# A Clinical Review of Granulosa Cell Tumours of the Ovary Cases in KKH

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## ABSTRACT

**Introduction: Granulosa cell tumour (GCT) represents the largest group of sex-cord stromal tumours and comprises 1.5 - 3% of ovarian malignancy. The aim is to determine the incidence of the disease, study the profile of local patients, and assess the use of imaging studies in the diagnosis of the tumour.**

**Material and Methods: Clinical records of 19 patients diagnosed with GCT between October 1988 and July 1997 in Kandang Kerbau Hospital (KKH) were reviewed.**

**Results: GCT accounts for 3.5% of ovarian malignancy (54 out of 1552) in Singapore, of which 94.7% are adult GCT. In our study, patients are mainly peri/postmenopausal women (63.2%) in their 50s who experience post-menopausal bleeding. There is a high incidence of association with endometrial hyperplasia (40%). Ultrasound scans are able to predict the size and involvement of the tumour rather accurately. In our study sample, 13 patients (68.4%) presented with Stage 1 of the disease, none with Stage 2, 1 with Stage 3 (5.3%) and none with Stage 4. The other 5 patients (26.3%) were unstaged. Only one patient required adjuvant chemotherapy.**

**Conclusion: The local data with regards to GCT is congruent with those found in foreign literature. However, in our study, there were no patients with recurrence whereas GCTs are known to be late recurring in up to 20% of patients 10 - 20 years after diagnosis. This is probably attributed to the relatively short period of follow-up in this study. Thus, despite the fact that there is no evidence of recurrence of disease in our current study, we still recommend a vigilant follow-up protocol on all patients as literature has proven that with early detection of recurrences, it is possible to achieve complete cure.**


**Keywords: granulosa cell tumours, recurrence, ultrasound studies**

*Singapore Med J 2001 Vol 42(5):203-207*

## INTRODUCTION

Granulosa cell tumours of the ovary are rare neoplasms, accounting for approximately 1.5 - 3% of all ovarian malignancies[1]. They are classified under the category of sex-cord stromal tumours; juvenile (5%) or adult type[2]. The former has hyperchromatic granulosa cells with round nuclei, high mitotic rate and prominent luteinization. Although they are considered malignant, they have a characteristic natural history of slow and indolent growth, leading to a large tumour size at the time of presentation[3]. Recurrent disease develop in up to 25% of patients, often many (10 to 20) years after removal of the original tumour[4]. As such, the tumours are not only tedious to study, but it is also extremely difficult to measure the impact of any therapy on survival.

This review aims to collate data of all granulosa cell tumours diagnosed in Kandang Kerbau Hospital (KKH) over the last 10 years and to provide the reader with an understanding of the incidence, profile of patients and behaviour of the tumour in our local context. It also tries to assess the usefulness of imaging studies in the diagnosis of the neoplasm. However, due to the limited number of cases available for study and the short period of follow-up, this review cannot provide certain information such as mean survival, treatment success, but can be used as an ideal reference for the further studies in future.

## MATERIALS AND METHODS

Patient Population

Singapore Cancer Registry was screened for all patients diagnosed with primary or recurrent (adult and juvenile) granulosa cell tumours between October 1988 and July 1997 in KKH. This was supplemented by data from our KK GCC Database and the histopathological department of our hospital. Medical records of these 19 patients were reviewed and clinical data extracted. There was a total of 1552 ovarian malignancies diagnosed in Singapore over this 10-year period, of which 54 (3.5%) were granulosa cell tumours (19 in KKH and 35 in other centres).

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Data Studied

The following clinical parameters were evaluated: patient's age at diagnosis, gravida, parity, symptoms and signs, tumour markers and hormonal assays, dilatation and curettage results, radiologic workup, type of surgery performed, findings at the time of surgery, stage, grade, histology of tumour tissue, post-operative treatment and follow-up. Slides of the patients were reviewed by one independent pathologist*.

There were originally 20 records of granulosa cell tumours extracted but one was rejected after histological review as it did not fit the pathological features of granulosa cell tumour.

Due to the small number of patients, no formal statistical analysis was attempted.

