Male Extragonadal Germ Cell Tumors of the Adult

Jonas Busch\textsuperscript{a} Christoph Seidel\textsuperscript{b} Friedemann Zengerling\textsuperscript{c}

\textsuperscript{a}Department of Urology, Charité Universitätsmedizin Berlin, Berlin, Germany;
\textsuperscript{b}Department of Oncology, Hematology and Bone Marrow Transplantation, Universitätsklinikum Hamburg Eppendorf, Hamburg, Germany;
\textsuperscript{c}Department of Urology, Universitätsklinikum Ulm, Ulm, Germany

\section*{Introduction}

The vast majority of male germ cell tumors (GCTs) derive from testicular tissue, while 2–5\% manifest extrascrotally and are, therefore, called extragonadal germ cell tumors (EGCTs) \cite{1, 2}. According to a recent study by the National Cancer Register of Finland, the incidence of EGCTs is about 0.18/100,000 \cite{3}. For gonadal GCTs comprehensive recommendations for a stage-adapted therapy have been published, while for the treatment of EGCTs only a limited number of appropriate reference tools exists. Broadly speaking, the treatment of EGCTs follows the same principles as those for gonadal GCTs \cite{4–6}.

Males can develop EGCTs at any age, and the tumors can be categorized as neonatal, prepubertal and postpubertal (adult) EGCTs. This review concentrates on postpubertal/adult EGCTs; reports on prepubertal and neonatal EGCTs have been published elsewhere \cite{7}. In the following, if not stated otherwise, EGCT refers to adult EGCTs.

EGCTs show the same serological, histological and cytogenetic characteristics as gonadal GCTs \cite{8}. They normally manifest in the mid axis of the body, predominantly in the mediastinum or in the retroperitoneum, while clinical and ultrasound findings reveal no suspicious testicular lesions \cite{1, 9}.

\section*{Theories of Origin, Driving Mechanisms and Localizations}

EGCTs most likely originate from a urogenital misplacement of gonadal cells during embryogenesis \cite{9}. Physiologically, primordial gonadal cells derive from the ectoderm and distribute following the urogenital ridge and are then termed gonocytes. These gonocytes further differentiate into oocytes or pre-spermatogonia depending on the constitution of the sex chromosomes and the microenvironment \cite{2, 10}. Disturbances in this process result in a misplacement...
of these cells at different localizations within the mid axis of the body. A malignant transformation of these cells, depending on the influence of their microenvironment, leads to EGCTs with different histological features.

Another theory implies that EGCTs develop through a malignant transformation of germ cells that have regularly spread into liver, bone marrow and brain during embryogenesis to participate in important regulatory, hematological or immunological processes. Earlier theories, following the idea that every EGCT originates from the testes, even if they are histologically unsuspicious, are no longer part of the current scientific opinion. The present consensus is that EGCTs represent a malignant transformational process of germ cells without evidence of a gonadal primary tumor. With respect to localization, EGCTs are classified into 2 major forms: retroperitoneal and mediastinal EGCTs. EGCTS of other localizations are rare. Of note is that mediastinal non-teratomatous EGCTs are sometimes considered as a separate tumor entity, due to their necessity of a more complex, multimodal therapy [11, 12].

**Anatomic Sites**

Accounting for 50–70% of all EGCTs, the anterior mediastinum is the most common localization, followed by the retroperitoneal space (30–40%) [2]. EGCTs in the pineal gland or the sacrococcygeal region are significantly less common. Other localizations such as the prostate, the urinary bladder and the liver have been described occasionally [13, 14].

**Mediastinal EGCTs**

Mediastinal EGCTs occur almost exclusively in men. In a case series of 322 patients only 2 female patients with confirmed primary mediastinal EGCTs were reported [15]. The discrimination between pure seminoma, non-seminoma and teratoma is of particular clinical importance. Teratomas and pure seminomas are the most common histological subtypes of mediastinal EGCTs. Teratomas are divided into mature and immature teratomas. Mature mediastinal teratomas are considered benign and are treated by surgical resection alone rather than by chemo- or radiotherapy.

About 43% of all mediastinal tumors harbor parts of a teratoma [7]. About 63% of them are mature teratomas, 4% are immature teratomas and 33% are teratomas with other malignant components, for example GCT or sarcoma components [7]. Mature teratomas consist of a composite of 2 or 3 germ layers containing mature fatty tissue, well-differentiated epithelial and glandular tissue and cartilaginous tissue. Respiratory epithelium, smooth muscles, teeth and hair are further possible elements. In contrast, immature teratomas are characterized by immature mesenchymal components and glandular epithelium. Immature neuroepithelium is also a common component. Teratomas with malignant GCT components, for example seminoma, embryonal carcinoma or yolk sac tumor are considered as malignant non-teratomatous GCTs.

