Journal of Ovarian Research

RESEARCH

Open Access

Is it time to abandon staging surgery and prolonged follow-up in patients with primary adult-type granulosa cell tumor?

Geertruid J. Brink[1*], Jolijn W. Groeneweg[1], Ariane A. Sickinghe[1], Hans W. Nijman[2], Luc R.C.W. van Lonkhuijzen[3], Christianne A. R. Lok[4], Jurgen M. J. Piek[5], Eva Maria Roes[6], Cornelis D. de Kroon[7], Ward Hofhuis[8], Geertruida N. Jonges[9], Eelke H. Gort[10], Petronella O. Witteveen[10] and Ronald P. Zweemer[1]

Abstract

Background As current literature does not provide sufficient data to support clear guidelines in patients with a rare adult-type granulosa cell tumor, we aim to investigate: (1) whether additional staging surgery following primary surgical treatment is necessary; (2) how long standard follow-up should be and (3) risk factors for disease recurrence.

Methods A national multicenter prospective study was initiated in April 2018. Patients with suspected or confirmed adult-type granulosa cell tumor were eligible. Data on staging, follow-up and risk factors were both retrospectively and prospectively collected from medical records, and patients were followed until April 2024 or until death. Descriptive statistical analysis and survival analysis were performed using Cox regression methods and Kaplan-Meier analyses.

Results In total, 208 patients with histopathologically confirmed adult-type granulosa cell tumor were included, with a median follow-up of 5.5 years (IQR: 2.2–12.3 years). Vaginal bleeding and abdominal pain were the most common symptoms at diagnosis. Median time until first recurrence was 4.2 years (range 2 months– 32 years). Additional staging surgery did not reduce the risk of recurrence. During follow-up, most patients had no symptoms at the time of detection of recurrence. No difference in overall survival was found between patients who were diagnosed with a recurrence during follow-up, and those who were no longer in follow-up and presented with symptoms.

Conclusions Staging surgery does not improve recurrence free survival in patients with adult-type granulosa cell tumor. Our results suggest that adult-type granulosa cell tumor patients can be discharged from follow-up of adult-type granulosa cell tumor after five years.

Keywords Granulosa cell tumor, Ovarian cancer, Rare disease, Follow-up, Staging surgery

*Correspondence:
Geertruid J. Brink
g.j.brink-7@umcutrecht.nl

Full list of author information is available at the end of the article

Background

A 52-year-old female presents to your clinic with postmenopausal bleeding [1]. On ultrasound, you see slightly thickened endometrium and a four centimeter adnexal mass, mostly cystic. You take a pipelle endometrial biopsy and microscopy shows no signs of hyperplasia, atypia, or malignancy. You decide to follow-up on the adnexal mass. Six months later, there is no postmenopausal bleeding anymore, but the adnexal mass is increased by half a centimeter. With the patient, you decide to remove the adnexal mass and a bilateral salpingo-oophorectomy is performed. To your surprise, the pathology report reveals an adult-type granulosa cell tumor with a ruptured capsule. Should you perform an additional staging surgery? Should you treat the patient adjuvantly? What is your follow-up plan, and what are the chances of recurrence?

Adult-type granulosa cell tumor (aGCT) is a rare ovarian cancer, with an estimated global incidence rate of 2.6/100.000 women per year [2, 3]. Primary treatment consists of surgery, often combined with peritoneal staging including a hysterectomy, bilateral adnexectomy, omentectomy, peritoneal biopsies and abdominal fluid collection [4]. Current guidelines are inconclusive about peritoneal staging in aGCT patients [5–8]. One-third of patients develops a recurrence (range 11–35%), which can occur as late as 15 years after initial presentation [1, 2, 6, 9–14]. FIGO stage, tumor size, tumor rupture and mitotic index are known risk factors for recurrence [2]. Recently, Plett, Ricciardi [13] showed that FIGO stage is the most important prognostic factor. Previously, Bryk, Färkkilä [9] found that other known prognostic factors, such as infertility, older age, or tumor size did not affect survival rates. Cytoreductive surgery is considered the best choice for treatment of recurrence [4]. After multiple surgeries, or in case of an inoperable recurrence, systemic therapy may be the only remaining option, although there is no consensus on the preferred treatment regimen [15].

With this study, our aim is to provide guidance on: (1) whether additional staging surgery is necessary; (2) how long you should follow-up with a patient and (3) which risk factors your patient may have.

Methods

The study was conducted and approved by the Medical Ethics Committee of the University Medical Centre Utrecht (UMCU METC 17–868) and by the institutional review boards of all participating centers. From April 2018 to April 2024, patients were enrolled and all patients provided written informed consent.

A collaborative network was established in the Netherlands, in which each aGCT case was discussed with experts from one of the regional cancer centers. This approach ensured that the majority of patients were referred for inclusion in one of the participating centers. Since all patients were discussed within a regional cancer center, pathology slides were requested and subsequently re-evaluated by an academic pathologist. Consequently, we decided against conducting a central pathology review for this study.

Data collection

Data were retrieved from medical records from the participating centers. Data on primary diagnosis and treatment for patients that were entered at the time of recurrent disease, were retrospectively collected. Data were entered in an electronic database (Castor EDC) by two trained researchers (AS and GB) [16]. During the study, source data verification and monitoring occurred regularly [17]. If the medical records were incomplete, records were requested from referring gynecologists and hospitals. Data processing was performed using a coded set, with the participant code available only to study group members and research nurses at participating hospitals. Patients were followed until April 2024 or until death.

