chemotherapy

All seminomas from tumor stage II C and all non-seminomas from a confirmed tumor stage II are treated according to the risk stratification according to the IGCCCG risk classification by means of chemotherapy with three (for good prognosis group) or four cycles (for intermediate or poor prognosis group) of PEB, each 21 days apart. It should be noted that the tumor marker level immediately before the start of therapy is used for risk group classification. If there is a contraindication to bleomycin, 4 cycles of PE (cisplatin, etoposide) can be given instead of 3 cycles of PEB in the good prognosis group and alternatively 4 cycles of PEI (cisplatin, etoposide and ifosfamide) instead of 4 cycles of PEB in the intermediate prognosis group [3, 23, 24], see Appendix on treatment protocols.

Prognostic categories are summarized in [Table 8](#).

Table 8: Data from the IGCCCG update for non-seminomas (according to [69])

Original IGCCCG forecast groups	Original IGCCCG estimates 1997		Updated estimates in patients with non-seminoma and available pre-therapeutic IGCCCG prognostic groups	
	5-year PFS in % (95% CI)	5-year OS in % (95% CI)	5-year PFS in % (95% CI)	5-year OS in % (95% CI)
Good	89 (87-91)	92 (90-94)	90 (89-91)	96 (95-96)
Intermediary	75 (71-79)	80 (76-84)	78 (76-80)	89 (88-91)
Bad	41 (35-47)	48 (42-54)	54 (52-56)	67 (65-69)

Legend:

IGCCCG - International Germ Cell Cancer Collaborative Group; CI - confidence interval; PFS - progression-free survival; OS - overall survival

7.1.4.2 Importance of dose-intensified procedures and primary high-dose chemotherapy in patients with advanced tumors

In recent years, intensified chemotherapy strategies have been investigated, particularly for the group of "intermediate" and "poor prognosis" patients. For the first time, a prospective randomized phase III study (GETUG13) showed an advantage in the primary endpoint of progression-free survival in patients with inadequate marker decline after the first cycle of BEP, but not in overall survival, with subsequent treatment intensification. Patients with inadequate marker decline were randomized to either the standard treatment arm (a total of 4 cycles of PEB) or the intensified arm consisting of additional paclitaxel, ifosfamide and oxaliplatin. The overall survival rate for the latter patients was 75% with significantly increased toxicity, especially neurotoxicity [25].

The value of high-dose chemotherapy (HDCT) in primary therapy has also been investigated in several studies, particularly for the group of "poor-prognosis" patients according to IGCCG. As part of a multicenter phase II study of the German Study Group for Testicular Tumors, sequential HDCT with cisplatin, etoposide and ifosfamide (HD-PEI) was used and a long-term survival rate of 75% was shown [26].

A randomized phase III study from the USA, which compared the administration of four cycles of PEB versus two cycles of PEB followed by two cycles of high-dose chemotherapy with carboplatin, etoposide and cyclophosphamide (CEC), was unable to show a general benefit in terms of progression-free and overall survival in favor of HDCT [27].

The published, randomized phase III study by the EORTC, which compared four cycles of PEB with sequential high-dose PEI administration, showed a numerical advantage of around 15% for both progression-free and overall survival, but no statistically significant benefit in favor of HDCT overall. However, this study was only able to recruit 60% of the planned number of patients at the time of evaluation, so that the differences achieved are certainly worthy of note [28]. In summary, the general use of high-dose chemotherapy in primary therapy is therefore still not a standard at present.

Patients with inadequate tumor marker decline after the first cycle, CNS metastases or primary mediastinal non-seminoma as well as with multiple metastases should be treated at specialized centers and the data should be prospectively recorded and analyzed as part of a registry study (contact via: <http://www.hodenkrebs.de>). In any case, a second opinion from an expert center should be sought before deciding on treatment, as the prognosis of advanced metastatic patients depends crucially on the initial treatment.

7.1.4.3 Antithrombotic prophylaxis

According to current studies, risk factors for the occurrence of thromboembolic events during cisplatin-based chemotherapy are a higher tumor stage or the diameter or size of retroperitoneal lymphadenopathy and the presence of central venous catheters [70, 84]. During the phase of cisplatin-containing chemotherapy, antithrombotic prophylaxis with low-molecular-weight heparin or one of the new oral direct anticoagulants should be given to reduce the risk of thromboembolic events during chemotherapy for metastatic germ cell tumors [68, 84].