Malignant non-teratomatous mediastinal EGCTs are differentiated into seminomas and non-seminomas [16]. Among mediastinal EGCTs, seminomas account for 40% of the non-teratomatous tumors and are thereby more common than in EGCTs in general, where they account for only 20–24% of the tumors. In a large case series of 635 patients from 11 medical centers with mediastinal and retroperitoneal EGCTs, 104 patients had pure seminomas and 524 had non-seminomatous tumors [9].

Mediastinal seminomas often infiltrate the thymus, which can lead to a cystic formation or hyperplasia of the thymus epithelium. The histology of all non-teratomatous components is identical to gonadal GCTs. In contrast to gonadal non-seminomatous GCTs, mediastinal non-seminomatous EGCTs contain embryonal carcinoma less frequently and yolk sac tumor components more frequently. In a series of 64 patients, histology revealed a pure yolk sac tumor in 60% of the patients, a choriocarcinoma in 12%, and a pure embryonic carcinoma in about 9% of the patients [17].

**Retroperitoneal EGCTs**

Retroperitoneal EGCTs have a clinical behavior very similar to that of gonadal GCTs [7]. The genesis of retroperitoneal GCTs is still under debate [2]. Undisputed is an association between retroperitoneal EGCTs and premalignant lesions of 1 or both testicles. A recent retrospective analysis of 26 patients with a retroperitoneal EGCT revealed a pathological finding on clinical examination of the testes in 11 patients (42%) [18]. 14 patients (54%) showed a testicular atrophy and/or induration, 1 patient had an enlarged testicle. Ultrasound examination demonstrated a suspicious lesion in 20 of 20 patients. Finally, pathological review of the testicular tissue was performed for 25 of the 26 patients. It yielded scarring tissue in 12 patients (48%), intratubular neoplasia in 4 (16%) and vital tumor tissue in 3 patients (12%). Consequently, the authors raised the question of whether primary retroperitoneal EGCTs really exist or if they are always associated with a pathological intrascrotal finding [18].

**Pineal GCTs**

Because EGCTs of the pineal gland are relatively rare, their exact incidence is largely unknown. In 2008, Villano et al. [19] published an overview on pineal GCTs, summarizing the data of 3 different tumor databases: the Surveillance, Epidemiology and End Results (SEER) database (1973–2001); the National Cancer Data Base (NCDB; 1985–2003); and the Central Brain Tumor Registry of the United States (CBTRUS; 1997–2001) [20–22]. Evaluating the SEER database, tumors located in the region of the pineal gland were found in 335 of 44,251 individuals with brain tumors (0.76%) [19, 20]. Of all GCTs in the SEER population, 2.04% occurred in the central nervous system and 1.08% (i.e. 53.0% of all central nervous GCTs) were located specifically in the pineal gland. Analysis of the other 2 databases revealed that 39.4% and 48% of tumors in the pineal gland, respectively, had a GCT histology [19, 21, 22]. The ratio between male and female patients was between 14.3:1 and 21.4:1 [19]. Pathological examination revealed the presence of germinoma in 73–85% of the cases [19]. Germinoma is a GCT of...
the central nervous system that resembles ovarian dysgerminoma or testicular seminoma. The GCTs from these 3 databases were diagnosed at the ages of 0–86 years with a clustering in the second decade of life [19–22]. Only rare cases were diagnosed in individuals older than 30 years. Mixed GCTs had with 14.3 years the lowest mean age at presentation, whereas germinomas were diagnosed at a mean age of 19.2 years [19]. Overall, the incidence of pineal GCTs was calculated 0.025 per 100,000 people [19]. The 5-year survival rate was 73.7% [19].

**Sacroccygeal EGCTs**

Sacroccygeal EGCTs are considered to be congenital and occur almost exclusively in infants. In adults, mature teratomas are the most common presentation of sacroccygeal EGCTs, but non-teratomatous GCTs have also been documented [23]. Mature teratomas in adulthood have a benign presentation in contrast to the sacroccygeal EGCTs in childhood, which are associated with a clearly worse prognosis [24]. It is assumed that more aggressive forms already manifest in childhood, whereas more indolent forms become apparent at a later time point in adulthood. A malignant transformation of mature teratomas has been described. However, this corresponds to the development of non-germinal tumors. In these cases, the patients develop adenocarcinomas from tumor residues after incomplete resection of infantile teratomas as well as from existing mature teratomas in adults [25].

