Republic of Iraq Ministry of Higher Education & Scientific Research University of Al-Qadissiya College of Veterinary Medicine



# **Granulosa cell tumors**

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لِمُ لِلَّهِ ٱلرَّحْمَدِ ٱلرَّحِيمِ بْدُ

فَنَعَالَى ٱللَّهُ ٱلْمَلِكُ ٱلْحَقُّ وَلَا تَعَجَلْ بِٱلْقُرْءَانِ مِن قَبْلِ أَن يُقْضَى إِلَيْكَ وَحْيُهُ وَقُل زَبِّ زِدْنِي عِلْمَا ٢

صَبْ قَالَسْ، الْعُظَمِنِ،

من سورة طه

# **Certificate of Supervisor**

I certify that the project entitled (**Granulosa cell tumors GCTs**) was prepared by **Ali Fadhil** under my supervision at the College of Veterinary Medicine / University of Al-Qadissiya.

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# **Certificate of Department**

We certify that **Ali Fadshil** has finished his/her Graduation Project entitled (**Granulosa cell tumors GCTs**) and candidate it for debating.

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/ / 2018

# Dedication

Anyone who has a curiosity to learn.

#### Acknowledgement

First and foremost, I would like to thank the most gracious and most merciful "Allah", and Ahl al-Bayt (peace be upon them) for helping me along my life.

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## Summary

Granulosa cell tumors (GCTs) are a tumors of cell types containing more than the small constituents of granulosa cells (Chadha-Ajwani, 1987) affected human as well as domestic animals in all ages with more occurrence in old ages. Although, it is a low grade neoplasms, GCTs may causing death.

One the most affected methods to decrease reproductive losses due to GCTs is the cognition more about this disease.

This review conducted to explain the scientific definition of GCTs, its clinical finding, history, types of GCTs, histopathology, diagnosis, treatment, and prognosis.

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Chapter one Introduction

#### Introduction

Reproduction is highly important in both human being, for reserving human species, and in animas for their economic benefits and to provident meat, milk, wool,...etc. So, any defect in animal reproduction will cause deficiency in meat, milk, etc. On the other hand, any reproductive problem in human will threats human being.

One of the important reproductive problems in both human and domestic animals are granulose cell tumors (GCTs) which represent 5% of all ovarian malignancies (Farikkila, 2012). GCTs are responsible for most death from sex cord-like tumors category, despite they considered a low grade neoplasm (DeAngelo et al.,2009).

This review was conducted to explain a concentrated scientific informations about GCTs in both human and domestic animals.

**Chapter two** 

**Review of literatures** 

#### **Review of literatures**

#### **Definition:**

Varangot gave the following definition for GCT :"the term GCT is indicate to all tumors for which the cellular prototype represents structure analogous to cells of the granulosa that cause somatic changes as a result of excessive production of female sex hormones" (Chadha-Ajwani ,1987).

(Shokralla and Fathalla, 2015) define GCT as a hormone active tumors that originate from granulosa cells which produce estradiol. In 1973, WHO define GCT as those tumors of female cell types containing more than a small component of granulosa cells. GCT is hormonally active and highly vascularized subtype of cancer, 5% of all ovarian malignancies(Farkkila,2012).GCTs are rare neoplasms of the ovaries which progress slowly and are of ten diagnosed in an early stage(Shokralla and Fathalla,2015).GCTs orginate from ovarian Sex cords may be unilateral , measuring 4 16 and cm diameter (koivisto,etal.,2012).these types of cancer are composed of granulosa cells with or without an admixture of theca cells (Chadha Ajwani, 1987). In general, neoplastic disease in humans and domestic animals tend to increase with age however it was detected in a newborn Holestein calf (kanagawa,etal.,1964).

#### **History:**

The first documented description of ovarian gct in the literatures was by C.Von Rokitansky in 1859(Chadha Ajwani, 1987). H.shorder, In 1901 used the term "folliculoma" to describe a tumor that reproducing granulosa cells with follicular rosettes and he belived it arose from follicular epithelium with endometrium hyperplasia but saw no cause and effect link between these two observations(chadha Ajwani,1987). At 1922, R.shorder published a very detailed case in which endometrial hyperplasia had caused metrorrhagia and he considered that the influence of the tumor was resambles persistent follicle and that GCTs could create state analogous to that of "metropathia а

hemorrhagica"(Chadha\_Ajwani,1987).At 1937, J.varangot give the name granulose cell tumor for this type of ovarian cancer .(Chadha\_Ajwani,1987).

