Cancer Association of South Africa (CANSA)

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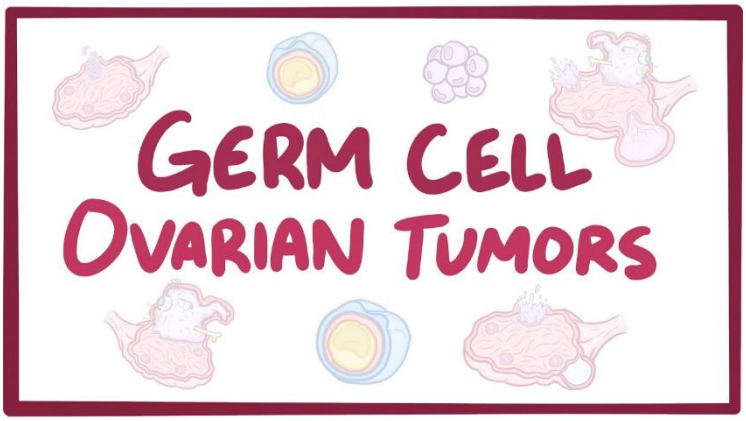
Fact Sheet
on
Germ Cell Tumour of the Ovary

Introduction

Germ cell tumours begin in the reproductive cells (egg or sperm) of the body. Ovarian germ cell tumours usually occur in teenage girls or young women and most often affect just one ovary.



[Picture Credit: Germ Cell Ovarian Tumours]

The ovaries are a pair of organs in the female reproductive system. They are situated in the pelvis, one on each side of the uterus. Each ovary is about the size and shape of an almond. The ovaries make ova (eggs) and female hormones. Ovarian germ cell tumour is a general name that is used to describe several different types of cancer. The most common ovarian germ cell tumour is called dysgerminoma.

Acosta, A.M., Sholl, L.M., Cin, P.D., Howitt, B.E., Otis, C.N. & Nucci, M.R. 2020.
Aims: Tumours of the female genital tract with a combination of malignant Mullerian and germ cell or trophoblastic tumour (MMGC/T) components are usually diagnosed in postmenopausal women, and pursue an aggressive clinical course characterised by poor response to therapy and early relapses. These clinical features suggest that MMGC/T are somatic in origin, but objective molecular data to support this interpretation are lacking. This study evaluates the molecular features of nine MMGC/T, including seven tumours containing yolk sac tumour (YST), one tumour containing choriocarcinoma and one tumour containing epithelioid trophoblastic tumour. The objectives were to: (i) investigate whether MMGC/T show a distinct genetic profile and (ii) explore the relationship between the different histological components.
Methods and results: Next-generation sequencing of paired samples demonstrated that the mutational profile of the Mullerian and non-Mullerian components of the tumour were almost identical in all cases. Moreover, the driver mutations identified were those expected in the specific subtype of Mullerian component present in each case. In contrast, variants expected in postpubertal germ cell tumours and gestational trophoblastic tumours were not identified, and FISH for i(12p) was negative in all cases tested. In this study, mismatch repair-proficient MMGC/T (eight of nine) were characterised by a complex copy-number variant profile, including numerous focal, regional, arm-level and chromosome-level events.
Conclusions: Comparison of paired samples supports that the YST and trophoblastic tumour components of MMGC/T have a somatic origin and often show numerous copy-number variants, suggestive of underlying genomic instability.

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Safdar, N.S., Stall, J.N. & Young, R.H. 2020.

"One hundred malignant mixed germ cell tumors of the ovary that occurred in patients 3 to 55 years (mean: 20 y) of age are described. The clinical presentation was usually that of any highly malignant tumor of the ovary (abdominal pain and distension), but rarely (3 cases) endocrine manifestations were present. The tumors were usually unilateral (96%), ranged from 4 to 38 cm (mean: 16 cm), and were uniformly solid or, more often, solid and cystic; occasionally the typical appearance of dysgerminoma could be appreciated. The most common tumor type was yolk sac tumor (91%), followed by dysgerminoma (61%), immature teratoma (58%), embryonal carcinoma (38%), and choriocarcinoma (11%). A variety of admixtures were encountered; dysgerminoma and yolk sac tumor was the most common combination (25% of the tumors) with the 2 components often being sharply demarcated. Immature teratoma and yolk sac tumor was the next most common pairing (20%) followed by yolk sac tumor and embryonal carcinoma, with or without immature teratoma (16%). Tumors with a choriocarcinoma component had the most varied combinations of tumor types. Embryoid bodies were seen in 21% of the tumors, most often as fragmented forms arranged in a nodular manner with yolk sac tumor and/or embryonal carcinoma; uncommonly they occurred singly or in clusters. Numerous confluent well-formed embryoid bodies (polyembryoma) were prominent in 2 tumors. Three tumors had a focal diffuse embryoma pattern. The specific tumor types showed the known diverse spectrum of microscopic appearances, but the frequent haphazard arrangement of 2 or more subtypes often resulted in complex morphology. Overgrowth of another neoplastic component, most often primitive neuroectodermal tumor, occurred in 10% of the tumors further complicating the histologic picture. This is the largest series of ovarian malignant mixed germ cell tumors reported and details their characteristics including associations of their subtypes and the frequent apparent role of embryoid bodies in giving rise to yolk sac tumor and embryonal carcinoma components."