**Demarcation from Other Tumor Entities**

According to their localization, mediastinal tumors can be grouped into lesions of the anterior, the middle and the posterior mediastinum. The most common malignant tumors of the anterior mediastinum are lymphomas, thymic carcinoma, thyroid cancer and EGCTs. Neurogenic tumors present most commonly in the posterior mediastinum. Benign lesions of the anterior mediastinum can be a thymoma or a thymic cyst. A bronchogenic cyst can manifest as a benign lesion in every part of the mediastinum. Enteric cysts are benign lesions of the posterior mediastinum (paraesophageal and gastroesophageal). Inflammatory swellings and benign lymph node enlargements, for example in patients with Castleman’s disease, must also be considered for differential diagnosis.

Retroperitoneal tumors are caused by benign or malignant processes. They can occur in retroperitoneal parenchymatous organs, e.g. the pancreas, kidneys or adrenal glands or as primary processes of the retroperitoneum. Lipoma and liposarcoma as mesenchymal tumors of benign and malignant behavior can also be found in the retroperitoneum. Schwannomas or ganglioneuroblastomas can manifest as benign neurogenic tumors of the retroperitoneum, whereas malignant neurogenic tumors can arise as schwannomas and neuroblastomas.

Tumors that arise from enlarged lymphatic tissue can be due to a lymphoma, a post-transplantation lymphoproliferative disease or by lymph node metastases of other malignant diseases.

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**Clinical Appearance and Diagnostic Work-Up**

Most EGCTs are located in the retroperitoneal space or in the mediastinum, but can be found at others locations, although less frequently, as already mentioned (hypophysis, sacroccygeal, gastrotintestinal, liver, orbita, and prostate). A retroperitoneal location of GCT tissue may, especially if there is evidence of testicular scarring tissue, raise the question of whether the retroperitoneal tumor represents a true EGCT or rather a tumor with primary origin in the testis that has metastasized and has turned into scarring tissue locally (‘burned out tumor’) [1].

The clinical appearance of EGCTs varies significantly. In a large meta-analysis of 635 patients with EGCTs, Bokemeyer et al. [9] were able to demonstrate that tumors located in the mediastinum cause symptoms like dyspnea (25%), chest pain (23%), cough (17%), fever (13%), a vena cava syndrome or fatigue. Patients with retroperitoneal EGCTs may complain particularly about abdominal pain (29%) or back pain (14%), weight loss (9%), fever (8%) and vena cava syndrome or other thrombosis (9%) [9].

In most cases, this pluriform clinical appearance is the reason why patients consult their physician [26]. Their symptoms are caused by the growing tumor mass, which after appropriate imaging procedures (ultrasound followed by computed tomography/magnetic resonance imaging (CT/MRI)) should be confirmed histologically. Depending on the localization, this can be done by fine-needle aspiration cytology, by percutaneous biopsy or by mediastinoscopy [1]. Pathological diagnosis should include the GCT-specific markers alpha-fetoprotein (AFP), human chorionic gonadotropin (β-HCG) and lactate dehydrogenase (LDH) to make a correct classification of the patient according to the International Germ Cell Cancer Collaborative Group (IGCCC) [27] and the recent guideline recommendations [4, 6]. Examination of the testes is necessary to rule out a testicular origin. In rarer cases, patients with smaller lesions might complain of none or only minor symptoms or their tumor mass might become evident during routine imaging or otherwise indicated surgical procedures.

The question of whether a clinically and sonographically non-suspicious testis has to undergo histological assessment if the presence of an EGCT has been established was discussed at the European Consensus Conference in 2011. The majority of the participating experts voted against a biopsy, especially because a cisplatinum-based chemotherapy might eradicate premalignant testicular intraepithelial neoplasia (TIN) lesions effectively [6]. In the large series of Bokemeyer et al. [9] mentioned above, about 11% of all patients underwent a testicular biopsy. In 3% of the cases a Sertoli cell-only syndrome was diagnosed, 31% had atrophic or fibrotic testicular tissue and only 9% TIN lesions. A metachronous GCT was most common in seminomatous EGCTs, which harbor a cumulative risk of 10% within the next 10 years. This risk appears to be higher than that in other series of metastatic GCTs. On the other hand, these secondary testicular tumors are quite easy to detect and, especially in the case of a seminoma, highly curable [1].
**Therapy and Prognosis of EGCTs**

As mentioned above, the treatment of EGCs is performed in analogy to metastatic GCTs with gonadal origin. In this, cisplatinum-based polychemotherapy plays a key role for an effective treatment [4, 6].