### **Types of GCTs :**

GCTs are divided into two subtypes based on histology and clinical characteristics: Juvinile and adult GCT the first type is generally diagnosed in children and adolescents comprises 5% of all GCTs ,while the adult comprises 95% .(Farkkila,2012).

The juvenile type is characterized by an early age of onset, increased risk of local and systemic failure and its with pronounced malignant signs(Outwater et al .,1998).

The juvenile GCT usually occurs before the normal age of puberty and is associated with histological features that distinguish it from the adult type of GCTs (Koukourakrs et al.,2008).

There is a type of ovarian cancer may diffused with GCTs which called granulosa theca cell tumors these are stromal tumors derives from cells of the umblical cord those are composed of granulosa cells ,fibroblasts and theca cells (Kastratoric et al.,2008).

The male adult testicular GCTs ,a rare sex cord stromal tumors ,only 28 cases have been reported in the literature (Hanson and Ambzye,2011).

#### **Etiology:**

Granulosa cell tumors are thought to arise from the rapidly proliferation of granulosa cells of preovulatory follicles(Farkkila,2012). These tumors are hormone active originating from granulosa cells which produce estradiol(Shokralla and Fathalla,2015).

There is some evidence that GCTs formation occurs due to genetic changes which lead to growth and transformation of normal cells into malignant type, this involves misregulation of cell proliferation and apoptosis (Farkkila,2012).

### **Clinical findings:**

The most prominent symptom of granulosa cell tumor seems to be nymphomania, but this is not constant sign (Kanagawa etal .,1964).

The affected female generally have hormonal imbalance such as excessive estrogen and/or progesterone, which may causing prolonged estrus ,cystic endometrial hyperplasia with mucupurulent or purulent (pyometra)discharge and dermatological changes (Koivisto etal .,2012).

Another important symptom of ovarian granulosa cell tumor ,especially in heifers ,is marked mammary development, with milk secretion which associated with chronic nymphomania (kanagawa etal .,1994).

Mares with ovarian granulosa cell tumors teased other mares in heat as if she were stallion and the mare in heat respond to the affected mare by postureing to urinate (Patrick,2013).

The most commonly presenting symptoms in women are abdominal uterine bleeding due to excessive estrogen production by the tumor, also abdominal symptoms caused by a large pelvic mass (Farkkila,2012).

80% to 90% of patients less than eight years of age have a sign of precoious psendopregnancy because all granulosa cell tumors are hormonally active, producing estradiol (Koukourakis etal., 2008).

(De Angelo et al.,2009) found that the most common symptoms in adult granulosa cell tumor in women were post menopausal bleeding,palpable abdominal mass and abdominal pain.(Koukourakis etal .,2008)reveals that the abdominal swelling ,pain,and palpable mass in the lower abdomin all are important presenting symptoms in all affected women

Although granulosa cell tumors concided a low grade neoplasm ,but is responsible for most death from sex cord\_like tumors category(D angelo etal .,2009).

### Histopathology:

Inspite of description of the characteristic histological appearance in most GCTs, it appeard sometimes to be difficult to differentiate them from those undifferentiated carcinoma ,carcinoid,a poorly differentiated

sertoli\_leydig cell tumors ,endometrioid stromal sarcoma or a small cell tumor.(Chadha\_Ajwani,1987).

Spread of granulosa cell tumors is local ,the tumors may also spread hematogenousely,and affected women can develop metastasis in the lungs, liver,and brain years after initial diagnosis (Koukourakis et al.,2018).

Macroscopically ,granulosa theca cell tumor is solid as viewed after incition of pale yellow color (Kastrovic *et al* .,2008). Between 80% and 90% of GCTs are contained to the ovary (koukourakis *et al* ., 2008).

Histopathologically ,GCT may be found accompanied in part by theca cell tumor and luteoma (Kangawa *et al* .,1964).