Germ Cell Tumour of the Ovary

Ovarian malignant germ cell tumours (OMGCTs) are heterogeneous tumours that are derived from the primitive germ cells of the embryonic gonad. OMGCTs are rare, accounting for about 2.6% of all ovarian malignancies, and typically manifest in adolescence. Ovarian Germ Cell Tumours (OGCT) are Subdivided into the following Clinicopathological Entities:

Subtype	Frequency of OGCT	Benign / Malignant	Uni- or Bilateral	Tumour Markers Expressed	Metastasis Route
Dysgerminoma	35 – 50%	Malignant	10-15% are bilateral	Serum lactic dehydrogenase	Via Lymphatic System
Endodermal sinus Tumour (EST)	20%	Malignant	Usually Unilateral	AFP and hCG	Intraperitoneally And Haematogenously
Embryonal Carcinoma	Rare	Malignant	Usually Unilaterally	AFP and hCG	Intraperitoneally
Polyembryoma	Rare			AFP and hCG	
Choriocarcinoma	Very Rare	Malignant	Usually Unilaterally	hCG	
Teratoma	Immature Account for 20% of Of malignant GCT	Benign or Malignant	12-15% are bilateral	Immature teratomas sometimes secrete AFP, serum LDH and CA-125	
Mixed GCT	10-15%	Dependent upon the cell types present		Dependent upon the cell types present	

Tumour Grade and Tumour Stage

Tumour grade and stage are terms used to describe the severity of a tumour, while tumour grade describes the appearance of cancerous cells in the tissue by examining them under a microscope.

Tumour stage encompasses:

- The location of the tumour.
- The size and/or extent of the original tumour.
- Whether cancer cells have spread to lymph nodes or anywhere else in the body.
- The number of tumours present.

Doctors use tumour grade, cancer stage, and a patient's age and general health to decide the course of treatment for the patient and determine prognosis. Prognosis describes all factors including the disease course, cure rate, chances of survival, and risk of recurrence of cancer.

What are the cancer stages?

Different systems of cancer staging are used to describe the types of cancer. Below is a common method in which stages are ranged from 0 to IV.

- Stage 0: The tumour is confined to its place of origin (in situ) and has not spread to nearby tissue.
- Stage I: The tumour is located only in the original organ, is small, and has not spread.
- Stage II: The size of the tumour is large but has not spread.
- Stage III: The tumour has become larger and may have spread to surrounding tissues and/or lymph nodes.
- Stage IV: The tumour has spread to other distant organs of the body, which is known as the metastasis stage.

TNM staging

Another common staging method used for cancer is the TNM system, which stands for tumour, node (which means spread of the tumour to lymph nodes), and metastasis. When a patient's cancer is staged using the TNM system, a number will be present along with the letter. This number signifies the extent of the disease in each category - tumour, node, and metastases.

Another system of cancer staging divides cancer into five stages, which include:

- In situ: Abnormal cells are present but have not spread to nearby tissue.
- Localized: Cancer is located only in the original organ and shows no sign of its spread.
- Regional: Cancer has spread to nearby lymph nodes, tissues, or organs.
- Distant: Cancer has spread to distant parts of the body.
- Unknown: The stage cannot be figured out due to a lack of enough information.

What are the cancer grades?

Cancer grades are based on examination of the suspected tissue sample under a microscope. This involves surgically removing a piece of the suspected cancerous tissue and sending it to the lab for analysis. The entire procedure is known as a biopsy.

A doctor who specializes in diagnostic tests (pathologist) examines the cells of the tissue and determines whether they are harmless (benign or noncancerous) or harmful (malignant or cancerous). They describe the microscopic appearance of the cells and assign a numerical "grade" to most cancers.

Generally, a lower grade indicates slow-growing cancer and a higher grade indicates fast-growing cancer.

