Defining the Relationship Between Ovarian Adult Granulosa Cell Tumors and Synchronous Endometrial Pathology: Does Ovarian Tumour Size Correlate With Endometrial Cancer?

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Research Article

Keywords: Adult granulosa cell tumour, endometrial carcinoma, tumour size

Posted Date: September 25th, 2023

DOI: https://doi.org/10.21203/rs.3.rs-3029359/v2

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Abstract

Objective: The main feature of adult granulosa cell tumours (AGCT) is their capacity to secrete hormones, with nearly all of them capable of synthesizing oestradiol. Endometrial pathology is caused by granulosa cell-produced oestrogen. The primary goal of this study is to identify synchronised endometrial pathologies, particularly endometrial cancer, in AGCT patients who had undergone a hysterectomy. The secondary objective is to define the factors related to synchronised endometrial cancer in AGCT.

Materials and Methods: The study cohort comprised retrospectively of 316 AGCT patients from ten tertiary gynaecological oncology centres. AGCT surgery consisted of bilateral salpingo-oophorectomy, hysterectomy, peritoneal cytology, omentectomy and the excision of any suspicious lesion. Endometrial hyperplasia was categorised as simple hyperplasia without atypia, complex hyperplasia without atypia, complex hyperplasia with atypia or endometrial intraepithelial neoplasia (EIN). The median tumour size value was used to define the relationship between tumour size and endometrial cancer. The relationship between each value and endometrial cancer was evaluated.

Results: EIN or hyperplasia with complex atypia was detected in 7.7% of patients and endometrial cancer in 3.2% of patients. The relationship between tumour size and endometrial cancer was evaluated by taking the tumour size as a cut-off value of 150 mm. Four patients with a tumour size of \( \leq \) 150 mm (3.2%), and four patients with a tumour size >150 mm (12.1%) had endometrial cancer. \( p=0.036 \). Tumour size was statistically significant in relation to endometrial cancer in menopausal AGCT patients.

Conclusion: Our present study determined that 7.3% of patients had complex hyperplasia with atypia or EIN, and 3.1% of patients had endometrial carcinoma. During the menopausal period, endometrial cancer risk was 4.5%. The study revealed that the likelihood of developing endometrial cancer increased to 12% from 3.2% when the size of the tumour was >150 mm in menopausal patients.

Introduction

Granulosa cell tumours account for 2–5% of malignant ovarian tumours and 90% of malignant sex cord stromal tumours [1]. Granulosa cell tumours were classified as either juvenile form or adult form [2, 3]. Adult granulosa cell tumours (AGCT) account for 95% granulosa cell tumours [3, 4]. AGCTs are most commonly diagnosed in women over the age of 30 years, with the average age being around 55 [3].

The current guidelines for the treatment of AGCT state that standard cytoreductive surgery, when feasible, remains to be the most effective treatment for metastatic or recurrent AGCT. Cytoreductive surgery includes bilateral salpingo-oophorectomy, hysterectomy, peritoneal cytology, omentectomy, endometrial biopsy, peritoneal biopsies and the removal of any suspicious lesions [5, 6]. However, fertility-sparing surgery is appropriate for selected patients [7].

The main feature of AGCTs is their capacity to secrete hormones, with nearly all of them capable of synthesising oestradiol [8]. Exposure of the endometrium to high levels of oestrogen produced by
granulosa cells is responsible for the development of various types of endometrial pathology [9]. Endometrial hyperplasia and associated endometrial cancer have been reported in 10% to 50% of granulosa cell tumours [10, 11]. Generally, endometrial adenocarcinoma formed in the AGCTs is well differentiated, can be found at an early stage and has a good prognosis [12].

The primary aim of this study was to identify synchronised endometrial pathologies, particularly endometrial cancer, in AGCT patients who had undergone a hysterectomy. The secondary aim of the study was to define the factors related to synchronised endometrial cancer in AGCTs.