7.1.5 Residual tumor resection (RTR)

7.1.5.1 Seminoma

In patients with pure seminoma and post-chemotherapeutic tumor residues, RTR is not indicated for residual findings, as these contain almost exclusively necrotic tissue and a wait-and-see approach should be chosen. Necrosis can be assumed for residues > 3 cm. The performance of a PET-CT [29, 30] is not recommended, as the false positive rate of a PET-CT is high, even 8 or more weeks after treatment; the positive predictive value is only 20% [62, 72].

7.1.5.2 Non-seminoma

In all non-seminoma patients with tumor residuals >1 cm after primary chemotherapy (in individual cases also with a size of less than 1 cm) and normalized tumor markers or a marker plateau, RTR is mandatory and should be performed within 4-6 weeks after completion of chemotherapy with the aim of completely removing all tumor residuals. This often complex procedure should only be performed at a center designated for testicular tumor surgery with appropriate surgical expertise and the availability of multivisceral surgery (liver, thoracic, vascular surgery) [31]. The aim is to remove all remaining tumor cells; in 30-40% of patients histology shows teratoma, in about 10-20% of cases even vital tumor [32, 33, 34, 35, 36].

7.1.6 Relapse and refractory disease

A disease of the opposite testicle and thus a secondary tumor disease should always be ruled out first using sonography (metachronous disease).

7.1.6.1 Treatment structure

About 5-10% of all patients with germ cell tumors and about 30% of patients with metastatic disease require relapse or salvage therapy at some point in their disease [61].

The treatment of patients with seminoma and non-seminoma and relapse from stage I disease is analogous to the treatment algorithms for patients with primary metastatic disease (see chapter 7.1.4). As a rule, three to four cycles of cisplatin, etoposide and bleomycin (PEB) are used in these patients, depending on the tumor stage. The majority of these patients will become permanently disease-free as a result (see Table 8).

The much more intensive relapse chemotherapy ("salvage chemotherapy") is limited to metastatic patients who respond poorly to primary chemotherapy, who do not achieve a complete remission of their disease, or who develop a relapse from a complete remission after primary chemotherapy. In principle, two treatment strategies are possible: conventional-dose chemotherapy or high-dose chemotherapy followed by autologous stem cell reinfusion. The salvage strategy should be determined at a center with the appropriate expertise.

7.1.6.2 Prognostic factors

In recent years, the importance of prognostic factors has also been recognized for salvage therapy. In a retrospective analysis published in 2010 of almost 1600 patients worldwide with relapsed or refractory disease who had received either conventional chemotherapy (CDCT) or high-dose chemotherapy (HDCT) as their first salvage treatment, seven independent variables with a significant impact on progression-free survival (PFS) and overall survival (OS) were identified, and an internationally accepted prognostic score was determined. Depending on these variables, five prognosis categories (groups: very low, low, intermediate, high, very high risk) are distinguished in the first relapse [37].

Table 9: Prognostic factors at relapse

	Favorable	Unfavorable
Histology	Pure seminomas	Non-seminomas
Primary localization	Gonadal	Extragonadal Primary mediastinal NSGCT
Response to therapy	CR and PRm-	PRm+, SD and PD
Progression-free interval	Three or more months after last chemotherapy	Less than three months after last chemotherapy
Metastasis localization	Lymph node or pulmonary metastases	Liver, bone or brain metastases
Tumor markers	AFP normal HCG \leq 1,000 U/l	AFP \leq 1,000 AFP $>$ 1,000 HCG $>$ 1,000 ng/ml
Therapy line	First salvage therapy	Second or subsequent salvage therapy Patients with late recurrences $>$ 2 years

Legend:

AFP - alpha-fetoprotein in serum; HCG - human chorionic gonadotropin in serum; CR - complete remission; PR - partial remission; PRm- - partial remission, tumor marker-negative; PRm+ - partial remission, tumor marker-positive; PD - progressive disease; NSGCT - non-seminomatous germ cell tumor

7.1.6.3 Salvage chemotherapy

7.1.6.3.1 Conventional chemotherapy (CDCT)

With 50-70%, the percentage of patients with a favorable response to relapse chemotherapy is significantly lower than after primary therapy. Long-lasting remissions are only observed in around 15-60% of patients. The most successful regimens combine cisplatin (not replaceable by carboplatin) and ifosfamide either with etoposide (PEI/VIP), vinblastine (VelP) or, more recently, with paclitaxel (TIP) without any clear superiority of a particular drug combination. The standard of combination chemotherapy is the administration of 4 cycles at 21-day intervals [38]. Regimens of conventionally dosed salvage chemotherapy are summarized in the Appendix Treatment protocols.

