ORIGINAL ARTICLE
KLİNİK ARAŞTIRMA

Rare ovarian granulosa tumors: A retrospective analysis

Nadir over granüloza tümörleri: Retrospektif bir analiz

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SUMMARY

Aim: Granulosa cell tumors (GCTs) of the ovary, representing 5-8% of all ovarian cancers, are a rare subtype of sex cord-stromal tumors. These tumors are generally low-grade malignancies with a favorable prognosis. However, clinical presentation and outcomes can vary widely among patients. This study analyzes the clinical and pathological characteristics of GCTs in 17 patients diagnosed within a cohort of 596 individuals evaluated at our institution.

Material and Methods: We retrospectively reviewed clinical data from 596 patients treated between January 2017 and February 2023. Seventeen patients diagnosed with ovarian granulosa cell tumors were selected for detailed analysis. Data included age, menopausal status, symptoms, radiological findings, serum CA-125 levels, FIGO stage, surgical interventions, adjuvant therapies, and follow-up outcomes.

Results: The patients' ages ranged from 39 to 64 years (median 47, mean 50.41), with 52.9% premenopausal. Common symptoms were abdominal mass (82.4%), dysmenorrhea (29.4%), abdominal pain (17.6%), and cervical lymphadenopathy (70.6%). Radiological imaging showed cystic masses in 41.17% and mixed cystic-solid components in 17.64% of cases. Tumor sizes averaged 7 cm (range 2-20 cm). Elevated CA-125 was observed in 47.1%. No recurrences or metastases were detected during follow-up.

Conclusion: GCTs of the ovary generally have a favorable prognosis with low recurrence rates. This study highlights the importance of a multidisciplinary approach and individualized surgical intervention. Further research is necessary to enhance understanding and management of these tumors.

Keywords: Chemotherapy, ovarian granulosa cell tumour, ovarian tumors, prognostic factors

ÖZET

Amaç: Overin granüloza hücreli tümörleri (GHT'ler), tüm over kanserlerinin %5-8'ini oluşturan nadir bir seks kord-stromal tümör alt tipidir. Bu tümörler genellikle düşük dereceli maligniteler olup, iyi bir prognoz ile ilişkilidir. Ancak, klinik prezentasyon ve sonuçlar hastalar arasında geniş bir yelpazede değişkenlik gösterebilmektedir. Bu çalışma, kurumumuzda değerlendirilen 596 bireyden teşhis edilen 17 hastada GHT'lerin klinik ve patolojik özelliklerini analiz etmeyi amaçlamaktadır.

Materyal ve Metodlar: Ocak 2017 ile Şubat 2023 tarihleri arasında tedavi edilen 596 hastanın klinik verileri retrospektif olarak incelendi. Over granüloza hücreli tümörü teşhisi konulan 17 hasta ayrıntılı analiz için seçildi. Veriler yaş, menopoz durumu, semptomlar, radyolojik bulgular, serum CA-125 seviyeleri, FIGO evresi, cerrahi müdahaleler, adjuvan tedaviler ve takip sonuçlarını içermektedir.

Bulgular: Hastaların yaşları 39 ile 64 arasında değişmekte olup, ortanca yaş 47, ortalama yaş ise 50,41 idi ve hastaların %52,9'u premenopozal idi. Yaygın semptomlar abdominal kitle (%82,4), dismenore (%29,4), abdominal ağrı (%17,6) ve servikal lenfadenopati (%70,6) idi. Radyolojik görüntüleme, hastaların %41,17'sinde kistik kitleler ve %17,64'ünde karışık kistik-solid komponentler gösterdi. Tümör boyutları ortalama 7 cm olup (2-20 cm arası), hastaların %47,1'inde yüksek CA-125 seviyeleri gözlendi. Takip süresince nüks veya metastaz tespit edilmedi.

Sonuç: Over granüloza hücreli tümörleri genel olarak düşük nüks oranları ile iyi bir prognoza sahiptir. Bu çalışma, multidisipliner yaklaşımın ve bireyselleştirilmiş cerrahi müdahalenin önemini vurgulamaktadır. Bu tümörlerin yönetimi ve anlaşılmasını iyileştirmek için daha fazla araştırmaya ihtiyaç vardır.