## RESULTS

Clinical Characteristics

The mean age at diagnosis was 50.6 years (range: 19 to 67 years) for the more common adult form in peri- or postmenopausal (63.2%) females. There is a high incidence of occurrence in nulliparous (36.8%) females. There are 13 Chinese (68.4%), 4 Malays (21.1%) and 2 Indians (10.5%) in our study, which closely mirrors the Singapore racial demographics.

All patients were symptomatic, except one patient with juvenile granulosa cell tumour whose condition was discovered incidentally during an elective caesarean section and diagnosed retrospectively after histological confirmation of the tumour. The most common symptom was postmenopausal bleeding (57.9%), followed by abdominal pain and discomfort (36.8%), abdominal distension (26.3%) and irregular menses (26.3%). The rarer forms of presentation (one patient each) included abdominal mass, frequency of micturition, loss of appetite and weakness. None of the patients gave any history of subfertility or exogenous hormonal ingestion, which might have caused ovarian hyperstimulation. Most patients noticed these symptoms for a few weeks (31.6%) or months (42.1%) before seeking medical attention. These was only a small proportion (5 patients) who waited a year or two before consulting a specialist.

14 of our patients (73.7%) have a palpable pelvic (9 patients) or pelvi-abdominal (5 patients) mass at the time of presentation. The rest of the 5 patients have no signs at their first consultation. Of the 5 patients with abdominal masses, 2 had ascites as well. None of those studied had signs of distant metastasis like cervical lymph nodes or enlarged liver at the point of initial diagnosis.

Investigations

Tumour markers were done in 73.7%[14] of the patients. CA125 were in the ranges of 4.1 - 251U/ml (normal range 0-35U/ml). The median was 26.3. CA 125 was raised above 35 in only 4 out of the 14 patients tested and they all demonstrated a significant reduction after surgical removal of tumour. There was no significant correlation between raised CA125 and the presence of ascites. Estradiol level was performed on 4 patients (20%) with 2 showing marked decrease in levels post-operatively. There was no correlation with the menstrual status of the patients. Serum inhibin was not routinely tested.

Of the 19 patients, 9 had a dilatation and curettage before surgery. Of this group, 3 had features of endometrial hyperplasia. As for the rest of the patients who did not undergo a pre-operative dilatation and curettage, there were 3 endometrial hyperplasia noted in histology specimens removed during surgery. (15 patients had their uterus removed and sent for histology whereas 4 patients who underwent unilateral salpingoophorectomy and/or omentectomy and/or lymphadenectomy had no histological diagnosis of the endometrium as the uterus was not removed). Thus, there was a 40% association between granulosa cell tumour and endometrial hyperplasia. However, none of our patients had associated endometrial carcinoma though there was an incidental finding of one patient with concurrent carcinoma of the colon and another with a past history of carcinoma of the breast that had been surgically treated.

Imaging Studies

26.3% of patients[5] had imaging studies, that is, ultrasound of the pelvis which revealed findings similar to that found intra-operatively. There was one instance whereby the diagnosis of granulosa cell tumour was made initially based on ultrasound and confirmed histologically. Of the 5 patients who did not have any imaging studies pre-operatively, reasons were namely: one underwent Caesarean section during which the tumour was discovered, two had endometrial hyperplasia on dilatation and curettage and two had abdominal masses measuring 12 and 16 cm, all of which necessitated surgery before any imaging studies were done.

Imaging studies were able to pick up the size of the tumour to a fairly accurate detail, most corresponded to the size of tumour found during surgery, only 10% were two standard deviations away from the actual size. The median size of tumour picked up on ultrasound was 10 cm. Ultrasound was also useful for discerning the make-up of the tumours. However it was not as sensitive where ascites were concerned.

Treatment and Findings

Broadly, a few different types of surgery were carried out: unilateral salpingoopherectomy (USO)[1], total hysterectomy bilateral salpingoopherectomy (THBSO)[4], THBSO with omentectomy[7], THBSO with lymphadenectomy[2], THBSO with omentectomy and lymphadenectomy[3] and laparoscopic surgery followed by a staging laparotomy (THBSO, omentectomy, lymphadenectomy[2]. USO was carried out on the one patient with incidental finding of an ovarian tumour during caesarean section. Open cystectomy was performed on one patient which subsequently revealed granulosa cell tumour on histology and that was followed by a staging laparotomy. Two patients had a laparoscopic cystectomy prior to the staging laparotomy. All the staging laparotomies involved THBSO and removal of omentum and lymph nodes.