Advanced metastatic disease with ascites is present in about 10% of cases (koukourakis et al .,2008). (De Angelo *et al* .,2009)found that the most cases of adult GCTs in women had ultrasonography showing cystic or solid -cystic abdominal masses .The gross appearance of GCTs varies according to amounts of neoplastic cells (koukourakis *et al*.,2008).

Ovarian GCTs are solid tumors that could be soft or firm and is yellow of gray, depending on ratio of intracellular lipid in the lesion(Koukourakis *et al.*,2008).

#### **Diagnosis:**

Diagnosis of GCT is generally based on, exploratoratory laparotomy, histopathology, abdominal palpation and abdominal radiography(Koivito et al., 2012).

In mare diagnosis may achieved by transrectal ultrasound examination (Patrick,2013).

The measurement of plasma Anti\_mullarian hormone level in combination with rectal palpation and ultrasononagraphy is highly important method to achieve a definitive and early diagnosis of GCTs (Okawa et al .,2017).

Biobsy for histopathological analysis is other diagnostic method to confirm the diagnosis of a granulosa\_theca cell tumor (Patrick,2013;Koukourikis et al,2008). Overproduction of estradiol may helpful in the diagnosis of the tumor because of its numerous symptoms(Shokralla and Fathalla,2015).

Clinical diagnosis, i.e inhibin, testosterone, and progesterone, when inhibin and testosterone are elevated more than the normal level, while progesterone is at the baseline level indicating a lack of luteal tissue (Patrick, 2013)

### Treatment:

The initial treatment is ovariohystrectomy and in case of metastasis ,chemotherapy (Morrow, 1986).

Total abdominal hysterectomy with bilateral salpingo-oophorectomy is the appropriate surgical treatment for menopausal women and those with more advanced disease (Koukourakis et al .,2008).

(Shokralla and Fathalla,2015) record that surgery is the main line of treatment and prolonged post-theraputic treatment is necessary.

The use of adjuvant radiotherapy or chemotherapy has sometimes been associated with prolonged disease-free survival and possibly complete survival (Koukourakis et al .,2008).

Early stages GCTs revealing strong adverse prognostic factors should be treated with adjuvant chemotherapy (Vimla et al.,2005).

Chemotherapy is the treatment of choice for patients with advanced ,recurrent,or metastatic GCTs, and bleomycim,etoposide,and cisplatin may be the preferred regimen(Koukourakis et al., 2008).

### **Prognosis:**

In mare, prognosis is excellent, the presurgical elevation of testosrerone level will decrease to normal level within 24 hours postsurgical removal

of the affected ovary (Patrick, 2013).

The same prognosis aslo seen in cow with GCT treated by unilateral ovariectomy, when retain fertility was achieved and the treated cow conceived(Okawa et al.,2017).

In human, GCT characterized by an indolent course of disease, with a five years survival rate of 90%,however recurrence occur in 20-30% of affected women, also those with early stage disease, causing higher mortality(Farkkila,2012).

GCTs are tumors with relatively a good prognosis compared to epithelial ovarian cancer (Shokralla and Fathalla,2015).

In human, prognosis of GCT is excellent, because most of the patients present with stage I disease, although in more advanced stages and those with high-risk stage I disease with large tumor size, ruptured tumor, the prognosis is less favorable (Koukourakis et al.,2008).

The tumor size, mitotic rate and stage of disease level well-defined variables and influence the survival significantly and considered as an important prognostic factors (Vimla et al.,2005).

Stage is the just factor associated with disease free survival ,and fertility sparing surgery may be a treatment option for women with early stage disease that want to retain fertility (Lee et al.,2011). Recurrence of treated granulosa cell tumors is common (Vimla et al.,2005).

**Chapter three** 

Conclusions

### **Conclusions:**

1-GCTs were discovered in 1859.

2-GCTs are affected all ages with highly affection of old ages.

3-The most prominent clinical finding of GCTs is nymphomania.

4-the best diagnostic method for GCTs is ultrasonography and exploratory laparotomy.

5-the treatment of choice for GCTs is ovariohystrectomy, and in case of metastasis, chemotherapy.

6-the prognosis of GCTs is excellent in both human and domestic animals.

**Chapter four** 

Recommendations

#### **Recommendations:**

1-Planning to a series of molecular studies of GCTs in different species.

2-Induction of deep histopathological studies for GCTs in different species.

3-Try to treat GCTs by laser.

Chapter five

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