Anahtar kelimeler: Kemoterapi, over granüloza hücreli tümörü, over tümörleri, prognostik faktörler

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INTRODUCTION

Ovarian cancer, a predominant cause of mortality from gynecological malignancies worldwide, exhibits a variety of subtypes, each distinguished by unique cellular origins and pathological features. Among these, Granulosa cell tumors (GCTs) are particularly notable for their rarity and distinctive origin. Accounting for approximately 5-8% of all ovarian cancers, GCTs fall under the category of sex cord-stromal tumors. Unlike the commonly encountered ovarian epithelial tumors that originate from the epithelial cells on the ovarian surface, GCTs develop from sex cord-stromal tissue, which is crucial for hormone production and structural support of the ovaries. This origin lends GCTs distinct clinical behaviors and generally more favorable prognostic outcomes, often manifesting as low-grade malignancies.

Ovarian GCTs are characterized by a prolonged natural history and a propensity to recur years after initial treatment. They frequently present with symptoms induced by estradiol secretion, such as vaginal bleeding or, in younger patients, precocious puberty. In some cases, tumor rupture may lead to abdominal pain and hemoperitoneum. Typically, a pelvic mass is identified during physical examination, which is further investigated using imaging techniques to confirm the diagnosis. Surgical intervention is pivotal in the initial management of GCTs, serving dual purposes: providing a definitive histological diagnosis and allowing for appropriate cancer staging and debulking. This surgical approach not only facilitates the removal of tumor mass but also critically impacts the long-term management strategy, aiming to minimize the likelihood of recurrence and optimize patient outcomes (1-3).

Ovarian cancer remains a significant challenge in gynecological oncology, with various subtypes that present distinct pathological and clinical profiles. Among these, GCTs of the ovary are particularly noteworthy due to their unique characteristics and long natural history. Historical context is crucial in understanding these tumors: GCTs of the ovary were first described by Rokitansky in 1855, marking the initial recognition of this rare and distinct subtype of ovarian tumors. GCTs are extremely uncommon, constituting a minority of ovarian tumors, and are often described in terms of their indolent progression and potential for late recurrence (4).

Historical data, notably from a seminal study conducted by Fox, H, Agrawal, K, & Langley, FA. in 1975 (5), has been pivotal in shaping our understanding of GCTs. Their research, which analyzed 92 cases of ovarian GCTs, highlighted several key prognostic factors that influence outcomes in patients. They found that factors such as age over 40 at diagnosis, presentation with abdominal symptoms, presence of a palpable mass, large solid tumors, bilateral tumors, extraovarian spread, and numerous mitotic figures are indicative of a poorer prognosis. These findings underscore the malignant potential of GCTs and suggest that even tumors that appear to be low-grade can have significant long-term implications for patient survival. Their study also demonstrated the importance of considering all GCTs as potentially malignant due to their ability to cause death related to the tumor within 20 years in approximately half of the cases if left untreated. This underscores the necessity for vigilant long-term follow-up and management strategies tailored to mitigate these risks. The insights from Fox et al. (5) have provided a foundation for subsequent research and are crucial for informing current clinical practices, which emphasize early detection and comprehensive management to improve outcomes for patients diagnosed with this rare but significant subtype of ovarian cancer (5).

GCTs are often hormone-producing, which contributes to their early presentation and detection compared to other epithelial ovarian cancers, usually diagnosed at an advanced stage. The juvenile form of GCT may present in young girls, allowing for conservative management options such as unilateral salpingo-oophorectomy, given that 95% of these tumors are unilateral. Surgical resection remains the treatment of choice, with the extent of initial staging laparotomy being a key determinant in assessing the risk of recurrence. Prognostically, factors such as advanced stage, tumor size greater than 5 cm, high mitotic index (greater than 10 per high power field), nuclear atypia, and the absence of Call-Exner bodies are associated with poorer outcomes. These tumors are also characterized by their potential for late recurrences, necessitating prolonged follow-up. Tumor markers such as inhibin and estradiol are valuable during follow-up for detecting recurrences. While chemotherapy, radiotherapy, and hormone replacement therapy play limited roles in initial treatment, they may be considered in cases of recurrence. With optimal management, patients with GCTs can achieve better survival rates compared to those with other forms of ovarian malignancies (6,7).

Studying GCTs is imperative due to their distinct clinical and pathological features, which significantly impact management strategies and patient outcomes. Despite their relatively benign course, the presentation, response to treatments, and long-term outcomes of GCTs can vary widely, presenting challenges in clinical management and prognosis. The rarity of these tumors contributes to a limited understanding within the medical community, often leading to generalized treatment approaches that may not be optimal for all patients. Therefore, a deeper exploration into the nuances of GCTs is crucial for developing tailored therapeutic strategies that address their unique aspects effectively.