The mean tumour size was 9.3 cm in diameter, all were unilateral with 5 (including 4 who were unstaged intra-operatively) having local spread to the ovarian serosa (most common), omentum, fallopian tube and pelvic side wall. Tumour rupture occured intra-operatively in 13 patients, both iatrogenic and spontaneous. None had metastasis, lymphatic space invasion or positive peritoneal fluid cytology. One patient had a few suspicious cells in the peritoneal fluid but this was not associated with eventual morbidity or mortality. 13 patients did not have ascites at the time of surgery. Bloody peritoneal fluid was present in four of those with ascites and the rest[2] had clear fluid.

A moderate proportion (26.3%) of patients was unstaged as gynaecologists did not suspect the diagnosis of granulosa cell tumour intra-operatively. The rest that were staged were mostly Stage 1 (13 patients) with only one patient who was in Stage 3 at the time of diagnosis.

Call Exner cells were present in 2 patients and cellular atypia was found in 6 of them. The number of mitotic figures seen per 10 high power field ranged from zero to ten with the median at 3 - 4.

One patient with Stage 3 tumour was treated with adjuvant chemotherapy post surgery with nine courses of cisplatin and cyclophophamide.

Follow-up

Five patients were lost due to a default in follow-up but on tracing, they were noted to be well with no medical or surgical complications. One returned to her home country for further treatment and is currently receiving regular follow-up with no evidence of disease. One was followed-up by her general practitioner for juvenile granulosa cell tumour. Of those who are still receiving follow-up, all 12 of them had no evidence of disease during their last visit with gynaecologist.

**Table I. A profile of patients with granulosa cell tumour of ovary**

| Patient | Type | Age | Parity | Menopaused | Endometrial histology | Surgery | Stage |
|---|---|---|---|---|---|---|---|
| A | Juvenile | 24 | 0 | N | NA | RSO | 1A |
| B | Adult | 54 | 8 | Y | Cervicitis, sq metaplasia | THBSO | 1C |
| C | Adult | 45 | 3 | Y | Hyperplasia | THBSO, omentectomy | 3C |
| D | Adult | 47 | 0 | N | Endometritis | THBSO | NA |
| E | Adult | 65 | 3 | Y | Proliferative | THBSO, LN sampling | 1C |
| F | Adult | 64 | 3 | Y | Hyperplasia | THBSO, omentectomy | 1C |
| G | Adult | 61 | 0 | Y | Hyperplasia | THBSO | NA |
| H | Adult | 19 | 0 | N | NA | MIS cystectomy, then open LSO, omentectomy, LN removal | 1C |
| I | Adult | 51 | 6 | N | Proliferative | THBSO, omentectomy | NA |
| J | Adult | 63 | 7 | Y | Hyperplasia | THBSO, omentectomy | NA |
| K | Adult | 56 | 6 | Y | Atrophic | LAVHBSO, LN removal | NA |
| L | Adult | 55 | 5 | N | Hyperplasia | THBSO, omentectomy, LN removal | 1C |
| M | Adult | 59 | 0 | Y | Proliferative | THBSO, omentectomy | 1C |
| N | Adult | 50 | 1 | Y | Inactive | THBSO, omentectomy, LN removal | 1C |
| O | Adult | 67 | 0 | Y | Proliferative | THBSO, omentectomy | 1C |
| P | Adult | 60 | 4 | Y | Hyperplasia | THBSO | 1A |
| Q | Adult | 36 | 2 | N | NA | L cystectomy, omentectomy, LN removal | 1A |
| R | Adult | 35 | 0 | N | NA | MIS L cystectomy, then open omentectomy, LN removal | 1C |
| S | Adult | 49 | 3 | Y | Adenomyosis | THBSO, omentectomy | 1A |

## DISCUSSION

Adult form of granulosa cell tumour commonly presents itself in the fifth decade of life. The age at which this carcinoma is diagnosed in our study closely parallels that in other well-known studies, as evident in the following Table:

| Author | Years studied | No. of cases | Mean age |
|---|---|---|---|
| Anikwue[5] | 1955 to 76 | 32 | 50.2 |
| Evans[6] | 1910 to 72 | 118 | 51.0 |
| Goldston[7] | 1940 to 71 | 41 | 52.7 |
| Pankratz[8] | 1944 to 74 | 61 | 50.1 |
| Miller[4] | 1958 to 93 | 70 | 53.0 |
| Our Study | 1988 to 97 | 19 | 50.6 |