The most commonly used grading system is as follows:

- Grade I: Cancer cells that look like normal cells but are not growing rapidly.
- Grade II: Cancer cells that don't look like normal cells with their growth being faster than normal cells.
- Grade III: Cancer cells that look abnormal and have the potential to grow rapidly or spread more aggressively.

Sometimes, the following system can be used:

- GX: Grade cannot be assessed (undetermined grade)
- G1: Well-differentiated (low grade)
- G2: Moderately differentiated (intermediate grade)
- G3: Poorly differentiated (high grade)
- G4: Undifferentiated (high grade)

Incidence of Germ Cell Tumour of the Ovary in South Africa

The South African National Cancer Registry does not provide any information regarding the incidence of Germ Cell Tumour of the Ovary.

Causes and Risk Factors for Germ Cell Tumour of the Ovary

The cause of ovarian teratomas is unknown. Certain genetic conditions that cause extra or missing sex chromosomes can also raise one's risk.

No factors have been associated with the cause of Germ Cell Tumour, apart from an increased incidence associated with dysgenetic gonads. 5% of individuals with dysgerminomas are associated with constitutional cytogenetic abnormalities involving the entirety or part of the Y chromosome; 46,XY (testicular feminisation), gonadal dysgenesis and mixed gonadal dysgenesis (45,X, 46,XY). However, 95% of females with dysgerminomas are cytogenetically normal. In genetic syndromes with a high risk of cancer, rarely are Germ Cell Tumours found. It may be infrequently in individuals with Li-Fraumeni.

Signs and Symptoms of Germ Cell Tumour of the Ovary

Germ cell tumours of the ovary are rare. They usually affect younger women and most can be cured. Many germ cell tumours are not cancer (benign), but some are cancer (malignant).

The symptoms may include:

- pain or a feeling of pressure in the pelvis or tummy
- a feeling of fullness or gradual swelling of the tummy
- irregular periods or signs of pregnancy
- high temperatures (fevers), chills, feeling or being sick and pain in the abdomen.

Diagnosis of Germ Cell Tumour of the Ovary
Diagnosis relies on clinical findings, serum tumour markers and imaging.

Imaging includes pelvic ultrasonography and computed tomography of abdomen and pelvis (if extra ovarian metastasis is suspected) and chest X-ray (to detect metastasis to lung and mediastinum).

Dosage of human chorionic gonadotropin (hCG), lactate dehydrogenase (LDH) and alpha fetoprotein (alpha-FP) also contribute to the diagnosis, the prognosis and follow-up of the disease. 12 p isochromosome (i(12p)) and chromosome 12 over-representation are observed, in non teratomatous ovarian germ cell tumours while pure teratomas lack i(12p).

Diagnosis is only confirmed histologically after laparotomy or laparoscopy.

Treatment of Germ Cell Tumour of the Ovary
Most types and stages of germ cell cancers of the ovary are treated the same way, usually with surgery and chemotherapy.

Surgery**:** In general, all women with malignant germ cell tumours will have the same staging surgery that is done for epithelial ovarian cancer. For women who still want to be able to have children, the cancerous ovary and the fallopian tube on the same side are removed, but the uterus, the ovary, and the fallopian tube on the opposite side are left behind. This isn't an option when the cancer is in both ovaries. If preserving fertility is not a concern, complete staging including removing both ovaries, both fallopian tubes, and the uterus is generally recommended.

Sometimes, the doctor might consider removing only a part of one ovary to allow a woman to keep her ovarian function. Even when both ovaries need to be removed, a woman may wish to keep her uterus to allow future pregnancy through the use of in-vitro fertilization.

If cancer has spread beyond the ovaries , debulking surgery may be done as a part of the initial surgery. This removes as much cancer as possible without damaging or removing essential organs.