7.1.6.3.2 High-dose chemotherapy (HDCT)

Since the end of the 1980s, high-dose chemotherapy with autologous stem cell support has been established as a form of therapy in the relapse setting. To date, the combination of carboplatin and etoposide (CE) forms the basic framework. At almost all centers worldwide, HDCT is carried out in the form of sequential therapy with three high-dose cycles of CE [39, 40, 41].

Thanks to improved supportive therapy and the use of autologous peripheral blood stem cells (PBSC), hematopoietic reconstitution has become significantly faster, thus reducing the treatment-related mortality rate from formerly more than 10% to now less than 3%.

The value of HDCT as the first salvage therapy remains controversial and is still the subject of current debate. A subgroup analysis of almost 1600 patient data sets, which retrospectively investigated the effectiveness of HDCT compared to CDCT in the first relapse treatment, showed an advantage of 10- 15% in favor of high-dose chemotherapy with respect to both PFS and OS. In contrast, a Europe-wide, multicenter, prospective, randomized study (IT-94) found no clear benefit of high-dose salvage therapy for the total group of patients in the first relapse after cisplatin-containing chemotherapy. Points of criticism of the IT 94 study are the relatively small number of patients, the high percentage of low-risk patients and the choice of an HDCT regimen that can no longer be regarded as standard today. In addition, around one third of the patients assigned to the HDCT arm never received HDCT [42, 43].

As part of an international randomized phase III study, which compared conventional paclitaxel-containing (TIP) salvage therapy with sequential high-dose chemotherapy (CE), the benefit of HDCT in the first relapse should be prospectively validated in the "TIGER-trial" [44]. A total of 420 patients has been included in this trial. A total of 13 centers from Germany and Switzerland were involved, and 79 patients from Germany were recruited. Until the final results of this study are available, the choice of the first salvage therapy remains unclear. Both treatment options must be thoroughly discussed with the patient, considering possible advantages and disadvantages, and in consultation with an expert center.

However, there is no doubt about the benefit of HDCT for patients with multiple relapses and for patients with cisplatin-refractory disease who have not received HDCT as the first salvage therapy. A significant proportion of patients can achieve long-term remissions with that [45, 46]. Regimens for high-dose salvage chemotherapy are summarized in the Appendix Treatment protocols.

7.1.6.4 Residual tumor resection (RTR) for non-seminomas in the salvage setting

Complete resection of all remaining, radiologically detectable tumor residuals (even <1cm) after salvage therapy represents an essential contribution to treatment success. The proportion of patients with vital, undifferentiated histology is significantly higher after repeat chemotherapy (approx. 40%); complete removal of all residual lesions is essential [21, 36, 47, 48]. This often complex procedure should only be performed at a center designated for testicular tumor surgery with the possibility of multivisceral surgery and appropriate expertise [31]. Even with increasing tumor markers in the salvage situation, long-term remissions of approx. 20-30% can be achieved [63]. RTR for seminoma, on the other hand, is not advisable, as in the primary situation.

7.2 Special settings

7.2.1 Late recurrence

A late relapse means a relapse more than 2 years after the last cisplatin-containing chemotherapy. Late recurrences are generally rare, preferably in patients with initial non-seminomas, but very rarely also in patients with previous seminoma. Surgical resection of the tumor lesion is the treatment of choice in patients with resectable lesions and no or only moderate marker elevation. Patients with excessive marker elevation and/or multilocular, non-resectable lesions should first be treated with conventional or high-dose chemotherapy and only after that, all remaining tumor residues should be resected. Histologically, in addition to yolk sac tumors, tumor pathologies with somatic malignant transformation of a teratoma, e.g., into sarcomas, neuroectodermal tumors or adenocarcinomas, may be found. In order to reduce perioperative morbidity and mortality, all patients with late recurrences should only be treated at highly specialized centers [49, 50].