Two distinct types of granulosa cell tumours have been noted based on clinical presentation and histological characteristics, that is, the juvenile form and the adult form. Other than the histological differences noted earlier, the juvenile form tends to occur during the first three decades of life and is associated with a common form of isosexual pseudoprecocity (in up to 80% of cases)[2]. It has a low incidence (2%) of bilaterality and malignant potential. In our study, there is only one patient with juvenile granulosa cell tumour.

Granulosa cell tumours have clinical importance for two reasons. Firstly, their potential elaboration of large amount of hormonal products. Secondly, their propensity for indolent growth and late recurrence[9].

Hormone production is frequent, as is characteristic of ovarian stromal tumours, and this results in abnormal vaginal bleeding in two thirds to three quarters of patients[3] (84.2% in our study, including postmenopausal bleed and irregular menses). Estrogen production predominates and although not quantified routinely in all our patients, it is manifested by the increased incidence (40%) of endometrial hyperplasia, closely parallelling the 24-80% in reported literature[10]. Virilising symptoms eg. hirsutism, oligomenorrhoea and amenorrhoea occur in only 3% of patients in documented studies[2].

In the large published studies, up to 78 - 91% of tumours are diagnosed in Stage 1[3]. The majority of these tumours is of substantial size (more than 8 cm) by the time of presentation, averaging 11.9 cm in the Norris series[11], as compared to 9.3 cm in our local study. And these tumours, similarly, had no evidence of spread found at surgery.

Granulosa cell tumours disseminate mainly via the same routes as epithelial carcinomas: Direct extension to adjacent organs, for instance ovarian serosa, omentum, fallopian tubes, pelvic side wall, and lymphatic and haematogenous metastases[2]. However morbidity and mortality associated with such spread is not well described.

Of the many modalities of imaging, computed tomography and magnetic resonance imaging have been documented to be of aid in the diagnosis of granulosa cell tumour[12]. However, with increasing health care costs, it is not possible to subject all patients to such sophisticated investigations. In our study, the main imaging study done was abdominal-pelvic ultrasound which was precise in picking up sizes and occasionally even the type of tumour. However, it was not so sensitive in detecting the presence of ascites, possibly due to the small amount of fluid accumulation. It is also not possible to comment on the pick-up rate metastases as a large majority of our patients had Stage 1 of the disease. It is recommended that biochemical tumour markers such as CA125 should be used together with CT scanning at regular intervals for the follow-up of these patients[12].

Other studies have shown the association of Call Exner bodies, cellular atypia and mitotic figures with prognosis[13]. The absence of Call Exner bodies, and the presence of the latter two are known to paint a graver picture[14]. However since the survival rate in our series is more than 90%, we are unable to make a definitive association.

Use of adjuvant therapy is still controversial in the realms of granulosa sell tumours. Radiotherapy has not proven any benefits. Chemotherapy with cyclophosphamide, cisplatin, doxorubicin, actinomycin and 5 fluorouracil have been tried in many studies with varying results[2]. in our own population, the Stage 3 tumour was treated with nine courses (patient defaulted the 10th and last course) of cisplatin and cyclophosphamide.

Literature reported a 91.8% 5-year survival for Stage 1 patients and a 9 % risk of recurrence in Stage 1A. Up to 20% of all patients with any stage of the tumour can have recurrence 10-20 years after the initial diagnosis[15]. Interpretation of such data is difficult in this current study in view of the short period of follow-up, the mean duration being 30 months (range 4 months to 9 years), with a period of follow-up of eight years for the patient with Stage 3 disease. With the data we have at hand currently, there has been no recurrence and we are unable to predict the risk of recurrence accurately since the mean time for recurrence ranges from 6 to 8 - 9 years, which is far longer than what we have been following up on with our patients. It is therefore advisable and even mandatory to follow-up on patients with such seemingly benign tumours for a period of at least 20 years, as early detection of recurrences and early intervention make it possible to achieve complete cure. It is thus recommended that we have a vigilant follow-up protocol and adequate patient education in order to treat them thoroughly.

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