Nasioudis, D., Mastroyannis, S.A. Latif, N.A. & Ko, E.M. 2020
Objective: To evaluate trends in the surgical management of young women and pediatric patients with malignant ovarian germ cell tumors (MOGCTs) and associated survival outcomes.
Materials and methods: Using the Surveillance, Epidemiology, and End Results database we identified patients under 40 years who underwent surgery between 1994 and 2014. The Joinpoint Regression Program was employed to investigate the presence of temporal trends and calculate average annual percent change (AAPC) rates. For analysis purposes two age groups were formed; pediatric/adolescent (≤21 yrs) and young adult (22-40 yrs). Histology was categorized into dysgerminoma, immature teratoma, yolk-sac tumor, mixed germ cell tumor and other histology. Cancer specific survival was compared using log-rank tests.
Results: A total of 2238 patients were identified, with median age 21 years. Only 12.4% underwent hysterectomy. One third underwent omentectomy, and one half underwent lymphadenectomy (LND). A decrease in the rate of omentectomy (AAPC: -2.15, 95% CI: -3.4, -0.9) and hysterectomy (AAPC: -3.31, 95% CI: -6.1, -0.4) was observed. There was no change in the rate of LND (AAPC: 0.17, 95% CI: -0.7, 1.1). Pediatric patients were less likely to undergo omentectomy (30.2% vs 35.5%, $p < 0.001$), hysterectomy (3.5% vs 22%, $p < 0.001$) and LND (45.6% vs 54.7%, $p < 0.001$). There were no apparent survival differences according to the

performance of hysterectomy, omentectomy or LND, when stratified by early (stage I) and advanced stage (II-IV), ($p > 0.05$).
Conclusions: Pediatric patients with MOGCTs undergo less extensive surgical staging. A trend towards less extensive surgical procedures for young women over time was observed, without an apparent detrimental effect on cancer specific survival.

Chemotherapy**:** Most women with germ cell cancer will need to be treated with combination chemotherapy for at least 3 cycles. The combination used most often is PEB (or BEP), and may include the chemotherapy drugs cisplatin, etoposide, and bleomycin. Dysgerminomas are usually very sensitive to chemotherapy, and can sometimes be treated with the less toxic combination of carboplatin and etoposide. Other drug combinations may be used to treat cancer that has recurred (come back) or has not responded to treatment. Germ cell cancers can raise blood levels of the tumour markers human chorionic gonadotropin (HCG), alpha-fetoprotein (AFP), and/or lactate dehydrogenase (LDH). If the blood levels of these are high before treatment starts, they are rechecked during chemotherapy (usually before each cycle). If the chemotherapy is working, the levels will go down. If the levels stay up, it might be a sign that a different treatment is needed.

Berney, D.M., Stoneham, S., Arora, R., Shamash, J. & Lockley, M. 2020.
"The classification of ovarian germ cell tumours has remained unchanged for many years, while there have been considerable changes in the testicular classification. In recent years there has been concern about the overtreatment of clinical stage 1 testicular germ cell tumours with increasing use of surveillance for low-risk disease. We outline here the current classification of germ cell tumours of the ovary with particular regard to treatment and outcome and highlight some areas which may cause confusion, particularly pertaining to immature teratomas and mixed germ cell tumours. We suggest that some minor changes to the classification, evidenced by a recent retrospective series by some of the authors, may lead to less adjuvant chemotherapy for immature teratomas and may obviate the need for the grading of immature teratomas, by aligning with testicular experience in pure post-pubertal teratomas. Adoption of this will require retrospective and prospective re-evaluation, but may avoid long-term patient morbidity."

Karalok, A., Comert, G.K., Kilic, C., Turkmen, O., Kilic, F., Basaran, D., Boyraz, G., Tekin, Ö.M. & Turan, T. 2019.
INTRODUCTION: To evaluate the survival effect of cytoreductive surgery in advanced stage malignant ovarian germ cell tumors (MOGCT).
MATERIAL AND METHODS: Clinicopathological data of patients with MOGCT that were treated between 1991 and 2014. Maximal debulking was defined as no gross residual tumor after primary or recurrence surgery; optimal and suboptimal debulking were used for patients with residual tumors of ≤1cm and >1cm, respectively.
RESULTS: In total, 31 patients with advanced stage MOGCT were analyzed. The median age at diagnosis was 21 (14-57) years. The median follow-up duration was 64.1 months. Of these 31 patients; 7 patients underwent sub-optimal debulking, 5 patients had optimal surgery and 18 had maximal debulking. Five-year DFS according to surgical resection rates were 29% in suboptimal debulking group, 75% in optimal debulking group and 93% in maximal cytoreduction group ($p<0.001$). Three of seven patients who underwent sub-optimal debulking were died of disease, however no deaths were seen in patients with optimal and maximal debulking. Five-year OS was 32% in suboptimal debulking group, and 100% in optimal and maximal debulking groups ($p=0.001$).
DISCUSSION: The benefit of cytoreductive surgery is less well-established in MOGCT of ovary compared to ovarian tumors of epithelial origin due to rareness of this histological subtype. Patients with MOGCT are usually younger and preservation of fertility is an important issue which may lead to suboptimal procedures, sometimes in exchange for diminished survival. Our data demonstrated that maximal cytoreduction should be aimed in patients with advanced stage MOGCT, as it is significantly associated with improved overall survival.