**Methods**

A total of 430 patients diagnosed with AGCTs from ten tertiary gynaecological oncology centres were retrospectively included in our study. The clinicopathologic data were obtained by extracting information from the patients' files and from the electronic database of ten hospitals. Eight patients were excluded from the study because they had previously undergone a hysterectomy. Forty-seven patients were excluded from the study because they wanted a fertility-sparing approach. Fifty-nine patients were excluded from the study because the endometrial pathology result was not reported. The study cohort was formed with the remaining 316 patients. The study was approved by the institutional review board of Ankara City Hospital (approval:27/04/2021-14). All patients signed an informed consent giving permission for the Ankara City Hospital to use their clinical data.

All surgeries were performed by gynaecologic oncologists. AGCT surgery consisted of bilateral salpingo-oophorectomy, hysterectomy, peritoneal cytology, omentectomy and the excision of any suspicious lesions. In the presence of suspicious lymph nodes, and with the approval of the senior surgeon, lymphadenectomy was added to the surgical procedure. Gynaecologic pathologists examined every specimen obtained from the surgical procedures. Endometrial hyperplasia was categorised as simple hyperplasia without atypia, complex hyperplasia without atypia, complex hyperplasia with atypia or endometrial intraepithelial neoplasia (EIN). The dimensions of the tumours were determined using ultrasonography prior to the surgical procedure and were assessed through ultrasound imaging, wherein the largest diameter was chosen as the representative size. The median tumour size value was used to define the relationship between tumour size and endometrial cancer. In addition, tumour size was stratified with values of 50 mm. The International Federation of Gynaecology and Obstetrics (FIGO) 2014 was used for staging [13].

Statistical analyses were performed using the Statistical Package for the Social Sciences (IBM SPSS Inc., Chicago, IL) version 20.0. The normality of continuous variable distributions was evaluated using the Kolmogorov–Smirnov test. Categorical variables were expressed as number and percentage and were analysed using Pearson's Chi-square (χ²) test or Fisher's exact test, as appropriate. The Mann–Whitney U test was used to analyse the difference between samples that were from non-normal distributions.

**Results**
A total of 316 patients with a mean age of 53.3 years (range, 26–82 years) were analysed. The mean preoperative CA-125 was 58.1 IU/ml (range, 1-756 IU/ml). The FIGO stages were distributed among the patients as follows: 267 (84.5%) patients had stage I; 18 patients (5.7%) had stage II; 18 patients (5.7%) had stage III; and one patient (0.3%) had stage IV. A stage was not identified in 12 (3.8%) patients. 177 (56%) of the 316 patients were experiencing menopause. Lymphadenectomy was performed in 239 (75.6%) patients. In the group of patients who underwent lymphadenectomy, lymph node metastasis was positive in nine (3.8%) patients. Omental metastasis was positive in 11 (3.5%) patients. Ascites was present in 57 (18%) patients, with a median ascites volume of 100 cc (range, 20–2000 cc) in these patients. The peritoneal cytology was positive in 22 (7%) patients. The demographic, surgical and pathological features are shown in detail in Table 1.

Synchronised endometrial pathology results were as follows: Endometritis in seven (2.2%) patients, endometrial polyp in 23 (7.3%) patients, atrophic endometrium in 28 (8.9%) patients, proliferative endometrium in 131 (41.5%) patients, secretory endometrium in 26 (8.2%) patients, simple hyperplasia without atypia in 59 (18.7%) patients, complex hyperplasia without atypia in nine (2.8%) patients, complex hyperplasia with atypia or EIN in 23 (7.3%) patients and endometrial cancer in 10 (3.2%) patients (Table 1).

The clinical features of the 10 patients with endometrial cancer are detailed in Table 2. All these patients had endometrioid endometrial cancer as their tumour type. The patients' FIGO grades were determined to be grade 1 in nine cases, while one case was classified as grade 2. There were two premenopausal patients and eight menopausal patients. The size of the ovarian tumour ranged from 50 to 350 millimetres. The depth of the myometrial invasion was less than half in six patients, and there was no invasion in two patients; it was greater than or equal to half in one patient, and there was no available data for one patient.

The factors related with endometrial cancer in the entire cohort are shown in Table 3. Age, menopausal status, tumour size, the FIGO stage, ascites and CA-125 level were not statistically significant factors to predict endometrial cancer. No statistically significant correlation was observed between endometrial pathology (complex hyperplasia with atypia or EIN/cancer) and advancing age. The risk of developing complex hyperplasia with atypia or EIN/cancer increased from 7.4% to 13.3% with older age (≤52 years vs. >52 years) (p=0.070).