**Seminomatous EGCTs**

Seminomatous EGCTs are, independently of their localization, generally treated with 3 cycles of BEP (bleomycin, etoposide and cisplatin); in ‘good risk’ situations 4 cycles of EP (etoposide and cisplatin) are also an option. Pure seminomas have a better prognosis than non-seminomas, especially because seminoma cells are highly susceptible to cisplatinum-based chemotherapy and ionizing radiation, irrespective of their localization. Therefore, a surgical resection of residual tumor masses is not mandatory [12, 28]. In a case series of 52 patients with a retroperitoneal pure seminoma and 51 patients with a mediastinal pure seminoma, the 5-year progression-free survival (PFS) and the 5-year overall survival (OS) rates were 87% and 90%, respectively [28]. 75% of the patients were successfully treated with chemotherapy alone. Similar to the therapy standard for gonadal stage II GCTs, retroperitoneal seminomatous EGCTs can be treated with radiotherapy if tumor extension is limited. Poor prognostic factors for pure seminomas are the presence of liver metastases or metastases in 2 or more different organs [28].

**Non-Seminomatous EGCTs**

Mature teratomas are a distinct type of non-seminomatous GCTs and are discussed at the end of this section. Patients with a retroperitoneal non-seminomatous EGCT are classified as having a ‘good’, ‘intermediate’ or ‘poor prognosis’ according to the IGC-CCG criteria. Patients with a mediastinal non-seminomatous EGCT are classified as having a ‘poor prognosis’ because of their low 5-year OS rate of 40–45% [27, 29].

The therapy results of primary retroperitoneal EGCTs are similar to those of metastatic gonadal GCTs. The effectivity of a combined treatment of retroperitoneal non-seminomatous EGCTs in a multimodal approach of cisplatinum-based chemotherapy and surgical resection was analyzed in a retrospective series of 227 patients. 98% of the patients were initially treated with chemotherapy. 101 (45%) of the patients had a subsequent residual tumor resection. The 5-year PFS and OS rates were 42% and 65% [9]. Patients with relapse after first-line chemotherapy are treated with high-dose chemotherapy in analogy to gonadal GCTs. About 30% of the patients with relapsed retroperitoneal GCTs can still be cured with this approach.

A finding of < 10% of vital tumor in the resected post-chemotherapy tissue is associated with a favorable prognosis. Poor prognostic factors for pure seminomas are the presence of liver metastases or metastases in 2 or more different organs [28]. The prognosis of non-seminomatous EGCTs can be compromised by concomitant hematological diseases. About 6% of these patients develop hematological diseases, with acute megakaryoblastic leukemia (AML M7) and myelodysplastic syndrome being the most common entities [30]. In 38% of the cases, cytogenetic analyses revealed a chromosomal aberration of the isochromosome 12p, which is associated with GCTs [31]. The reason for this is widely unknown. Increased hematopoesis and leukemogenesis due to teratoma elements have also been suggested to be caused by the generation of leukemic cells by yolk sac elements within the GCTs.

The standard chemotherapy regimen for patients with a mediastinal non-seminomatous EGCT consists of 4 cycles of BEP. In most cases a multimodal therapy concept is recommended consisting of chemotherapy followed by residual tumor resection.

The therapeutic success of a multimodal concept was evaluated in a case series of 278 ‘poor prognosis’ patients of whom 97% were initially treated with chemotherapy [30]. A complete remission after chemotherapy was found in 19% of the cases, a marker-negative partial remission occurred in 45% of the cases. In 143 patients (50%) a residual tumor resection was performed. The 5-year PFS and OS rates were 44% and 45%, respectively. The poor OS can be explained by very limited therapeutic options in the presence of a relapsing tumor. For patients with a relapsed mediastinal EGCT, a larger case series reported a long-term disease-free survival of only 19% [32]. In patients with mediastinal tumors, the survival rate was with 11% even lower, compared to 30% in patients with retroperitoneal tumors.

In a recent review, Albany and Einhorn from Indiana University recommended 4 cycles of etoposide, ifosfamide and cisplatinum (VIP) for patients with mediastinal non-seminomatous EGCTs because of a better pulmonary tolerability compared to a chemotherapy regimen containing bleomycin [12]. Furthermore, residual tumor resection is recommended as an essential part of the management of mediastinal non-seminomatous EGCTs for a better evaluation of the response to therapy, elimination of chemoresistant tumor masses and possibly so that further chemotherapy cycles can be applied. Because of the limited prognosis of patients with mediastinal non-seminomatous EGCTs and the lack of effective salvage chemotherapy concepts, the authors also recommended a residual tumor resection even in the case of elevated tumor markers supposing that there may be a better outcome for patients after resection of vital tumor tissue [12]. According to this study, follow-up of these patients should include a chest CT every 2 months for the first year, every 4 months in the second and every 6 months from 3–5 years [12].

Mature teratomas are the most common GCTs located in the mediastinum. For teratomas of the anterior mediastinum surgical resection is the treatment of choice. However, if elevated tumor markers are found, polychemotherapy instead of surgical resection is necessary [12].

**Disclosure Statement**

The authors declare no possible conflicts of interest.