7.2.2 Brain metastases

Brain metastases are generally rare in patients with gonadal germ cell tumors. They can occur either synchronously at primary diagnosis or at relapse. An isolated CNS relapse is found in only about 2% of patients. A retrospective study compared the individual treatment modalities of chemotherapy, radiotherapy and surgical resection, in addition to identifying prognostic factors, and examined the survival rate of patients both at primary diagnosis and at relapse. It was shown that in addition to chemotherapy, subsequent radiotherapy and/or surgical resection is not always necessary in primary diagnosis. On the other hand, in the relapse setting, maximum utilization of all 3 modalities with the inclusion of high-dose chemotherapy appears to significantly improve the survival rate of patients. The benefit of surgical resection of isolated brain metastases alone has not been proven, however, this may be useful in some patients. The optimal approach for patients with CNS metastases should always be evaluated at a center with appropriate expertise [4, 51, 52].

7.2.3 Malignant somatic transformation (MST)

Overall, MST is rare. It may be detected in the orchiectomy tissue as well as after chemotherapeutic treatment in the resected residual tumor, and in rare late recurrences. In addition to neuroectodermal tumors of the embryonic type (ENET), rhabdomyosarcomas and adenocarcinomas are demonstrated histologically. Malignant transformation of a germ cell tumor can be detected in the tumor cells via the i12p chromosome. Prognostically, the 5-year survival is significantly lower than that of teratomas without malignant transformation. There is no general treatment recommendation. In addition to complete surgical resection for residual tumors, both

classic cisplatin-containing therapy for germ cell tumors and therapy according to the specific histology are possible options in the metastatic recurrent situation. Consultation of a center with special expertise is absolutely advisable [50].

7.2.4 Growing Teratoma

A growing teratoma is defined as a metastasis of a germ cell tumor increasing in size under ongoing therapy after successful chemotherapy with subsequent marker normalization. Diagnostic imaging often shows cystic, sometimes also solid parts. In principle, the initially planned chemotherapy should be completed in accordance with the IGCCCG classification and a complete surgical resection should be performed promptly in the event of a marker response. Exceptions are patients who develop clinically relevant symptoms (e.g., ileus) due to the growing teratoma. Complete resection is essential for long-term remission. The (often complex) treatment of the frequently very large tumors should only be performed at specialized centers [74].

7.3 Palliative therapy

7.3.1 Chemotherapy

In addition to paclitaxel, oxaliplatin and gemcitabine are also available as possible treatment options in the palliative setting, either as monotherapy or as part of combination therapies. The “GOP” regimen, which combines oxaliplatin with gemcitabine and paclitaxel, is particularly successful and is able to induce long-term remissions in patients even in relapse after previous HDCT, especially in combination with subsequent complete resection of remaining tumor lesions. Good palliative efficacy has also been demonstrated for the use of oral etoposide [53, 54, 79, 80].

If these drugs fail, the alternatives are limited and patients should be included in clinical trials (if possible and available).

7.3.1.1 Substances for systemic tumor therapy (alphabetical order)

7.3.1.1.1 Bleomycin

Bleomycin is a cytostatic antibiotic (glycopeptide) that induces strand breaks through interaction with single- or double-stranded DNA and inhibition of DNA polymerase. It is approved for the treatment of testicular cancer (seminoma and non-seminoma), Hodgkin's lymphoma, non-Hodgkin's lymphomas and for the intrapleural treatment of malignant pleural effusions. In germ cell tumors, it is typically used as part of the PEB/BEP first-line protocol in combination with etoposide and cisplatin. The prescribing information recommends administering a test dose at least 4 hours before the initial application. Side effects include gastrointestinal complaints (loss of appetite, weight loss, nausea/vomiting, mucositis), skin reactions (including painful swelling, nail changes and alopecia), myalgia/arthralgia, fever reactions and headaches, but above all pulmonary toxicity. The latter includes the risk of interstitial pneumonitis, acute respiratory distress syndrome (ARDS), pulmonary fibrosis and impaired pulmonary function. An increase in the risk of pulmonary toxicity of bleomycin must be expected when it is combined with other cytostatics toxic to the lungs (e.g., mitomycin C). Patients should be carefully monitored to detect early pathological pulmonary symptoms, taking into account known risk factors (e.g., age, dosing, pre-existing lung disease, radiotherapy). When administering G-CSF, an interval of at least 24 hours should be met. Bleomycin is mainly eliminated renally. Comedication with substances

that may impair renal function can lead to an increased toxicity of bleomycin as a result of delayed elimination. The simultaneous administration of bleomycin with other immunosuppressive drugs can lead to an increase in immunosuppression. Clinically, drug levels of phenytoin and digoxin were reduced during concomitant treatment with bleomycin, presumably due to reduced absorption. The simultaneous administration of bleomycin and live vaccines (e.g., yellow fever) is contraindicated.