Subgroup analysis was performed in menopausal patients (n:177). The mean age of this cohort was 59.8 years (range, 40–82 years), and the median tumour size was 75 mm (range, 3–900 mm). Endometrial cancer was detected in eight (4.5%) AGCT patients experiencing menopause. The factors related to endometrial cancer in menopausal patients are shown in Table 4. Endometrial cancer was detected in four (4.4%) patients with a median tumour size of ≤80 mm, and it was detected in four (5.8%) patients (p=0.699 with median tumour size >80 mm). Tumour size was ≤50 mm in two (3.7%) patients and >50 mm - ≤100 mm in two (4.2%) patients who had endometrial cancer. None of the AGCT patients with a tumour size >100 mm - ≤150 mm had endometrial cancer. In addition, four (12.1%) patients with a
tumour size >150 mm had endometrial cancer. For this reason, the cut-off value for the relationship between tumour size and endometrial cancer risk was evaluated as 150 mm. Therefore, in the tumour size ≤150 mm group four patients (3.2%) had endometrial cancer, and in the >150 mm group, four (12.1%) did (p=0.036). FIGO stage, ascites and CA 125 level were not statistically significant factors.

**Discussion**

Synchronised endometrial cancer is one of the most important characteristics of AGCT tumours. In our study, which included 316 AGCT patients, EIN or hyperplasia with complex atypia was detected in 7.7% of the patients, and endometrial cancer was detected in 3.2% of them. One patient had grade 2 endometrial cancer, while another had grade 1. Tumour size, age, menopausal status, stage and CA-125 level were not associated with endometrial cancer in the study cohort. However, tumour size predicted endometrial cancer in menopausal AGCT patients. Endometrial cancer risk increased from 3.2% to 12.1% in menopausal women whose tumours were >150 mm. The remarkable finding of the present study was that tumour size was statistically significant in relation to endometrial cancer in menopausal AGCT patients.

AGCTs are the most prevalent ovarian tumours that produce oestrogen. A broad spectrum of endometrial pathologies, including endometrial hyperplasia and carcinoma, has been attributed to persistent hypoestrogenism [12, 14, 15]. Several studies have examined concomitant endometrial abnormalities among AGCT patients; they found that the incidence of endometrial hyperplasia ranged from 21% to 60%, whereas the incidence of endometrial carcinoma ranged from 1.3% to 12.8% [11, 16]. In a study involving 150 patients, 29.2% had hyperplasia and 7.5% had endometrial carcinoma [17]. Another study involving 1031 patients found that 5.9% had concomitant endometrial cancer, 25.5% had hyperplasia and 8.3% had complex hyperplasia with atypia. [18]. An additional study with 68 patients found that 26.4% had endometrial pathology. For the endometrial pathology results, 14% of the patients had simple hyperplasia without atypia, 1.4% had simple hyperplasia with atypia, 2.9% had complex hyperplasia without atypia, 4.4% had complex hyperplasia with atypia and 2.9% had endometrial cancer [19]. In our study, the endometrial pathology results as follows: 18.7% of patients had simple hyperplasia without atypia, 2.8% had complex hyperplasia without atypia; 7.3% had complex hyperplasia with atypia or EIN and 3.2% had endometrioid cancer grade 1-2.