MATERIAL AND METHODS

This retrospective study was conducted at the Istanbul Training and Research Hospital, a tertiary care center with a comprehensive cancer treatment facility. The study encompasses a period from January 2017 to February 2023, during which patient data were collected and analyzed to assess the clinical and pathological characteristics of ovarian granulosa cell tumors.

Patients included in this study were specifically those diagnosed with ovarian granulosa cell tumors, as confirmed by histopathological analysis during the study period. The selection process involved reviewing the hospital's cancer registry and patient medical records to identify cases that met the diagnostic criteria for GCTs. From a broader cohort of 596 patients evaluated for various conditions, 17 were identified and confirmed to have ovarian granulosa cell tumors based on these criteria.

Comprehensive data extraction was performed from electronic medical records. The collected data included age at diagnosis, menopausal status, initial symptoms, and detailed information on radiological and surgical findings. Additionally, serum CA-125 levels at presentation, FIGO stage at diagnosis, type of surgical intervention, and the administration of any adjuvant therapy (chemotherapy or radiation) were meticulously recorded. Follow-up data, capturing recurrence rates and long-term complications, were also included.

Data were analyzed using descriptive and inferential statistics to explore associations between clinical variables and patient outcomes. Kaplan-Meier survival analysis was conducted to estimate the prognosis, and Cox regression models were employed to identify predictors of survival and recurrence. All statistical analyses were performed using SPSS software (version 26.0, IBM Corp.).

In cases where data were missing or incomplete, multiple imputation techniques were applied to estimate missing values, ensuring the robustness of the statistical analysis and minimizing bias. The proportion of missing data and the impact of imputation on the study results were assessed and reported.

The study protocol was reviewed and approved by the Ethics Committee of Istanbul Training and Research Hospital. The study was conducted in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments.

All patient data were anonymized and de-identified prior to analysis to protect confidentiality. Access to the data was restricted to the research team, and all electronic data were secured with password-protected access to ensure that patient information was safeguarded throughout the study.

RESULTS

The research encompassed a cohort of seventeen individuals who had been clinically diagnosed with ovarian granulosa cell tumors. These participants presented a diverse age range spanning from 39 to 64 years (Figure 1). Statistical analysis of the age distribution revealed that the median age at which the diagnosis was confirmed stood at 47 years. Additionally, the calculated mean age of the study participants was approximately 50.41 years. This age-related data is crucial as it provides insights into the typical age window during which these tumors are most likely to be diagnosed, suggesting a potentially heightened risk in the perimenopausal and early postmenopausal phases of a woman's life. Such information is essential for developing age-specific screening strategies and improving the understanding of the epidemiology of ovarian granulosa cell tumors.

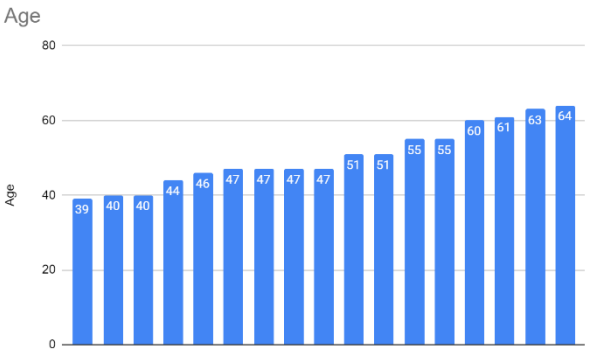

Figure 1. Age Distrubition

According to the extensive retrospective study conducted at Istanbul Training and Research Hospital, which reviewed clinical data from 596 patients between January 2017 and February 2023, it was determined that 52.9% of the patients were premenopausal at the time of their diagnosis with ovarian granulosa cell tumors. Furthermore, 35.3% of these patients were classified as postmenopausal, based on the data extracted from a subset of 17 specifically diagnosed cases (Figure 2). In the same study, 29.4% of the patients reported experiencing dysmenorrhea, and 17.6% presented with abdominal pain. This detailed data collection included age at diagnosis, menopausal status, initial symptoms, radiological findings, serum CA-125 levels, and FIGO staging at the time of diagnosis. Additionally, the types of surgical interventions performed—ranging from unilateral salpingo-oophorectomy to more extensive procedures such as total abdominal hysterectomy and bilateral salpingo-oophorectomy—were thoroughly documented. The study also noted any adjuvant therapies employed, such as chemotherapy or radiation, and systematically collected follow-up data to monitor outcomes including recurrence rates and long-term complications. This comprehensive analysis aids in understanding the demographic and clinical

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characteristics of patients affected by this specific type of ovarian tumor.