7.3.1.1.2 Carboplatin

Carboplatin is a platinum derivative mainly used in patients with gonadal germ cell tumors as a monotherapy in the adjuvant setting and in combination with etoposide for high-dose therapy before autologous hematopoietic stem cell transplantation. Carboplatin is not an adequate alternative for patients who are not suitable for treatment with cisplatin. It is approved for the treatment of ovarian carcinoma, cervical carcinoma, head and neck squamous cell carcinoma and small cell lung cancer (depending on the prescribing information provided by the various suppliers). Myelosuppression (with increased susceptibility to infection), nausea, vomiting, alopecia, diarrhea or constipation have been reported as common side effects. Rarely, neurotoxicity may also occur. Yellow fever vaccination during carboplatin therapy is contraindicated, and the use of live attenuated vaccines should be avoided if possible. A relevant pharmacological interaction is described for phenytoin (decreased efficacy of phenytoin). Concomitant treatment with immunosuppressants such as cyclosporine or tacrolimus leads to increased immunosuppression.

7.3.1.1.3 Cisplatin

Cisplatin is a platinum derivative that is used as standard therapy for gonadal germ cell tumors, typically in combination with etoposide and bleomycin (PEB/BEP) as standard therapy or with ifosfamide and etoposide (or vinblastine or paclitaxel) as "salvage" therapy. It is approved for the treatment of bladder cancer and a broad spectrum of other malignant neoplasms. Major side effects reported include nausea and vomiting, nephrotoxicity, polyneuropathy, ototoxicity, hematotoxicity, electrolyte imbalances, cardiotoxicity and diarrhea. Vaccination with live vaccines (e.g., yellow fever) under cisplatin treatment is contraindicated. The prescribing information points to relevant pharmacological interactions with other ototoxic or nephrotoxic substances, anticoagulants, anticonvulsants or phenytoin as well as increased activity when combined with paclitaxel, docetaxel, bleomycin, vinorelbine or cyclosporine.

7.3.1.1.4 Etoposide

Etoposide inhibits DNA topoisomerase II in the S and G2 phase of the cell cycle, resulting in DNA strand breaks. It is approved for the treatment of a broad spectrum of malignant neoplasms (small cell and non-small cell lung cancer, Hodgkin's and non-Hodgkin's lymphomas, acute myeloid leukemia, testicular cancer, ovarian carcinoma and gestational high-risk trophoblastic neoplasms in adult women). For gonadal germ cell tumors, it is used in first-line standard therapy in combination with cisplatin and bleomycin (PEB/BEP) or with cisplatin alone (CE) as well as for "salvage" therapy in combination with ifosfamide and cisplatin (PEI/VIP). According to the prescribing information, the main side effects are myelosuppression (with increased susceptibility to infection), the possible triggering of other primary cancers such as acute myeloid leukemia, gastrointestinal complaints (nausea/vomiting, diarrhea/obstipation, mucositis, dysgeusia, weight loss), skin reactions including alopecia, hepatotoxicity, cardiovascular complications (hypertension, hypotension, acute coronary syndrome, dizziness) and infu-

sion-associated reactions including anaphylaxis, as well as fatigue and weakness. Pharmacological interactions with other drugs include reduced clearance in combination with cisplatin (compared to etoposide monotherapy) or high doses of cyclosporine, increased clearance and reduced efficacy with concomitant administration of phenytoin, interaction with warfarin (INR increase) and increased myelosuppression due to combination with other hematotoxic drugs. The administration of live vaccines such as yellow fever during treatment with etoposide is contraindicated.