Age increases the risk of endometrial pathology in patients with AGCT. Ottolina et al. indicated that there was a statistically significant positive correlation between age >40 and the incidence of endometrial hyperplasia/cancer. Endometrial hyperplasia increased from 3.3% to 25.9% in patients over the age of 40 (p<0.001) [20]. Previous research suggests that the risk of developing endometrial pathologies before the age of 45 is relatively low, but this risk increases with older age [21, 22]. In our study, we were unable to determine the relationship between age and endometrial pathology (complex hyperplasia with atypia or EIN / cancer). The age range of patients diagnosed with endometrial cancer in our study was between 40 and 79 years old.
In previous research, the tumour size of AGCT varied from study to study. Ohel et al. analysed 172 cases of AGCT [23]. In approximately 54% of the cases, the tumour size ranged between 60 and 100 mm, while only 13.5% of cases had a tumour size greater than 150 mm. [23]. Another study of 118 AGCT patients found that the tumour size was 100–150 mm in 21.1% of patients and >150 mm in 27.1% of patients [11]. The correlation between the size of ovarian tumours and their oncological outcome was documented. Seagle et al. found that there was a positive correlation between tumour size and the risk of death among women diagnosed with stage I ovarian granulosa cell tumours. For every one centimetre increase in tumour size, there was a 4% (with a range of 2–6%) increase in the risk of death [24]. Thomakos et al. found that tumour size independently predicted recurrence-free survival. The study found that a one centimetre increase in tumour size was correlated with a 12% increase in risk [25]. In several studies, patients with a tumour size of 5 cm or less had a better progression-free survival rate and overall survival rate than tumours measuring more than 10 cm [9, 11, 14]. The correlation between the size of ovarian tumours and their oncological outcome was established, but this relationship was not distinctly established in the context of endometrial pathology. It is hypothesised that an increase in tumour size is positively correlated with an increase in oestrogen production from granulosa cells, potentially leading to the development of endometrial pathologies. Färkkilä et al. emphasised that AGCT cells were observed to not secrete soluble TRAIL (TNF-related apoptosis inducing ligand). Their study found that the levels of TRAIL protein were reduced in tumours that exceeded a diameter of 10 cm. There was a consistent negative correlation observed between the levels of circulating TRAIL and tumour size. A negative association exits between serum oestradiol levels and circulating TRAIL levels [26]. The findings indicate a positive correlation between tumour size and serum oestrogen levels. There is a lack of empirical evidence demonstrating a comparable correlation in a definitive manner. However, existing research has demonstrated a positive correlation between granulosa cell density and oestrogen production [27]. The transcription factor FOXL2 is essential for regulating follicular development and granulosa cell differentiation healthy ovaries [28, 29]. AGCT tumours exhibit a distinctive molecular characterisation due to the presence of a pathognomonic somatic missense point mutation 402C->G (C134W) in the transcription factor FOXL2. The presence of the FOXL2 402C->G mutation has been observed to result in the heightened proliferation and survival rates of granulosa cells, thereby facilitating hormonal alterations [30]. The mechanism by which the FOXL2 mutation causes tumour formation in AGCTs remains an active area of research. The current study established a correlation between tumour size and the risk of developing endometrial cancer in menopausal patients. The risk of concurrent endometrial cancer was 12.1% among patients whose ovarian tumour size was greater than 150 mm.

The retrospective study design is the most significant limitation of our study. The absence of a central pathologic examination is also a significant limitation. However, the large sample size is a significant strength of our study, as is the evaluation of the hysterectomy specimen. Therefore, to our knowledge, this is the first study to describe the factors associated with endometrial cancer detected in AGCTs.

**Conclusion**
In conclusion, it is imperative to conduct a comprehensive assessment for endometrial cancer in individuals with AGCT due to heightened oestrogenic activity. In addition, our current investigation ascertained that 7.3% of the patient cohort exhibited complex hyperplasia with atypia or endometrial intraepithelial neoplasia (EIN), while 3.1% of patients were diagnosed with endometrial carcinoma. The findings of the study indicate that there is a notable increase in the probability of synchronised endometrial cancer, rising from 3.2% to 12%, among menopausal patients when the tumour size exceeds 150 mm. However, further studies with larger sample sizes are needed to draw a more precise conclusion.

Declarations

Author Contributions

The author's contributions to the manuscript are listed below. All authors in the article met ICMJE requirements for authorship.

Abdurrahman Alp Tokalioglu: Manuscript writing, Drafting the work, Analysis of data

Okan Oktar: Interpretation of data for the work

Mustafa Sahin: Interpretation of data for the work

Cagatayhan Ozturk: Interpretation of data for the work

Ozgur Erdogan: Interpretation of data for the work

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Tolga Tasci: Analysis of data, Design of the work
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Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request. The institutional patient’s permit document does not include sharing the data without reasonable conditions.
Conflicts of Interest

We know of no conflicts of interest associated with this publication, and there has been no significant financial support for this work that could have influenced its outcome. As Corresponding Author, I confirm that the manuscript has been read and approved for submission by all the named authors.

Funding

None.

References