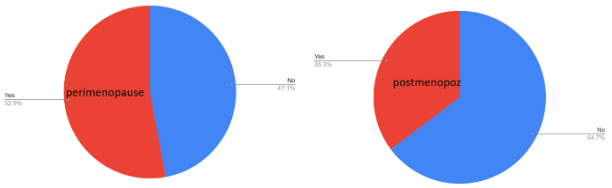

Figure 2. Perimenopause and Postmenopoz Status

Within the scope of the study, it was observed that 52.9% of the patients exhibited normal tumor marker values at the time of diagnosis. Conversely, 47.1% of the patients demonstrated elevated levels of the serum tumor marker CA-125, indicative of potential malignant activity. These findings underscore the variability in tumor marker expressions among patients diagnosed with ovarian granulosa cell tumors and highlight the importance of CA-125 as a diagnostic tool in assessing the presence and extent of the disease (Figure 3).

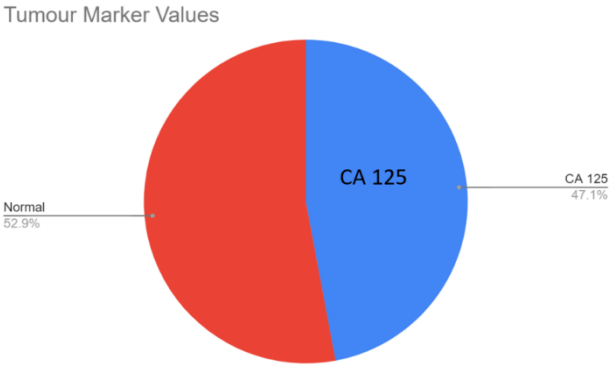

Figure 3. Tumour Marker Values

In the referenced study, 17.6% of the patients were found to have an abdominal mass, while a significant 70.6% exhibited cervical lymphadenopathy (LAP) at the time of diagnosis. These statistics highlight the prevalence of physical manifestations associated with the condition being investigated (Figure 4).

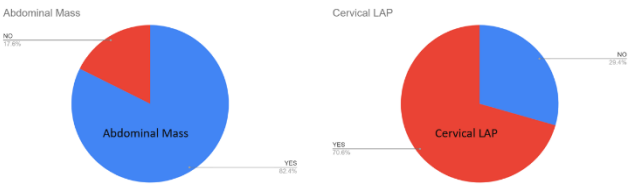

Figure 4. Abdominal Mass and Cervical LAP Status

In the detailed analysis of the study, cystic masses were identified in 41.17% of the patients, indicating a common presentation of the condition within the cohort.

Additionally, mixed cystic-solid components were observed in 17.64% of the patients, showcasing the diversity in tumor characteristics. The average tumor size noted across the cohort was 7 cm, with a range spanning from 2 cm to 20 cm, highlighting the variability in the size of the tumors at the time of diagnosis. To further illustrate these findings, two photographs depicting examples of the tumors identified have been included in this article, providing visual evidence of the diverse manifestations observed in this study (Figure 5-6).