7.3.1.1.5 Gemcitabine

Gemcitabine is an antimetabolite (pyrimidine analog). After intracellular phosphorylation, it is incorporated into the DNA instead of cytidine. Gemcitabine is approved for the treatment of advanced urinary bladder carcinoma (in combination with cisplatin) and various other solid tumors (non-small cell lung cancer, pancreatic cancer, ovarian carcinoma, breast cancer, according to the prescribing information for durvalumab in combination with cisplatin and durvalumab for biliary carcinoma). In "salvage" chemotherapy of previously treated patients with gonadal germ cell tumors, it is typically used in combination with oxaliplatin and paclitaxel. Severe side effects (grade 3 or 4), which occurred in more than 5% of patients in large randomized phase 3 studies, are neutropenia (10-30%), thrombocytopenia (5-10%), fatigue (5-20%), anemia (5-10%), nausea/vomiting (5%) and elevation of bilirubin and/or transaminases (5%). Clinically relevant pharmacological interactions have not been described. The use of live vaccines (e.g., yellow fever) should be avoided.

7.3.1.1.6 Ifosfamide

Ifosfamide is a cyclophosphamide isomer and belongs to the group of cytotoxic alkylating agents, which inhibit cell proliferation by incorporating an alkyl group into the DNA. It is approved for treatment of a wide range of malignant neoplasms such as lung cancer, breast cancer, ovarian carcinomas, malignant lymphomas and sarcomas as well as for combination therapy in testicular cancer. Side effects include myelosuppression with increased susceptibility to infection, encephalopathy and CNS toxicity, nephrotoxicity, cardiotoxicity and the possible triggering of secondary malignant neoplasia. Gastrointestinal complaints (nausea/vomiting, inappetence) and alopecia are common side effects. Special precautions are required to avoid ifosfamide-induced hemorrhagic cystitis (combination with mesna, see prescribing information). The prescribing information points at a large number of possible pharmacological interactions with other active substances, including CYP3A4 inhibitors (e.g., azole antifungals, sorafenib), CYP450 inducers (e.g., St. John's wort, carbamazepine, phenytoin, rifampicin, glucocorticoids, phenobarbital), CNS-active drugs (antiemetics, neuroleptics, sedatives, antidepressants, etc.) and numerous substances that can increase the side effects of ifosfamide. The administration of live vaccines during treatment with ifosfamide should be avoided.

7.3.1.1.7 Oxaliplatin

Oxaliplatin is a platinum derivative (see also cisplatin and carboplatin), which is approved in combination with 5-fluorouracil and folinic acid for the treatment of patients with colorectal carcinomas. In gonadal germ cell tumors, it is used in the palliative second-line situation in combination with gemcitabine and paclitaxel (GOP protocol). The main side effects when used in combination with 5-FU and folinic acid are gastrointestinal complaints (diarrhea/obstipation, nausea/vomiting, mucositis), myelosuppression and neurotoxicity, the latter primarily in the form of a dose-dependent peripheral neuropathy (PNP). In addition, increases in liver function

parameters (transaminases, bilirubin), fatigue and weakness are frequently observed, and allergies and skin reactions (including alopecia) may occur. More pronounced PNP must be expected in cisplatin-pretreated patients who receive oxaliplatin in combination with paclitaxel. Oxaliplatin is mainly eliminated renally. It is not metabolized with involvement of cytochrome p450 isoenzymes, so that pharmacological interactions with other active substances have not been reported. Particular attention should be paid to additive toxicities when oxaliplatin is used with other drugs causing toxicities that may also be caused by oxaliplatin. It is recommended in the prescribing information that the QT interval should be monitored particularly closely when oxaliplatin is administered concomitantly with drugs that are known to prolong the QT interval. The administration of live vaccines (e.g., yellow fever) during treatment with oxaliplatin is not recommended.