Gadducci, A., Giuliani, D., Cosio, S., Lissoni, A., Ferrero, A.M. & Landoni, F. 2019.

BACKGROUND/AIM: The aim of the study was to assess the clinical outcome of patients with malignant transformation of an ovarian mature teratoma.

PATIENTS AND METHODS: This study was conducted on 23 patients who underwent primary surgery at three Italian Gynecological Centers. Histologically, nine (39.1%) patients had squamous cell carcinoma, five (21.7%) had a thyroid carcinoma, six (26.1%) had a carcinoid, one (4.3%) patient had papillary renal carcinoma, one (4.3%) had medulloblastoma and one (4.3%) had intestinal-type mucinous adenocarcinoma.

RESULTS: All six patients with stage I squamous cell carcinoma had no evidence of disease (NED) after a median time of 141 months. Of the three patients with stage IIb-IIIc squamous cell carcinoma, two had NED after 119 and 154 months, and one died of the disease 9 months after diagnosis. All five women with stage I thyroid carcinoma had NED after a median of 60 months. Of the six patients with stage I carcinoid, five had NED after a median of 168 months, whereas one died due to carcinoid heart disease. The three patients with stage I renal carcinoma, medulloblastoma and mucinous adenocarcinoma had NED after 24, 141 and 149 months, respectively.

CONCLUSION: The clinical outcome of early-stage malignancies associated with mature ovarian teratomas is excellent following treatment.

Chen, Y., Ning, Y., Zhang, Q. & Xie, Y. 2018.

BACKGROUND: Lymphadenectomy has been widely used in the treatment of malignant germ cell tumor of the ovary (OGCT), which is a kind of ovarian cancers occurred mostly in young women and adolescent girls. But the clinical decision mainly depends on the doctor's experience without a well-defined guideline. This population-based study aimed to evaluate the prognostic impact of lymphadenectomy in different stages of malignant germ cell tumors of the ovary.

METHODS: Patients with known status of lymphadenectomy in different stages of OGCT were explored from the Surveillance, Epidemiology, and End Results (SEER) program database from 1973 to 2013. We used propensity score matching algorithm to reduce the selection bias between the two study groups. Survival curves, univariate and multivariate Cox proportional hazards model were applied to evaluate the prognostic impact of lymphadenectomy in different stages of OGCT.

RESULTS: We included 1,996 OGCT patients in the study, and 818 (41%) of them had lymph node resection. Compared to the LND- group, patients with lymph node resection tended to be at stage II and III, had larger tumor sizes and diagnosed as dysgerminoma. The influence of diagnosis ages, marital status and tumor grades were significantly decreased by applying the propensity score matching. Lymphadenectomy-positive (LND+) group demonstrated significantly worse survival than the lymphadenectomy-negative (LND-) group in later stages (stage III, overall, P=0.027, cancerspecific, P=0.006; stage IV, overall, P=0.034, cancer-specific, P=0.037). While, both the overall and cancer-specific survival showed no significant differences between LND+ and LND- in stage I (overall, P=0.411, cancer-specific, P=0.876) and stage II (overall, P=12, cancer-specific, P=0.061). Univariate (overall, HR=1.497, CI=1.010-2.217, P=0.044; cancer-specific, HR=1.524, CI=1.067- 2.404, P=0.050) and multivariate (overall, HR=1.580, CI=1.046-2.387, P=0.030; cancer-specific, HR=1.661, CI=1.027-2.686, P=0.039) Cox proportional model both verified the association between the lymph node resection and better survival in the whole cohort.

CONCLUSION: Lymphadenectomy significantly increased the survival probability of OGCT patients in stage III and IV, but had no significant influence on early-stage patients (stage I and II), indicating lymphadenectomy should be performed in a stage-dependent manner in clinical utility.

About Clinical Trials

Clinical trials are research studies that involve people. They are conducted under controlled conditions. Only about 10% of all drugs started in human clinical trials become an approved drug.

Clinical trials include:

- Trials to test effectiveness of new treatments
- Trials to test new ways of using current treatments
- Tests new interventions that may lower the risk of developing certain types of cancers
- Tests to find new ways of screening for cancer

The South African National Clinical Trials Register provides the public with updated information on clinical trials on human participants being conducted in South Africa. The Register provides information on the purpose of the clinical trial; who can participate, where the trial is located, and contact details.

For additional information, please visit: www.sanctr.gov.za/

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Germ Cell Ovarian Tumours
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Tumour Grade and Tumour Stage
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