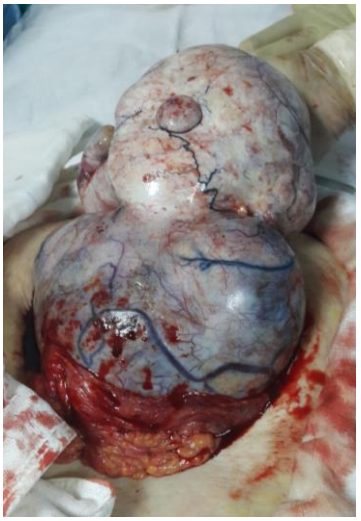

Figure 5. Illustrative Examples of Ovarian Granulosa Cell Tumors

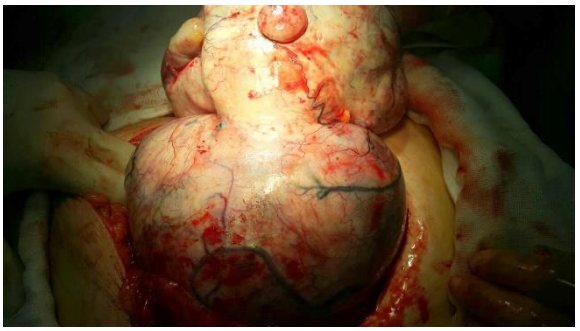

Figure 6. Illustrative Examples of Ovarian Granulosa Cell Tumors

DISCUSSION

The comparison between our study and the study conducted by Dridi et al. (8) provides an intriguing insight into the presentation and characteristics of adult granulosa cell tumors (AGCT) across different patient populations. Our study included patients ranging in age from 39 to 64 years, with a median age of 47 and a mean age of 50.41, indicating a somewhat younger demographic compared to Dridi et al., where the mean age was 53 years with a range of 35 to 73 years. About 52.9% of our patients were premenopausal at diagnosis, highlighting a younger onset of disease compared to Dridi et al.'s cohort, which included a higher likelihood of postmenopausal symptoms, as

indicated by the 32% incidence of postmenopausal bleeding. Abdominal masses were prominent in both studies, observed in 82.4% of our patients and 61% in Dridi et al.'s study. The presence of abdominal pain and other symptoms such as cervical lymphadenopathy (70.6% in our study) underscores the aggressive nature of some tumors or more advanced disease at presentation in our cohort. Dridi et al. did not report on cervical lymphadenopathy, which could suggest different diagnostic or reporting practices.

Radiological findings in our study indicated that 41.17% of patients had cystic masses and 17.64% had mixed cystic-solid components, whereas Dridi et al. reported a higher prevalence of cystic unilateral masses (80%). The size of the tumors also varied significantly, with our average tumor size being smaller at 7 cm (ranging from 2 to 20 cm) compared to Dridi et al.'s median size of 20 cm (ranging from 4 to 33 cm). This difference might reflect varying stages of disease progression or differences in the timing of diagnosis. Elevated levels of the serum tumor marker CA-125 were observed in 47.1% of our patients, closely aligning with the 42% reported by Dridi et al. This similarity indicates the consistent role of CA-125 as a marker for disease in AGCT, despite differences in other tumor characteristics and demographics (8).

Our study did not note any instances of recurrence or metastasis during the follow-up period, suggesting either a less aggressive form of the disease or effective management strategies. In contrast, the absence of similar long-term outcome data from Dridi et al. makes it difficult to compare the effectiveness of treatments or disease progression comprehensively.

When comparing our study with the research conducted by Seagle et al. (9), several points of alignment can be observed, specifically regarding the clinical presentation and diagnostic findings of ovarian granulosa cell tumors. Our patients ranged in age from 39 to 64 years with a median age of 47 and a mean age of 50.41, which is somewhat younger compared to the median age of 53 years reported by Seagle et al. This discrepancy might reflect different population demographics or potentially earlier diagnosis in our cohort. In our study, the average tumor size was 7 cm, ranging from 2 to 20 cm, which is smaller compared to the median tumor size of 9.0 cm reported by Seagle et al. The range in both studies, however, indicates a variability in tumor size at diagnosis, which could be influenced by the timing of diagnosis or the aggressiveness of the tumor subtype.

When comparing the findings from our study with the clinical data reported from the National Institute of Oncology in Rabat, Morocco, we can observe some similarities and distinctions regarding patient demographics, clinical presentations, and tumor characteristics (10). Our study had a median age of 47 years with a range from 39 to 64 years, indicating a younger patient demographic compared to the median age of 53 years reported in Sekkate et al. (10) study. This difference may suggest variations in the age of onset or diagnosis across different populations.The most common presenting symptoms in our cohort included abdominal mass (82.4%), dysmenorrhea (29.4%), abdominal pain (17.6%), and cervical lymphadenopathy (70.6%). In contrast, the Rabat study highlighted abdominal pain and vaginal bleeding as the most prevalent symptoms. This suggests differences in the clinical manifestations of granulosa cell tumors, which could be influenced by tumor location, size, or progression at the time of diagnosis. Our average tumor size was notably smaller, at 7 cm (ranging from 2 to 20 cm), compared to the mean tumor size of 14 cm in the Rabat study. The larger tumor sizes reported in Rabat could reflect later stages of detection or possibly different growth patterns of the tumors in their patient population.