7.3.1.1.8 Paclitaxel

Like docetaxel, paclitaxel is a cytotoxic chemotherapeutic agent from the taxane class. It acts as a mitosis inhibitor particularly in rapidly proliferating cells and leads to cell cycle arrest in the G2/M phase. It is approved for the treatment of breast cancer, ovarian carcinoma, non-small cell lung cancer and AIDS-associated Kaposi's sarcoma. For gonadal germ cell tumors, it is used in combination with cisplatin and ifosfamide or with gemcitabine and oxaliplatin. Severe possible side effects include infections, stomatitis and diarrhea as well as allergic reactions to the solvent cremophor. Premedication with glucocorticoids, H2 receptor antagonists and antihistamines is mandatory. Alopecia is one of the most troublesome side effects, and peripheral neuropathy (PNP), which can be irreversible, is particularly burdensome. PNP is expected to be aggravated by the combination with cisplatin or oxaliplatin in patients previously treated with cisplatin. The metabolism of paclitaxel is catalyzed in part by the cytochrome P450 isoenzymes CYP2C8 and CYP3A4. Therefore, special caution is required when paclitaxel is used together with other drugs that inhibit either CYP2C8 or CYP3A4 (e.g., azole antifungals, erythromycin, fluoxetine, gemfibrozil, clopidogrel, cimetidine, ritonavir, saquinavir, indinavir and nelfinavir), as the toxicity of paclitaxel may be increased due to higher paclitaxel exposure. The use of paclitaxel together with other agents that induce either CYP2C8 or CYP3A4 (e.g. rifampicin, carbamazepine, phenytoin, efavirenz, nevirapine) is not recommended, as efficacy may be impaired due to lower paclitaxel exposure.

7.3.1.1.9 Vinblastine

Vinblastine is a chemotherapeutic agent from the vinca alkaloid drug class and blocks mitosis by inhibiting the formation of microtubules. It is approved for the treatment of malignant lymphomas, breast and testicular cancers and Langerhans cell histiocytosis. For the treatment of relapsed or refractory gonadal germ cell tumors, it is used in combination with cisplatin and ifosfamide. The side effects of this combination are therefore attributable to the combination of these agents. Specific vinblastine-associated side effects include hematotoxicity (leukopenia, thrombocytopenia, anemia), neurotoxicity (PNP), nausea/vomiting and constipation. The potential increase in PNP due to the combination with cisplatin must be considered. The prescribing information points out that the use of vinblastine sulphate in patients who are simultaneously receiving drugs with an inhibitory effect on the metabolism of drugs via isoenzymes of the hepatic cytochrome CYP3A and in patients with liver dysfunction may lead to earlier occurrence and/or increased severity of side effects. Concomitant oral or intravenous administration with digitoxin may lead to reduced digitoxin levels in the blood. The concomitant use of phenytoin with vinblastine sulphate can lead to reduced phenytoin levels in the blood.

7.3.2 Immunotherapy and tyrosine kinase inhibitors

Unfortunately, no significant improvements in PFS and OS could be achieved with the administration of checkpoint inhibitors or tyrosine kinase inhibitors in any of the clinical trials conducted and have therefore not found their way into the treatment of relapsed patients [79].

7.3.3 Radiotherapy

In addition to stereotactic radiotherapy and the (now very rare) whole-brain radiotherapy for CNS manifestations, palliative radiotherapy is used to treat clinically symptomatic bone metastases or other manifestations with a palliative, pain-relieving intention.

7.3.4 Desperation surgery

In individual patients without marker normalization after successful relapse chemotherapy or multiple, chemotherapy-refractory relapses, surgery in the sense of a so-called "desperation surgery" can still lead to cure in individual cases, especially in the presence of singular and easily resectable tumor manifestations and a sole AFP increase. The prerequisite is the possible achievement of a complete resection of tumor lesions [55].

8 New treatment strategies for relapses after HDCT

In a phase I basket study including patients with germ cell tumors, heavily pretreated patients with tumors expressing claudin-6 showed good response rates and longer-term remissions with an acceptable toxicity profile using monotherapy with a claudin-6-directed chimeric antigen receptor (CAR)-T cell therapy or in combination with an mRNA vaccine [77]. Based on these promising results, a phase II trial (BNT211-02) is planned to start in 2024, which will also recruit patients in Germany, Austria and Switzerland.

9 Monitoring and follow-up

9.1 Follow-up

The aim of follow-up is to detect a relapse at an early stage with the aim of extending the survival time / increasing the chance of recovery, and to detect long-term side effects of the therapy and prevention at a later stage. The goal of improving the prognosis through structured follow-up at the beginning is justified by the possibilities of successful salvage therapy (see chapter 7.1.6.3). However, the prognostic relevance of the follow-up concept has not been evaluated in prospective studies [2, 32, 56, 57]. Recent studies show that CT can be replaced by MRI, especially in stage I seminoma, and that the reduction of cross-sectional imaging does not lead to an increased recurrence rate [75].