The study by Khosla et al. (11) presents data on ovarian granulosa cell tumors that complement our findings, enhancing our understanding of the disease. They reported a median age of 50 years, ranging from 17 to 71 years, which is similar to our reported median age of 47 years and range of 39 to 64 years. This similarity in age distribution underscores the common age group affected by this disease. Both studies indicate a predominance of middle-aged women, although Khosla et al.'s broader age range suggests a wider variability in the age at diagnosis. In terms of symptoms, while our study found that the most common presentations included abdominal mass (82.4%), dysmenorrhea (29.4%), abdominal pain (17.6%), and cervical lymphadenopathy (70.6%), Khosla et al. identified abdominal pain as the most prevalent symptom. This difference could be due to variations in tumor location, size, or the criteria used for symptom recording. The survival data from Khosla et al. are particularly notable. They reported estimated 5 and 10-year overall survival rates of 84.6% and 72.5%, respectively. Our study did not specify survival rates, but no instances of recurrence or metastasis were observed during the follow-up period, which could suggest favorable survival outcomes, potentially aligning with the high survival rates reported by Khosla et al.

LIMITATIONS

This study, while providing valuable insights into the clinical and pathological features of ovarian granulosa cell tumors, has several limitations that must be considered when interpreting the findings. One significant limitation is the small sample size of only 17 patients diagnosed with GCTs out of a larger cohort of 596 patients reviewed for various conditions. Although this number may seem small, it is important to acknowledge that GCTs are a very rare form of ovarian cancer. Consequently, a sample size of 17 patients is substantial and meaningful within this context,

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as it provides a rare opportunity to study this specific tumor type in greater detail than typically possible. However, the limited number of GCT cases may not fully represent the broader population of patients with this type of tumor, potentially affecting the generalizability of the study results. Despite the small sample size, the study provides critical preliminary data that can inform future prospective studies and clinical trials. The rarity of GCTs emphasizes the importance of such focused studies, even with smaller cohorts, as they contribute significantly to the limited pool of research available on this tumor type. By highlighting the need for more comprehensive research with larger, more diverse populations, this study contributes to the foundational knowledge necessary for advancing the understanding and management of ovarian granulosa cell tumors.

CONCLUSION

The extensive retrospective analysis of ovarian GCTs presented in this study highlights several critical aspects of this rare subtype of ovarian cancer, emphasizing its distinctive clinical presentation, treatment response, and favorable prognostic outcomes. GCTs, while constituting a minor fraction of ovarian cancers, exhibit unique characteristics that necessitate specialized attention and management strategies, which were meticulously examined in our cohort of 17 patients within a larger dataset of 596 individuals assessed at Istanbul Training and Research Hospital.

Our findings underline that the median age of diagnosis stands at 47 years, with a notable predominance of premenopausal status at diagnosis (52.9%). The clinical manifestations, including a high prevalence of abdominal masses and significant instances of dysmenorrhea and abdominal pain, align with the hormonally active nature of these tumors. The variability in presentation, such as the presence of cervical lymphadenopathy in a substantial portion of patients (70.6%), calls for a nuanced understanding of the disease's pathology. Radiological assessments revealed a mix of cystic and solid tumor components, confirming the heterogeneous nature of GCTs. Notably, no instances of recurrence or metastasis were observed, which may reflect the typically indolent nature of GCTs but also underscores the efficacy of the surgical and adjuvant treatments employed. Our surgical approach, ranging from conservative surgeries to more radical interventions like total abdominal hysterectomy, was guided by the tumor characteristics and patient factors, emphasizing the importance of individualized treatment plans. The non-recurrence observed echoes the potential for successful long-term outcomes with appropriate management.

Comparisons with other studies such as those by Dridi et al. (8), Seagle et al. (9), and Sekkate et al (10), alongside the study by Khosla et al (11), provide broader validation of our findings and highlight the global variability in GCT presentation and outcomes. These comparisons also stress the importance of early detection and tailored surgical management in improving prognosis and reducing the likelihood of late recurrences, which are characteristic of this tumor type.

This study significantly contributes to the ongoing discourse in gynecologic oncology by providing a deeper insight into the demographic and clinical dynamics of ovarian granulosa cell tumors. Our findings advocate for a multidisciplinary approach in the treatment of GCTs, incorporating patient-specific factors into decision-making to optimize outcomes. The favorable prognosis observed in our cohort, coupled with the low risk of recurrence, reaffirms the potential for positive outcomes with meticulous clinical and surgical management.

Future research should focus on longitudinal studies to further understand the long-term survival and quality of life of patients with GCTs, as well as exploring genetic and molecular aspects of the tumor to develop targeted therapies. Continued investigation into the unique pathological features of GCTs will enhance our ability to manage this rare but significant subtype of ovarian cancer effectively, aiming to maintain high survival rates and minimize adverse effects associated with treatment.

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