Recommendations for patients according to histology, stage and treatment strategy (e.g., active surveillance) according to EAU 2023 and ESMO 2018/2022 [1; 81]:

Table 10: Follow-up of patients with seminoma stage I under active surveillance or after adjuvant therapy (carboplatin or radiotherapy)

Procedure	Year 1	Year 2	Year 3	Years 4 and 5	>5 years
Medical history and clinical examination	2x	2x	2x	1x	Detection of late toxicity
Tumor markers	2x	2x	2x	1x	
Chest X-ray	0	0	0	0	
CT or MRI abdomen and true pelvis	2x	2x	After 36 months	After 60 months	

Table 11: Follow-up of patients with non-seminoma stage I under active surveillance

Procedure	Year 1	Year 2	Year 3	Years 4 and 5	>5 years
Medical history and clinical examination	4-6x	4x	2x	1-2x	Detection of late toxicity
Tumor markers	4-6x	4x	2x	1-2x	
Chest X-ray	2x	2x	1x (for LVI+)	After 60 months (if LVI+)	
CT or MRI abdomen and true pelvis	2x	After 24 months*	After 36 months**	After 60 months**	

Legend:

LVI+: Evidence of lymphovascular invasion in the primary tumor

* For LVI+ additional CT/MRI after 18 months (majority voting)

** Based on the vote of 47% of experts in 2016

Table 12: Follow-up of patients in complete remission after adjuvant or curative therapy

Procedure	Year 1	Year 2	Year 3	Years 4 and 5	>5 years
Medical history and clinical examination	4x	4x	2x	2x	Detection of late toxicity**
Tumor markers	4x	4x	2x	2x	
Chest X-ray	1-2x	1x	1x	1x	
CT or MRI abdomen and true pelvis	1-2x	After 24 months	After 36 months	After 60 months	
CT thorax	*	*	*	*	

Legend:

* at the same time as abdominal MRI/CT in patients with lung metastases at diagnosis

** Further follow-up in uro-oncology if teratoma was found in the resected residual tumor

Due to the high number of cured patients, the occurrence of possible late toxicities after active therapy (chemotherapy and/or radiotherapy) is of great importance in the long-term course. In addition to the development of second tumors, these include the development of a metabolic syndrome with an increased risk of myocardial infarction and stroke, pulmonary toxicity, neuro-, oto- and nephrotoxicity as well as endocrine dysfunction and chronic fatigue. Psychosocial components such as depression and fear of recurrence also play a major role in follow-up [64]. Patients must therefore be informed in detail about the possible long-term consequences after active therapy, in particular the risk of increased cardiovascular events. After completion of therapy, patients should be informed about the follow-up strategy, the expected risk of recurrence and any late toxicities of the treatment in a final consultation before the start of follow-up. Relevant treatment documents should be handed over in copy, a written follow-up plan should be compiled and patients should be informed about their individual lifestyle (smoking cessation, active lifestyle, weight control) including the contact details of counseling centers and patient advocates.

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11 Studies

SAKK 01/18 Seminoma, stage IIA/B, (clinicaltrials.gov, NCT), active

PRIMETEST seminoma, stage IIA/B (clinicaltrials.gov, NCT02797626), recruitment complete, follow-up study planned

TIGER First relapse after cisplatin-containing chemotherapy, (clinicaltrials.gov, NCT02375204), completed enrollment

BNT211-02 in preparation, phase II

15 Links

<https://hodenkrebs.de/> (Interdisciplinary Testicular Tumor Working Group)

<http://www.esmo.org/Guidelines/Genitourinary-Cancers/Testicular-Seminoma-and-Non-Seminoma> (ESMO guidelines)

<http://uroweb.org/guideline/testicular-cancer/> (EAU guidelines)

<http://www.ncbi.nlm.nih.gov/pubmed/23152360> (Consensus recommendations for germ cell tumors 2012)

https://www.leitlinienprogramm.onkologie.de/fileadmin/user_upload/Downloads/Leitlinien/Hodentumoren/LL-Hodentumoren (S3 guideline testicular tumors)

<https://www.e-konsil.org>

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17 Disclosure of Potential Conflicts of Interest

according to the rules of the responsible Medical Societies.