Outcomes

The following patient characteristics were collected at inclusion: age, BMI, history of infertility, history of cancer, history of abdominal surgery or gynecological surgery. The following characteristics were collected for primary diagnosis and possible recurrences: age at diagnosis, menopausal status at diagnosis, complaints at diagnosis, FIGO stage at diagnosis, type of imaging, location of tumor on imaging, type of treatment(s), tumor capsule status, concurrent endometrial cancer, tumor marker results and immunohistochemistry results. Tumor capsule status and immunohistochemistry results were retrieved from surgery reports and/or pathology reports. If FIGO stage was not reported, it was determined by researchers based on clinical data [4]. If more than one of the essential variables were missing, patients were excluded from analysis. Essential variables were defined as symptoms at diagnosis, year of diagnosis or recurrences, treatment types, follow-up time and disease status.

New recurrence was defined as signs of disease on imaging after surgery was described as no macroscopic residual disease or after systemic therapy if there was no sign of disease on imaging at the end of treatment. Recurrence free survival (RFS) was defined as the time between date of last treatment to date of first sign of recurrence on imaging. If no imaging was performed, the date of the surgery for the recurrence was used. Overall survival (OS) was defined as the time from diagnosis until death. Disease status was defined as no evidence of disease

(NED), alive with disease (AWD), dead of disease (DOD) or dead of other cause (DOC).

Statistical analysis

Statistical analyses were performed using SPSS Statistics for Windows, Version 29.0.1 (IBM Corp., Armonk, NY, USA). Continuous variables are presented as median with their range and categorical variables as number and percentage of the total. To estimate OS and RFS, Kaplan-Meier methods were used, and for comparison the log-rank test was used. To compare medians the Kruskal-Wallis test was used, with Dunn's multiple comparisons test. Univariate and multivariate Cox regression analyses on RFS and OS were conducted. Concurrent endometrial hyperplasia or endometrial cancer was not included as variable in the analysis due to many missing data. For the multivariate Cox regression analysis, variables that had a *p*-value lower than 0.200 in univariate analysis were taken into the model. A *p*-value below 0.05 was considered significant. Data visualization was performed using GraphPad Prism version 10.0.2 for Windows [18].

Table 1 Primary diagnosis

Characteristics (*n* = 208)	*n* (%) median (IQR)
Age at diagnosis in years	53 (43–64)
BMI at inclusion in kg/m^2 (*n* = 192)	26.0 (22.8–30.1)
Personal history of infertility (*n* = 195)	10 (4.8)
Other primary cancer (*n* = 206)	33 (15.9)
Menopausal status at diagnosis	
Premenopausal	78 (37.5)
Perimenopausal	25 (12.0)
Postmenopausal	103 (49.5)
Unknown	2 (1.0)
Symptoms at diagnosis	
Vaginal bleeding	61 (29.3)
Abdominal pain	35 (16.8)
Vaginal bleeding and abdominal pain	19 (9.1)
Gastrointestinal complaints	7 (3.4)
Acute abdomen	26 (12.5)
No symptoms	6 (2.9)
Other	28 (13.5)
Unknown	26 (12.5)
Assessment of mass	
Preoperatively suspected aGCT	58 (27.9)
Postoperatively diagnosed aGCT	136 (65.4)
Unknown	14 (6.7)
Surgery type	
Laparoscopy	81 (38.9)
Laparotomy	122 (58.7)
Unknown	5 (2.4)
Initial treatment	
Cystectomy unilateral	11 (5.3)
Ovariectomy unilateral	7 (3.4)
Adnexectomy unilateral	64 (30.8)
BSO	31 (14.9)
BSO + hysterectomy	51 (24.5)
Complete peritoneal staging	26 (12.5)
Other	18 (8.7)
Secondary surgery	
Complete staging surgery	20 (9.6)
Incomplete staging surgery	12 (5.8)
No secondary surgery	176 (84.6)
Adjuvant systemic treatment	10 (4.8)
Tumor size (median 10.0 cm)	
< 10 cm	91 (43.8)
> 10 cm	87 (41.8)
Unknown	30 (14.4)

Results

After exclusion of five patients due to missing data of more than one essential variable, 208 patients with histopathologically confirmed aGCT were included. During the inclusion period, 116 patients were included at primary diagnosis (55.8%) and 92 patients were included during follow-up or when they had a recurrence (44.2%). Importantly, for all 92 patients included during follow-up or recurrence, complete and essential data from their primary diagnosis were available. This ensured that both groups could be analyzed as a single cohort without compromising data integrity.

All patients were initially treated with surgery, mostly with laparotomy (58.7%). Thirty-two patients (15.4%) had a second surgical procedure, of whom 20 underwent peritoneal staging. At the time of initial surgery, tumor capsule remained intact in 104 patients (50%) while in 89 patients (42.8%) tumor capsule ruptured (both spontaneous and surgical), and in 15 patients (7.2%) capsule status was not stated. All details of primary diagnosis and its treatment are summarized in Table 1.

Forty-six patients (22.1%) underwent surgical staging, and of the 162 patients for whom surgical staging was not performed or not retrievable, the FIGO stage was deducted from available clinical, radiological and pathological data. An overview of the FIGO stages per patient subgroup are shown in Table S1.

Tumor size was larger than ten centimeter in 87 patients (41.8%). Concurrent endometrial hyperplasia or cancer was found in 17 patients (8.1%), other details of the histopathological examination are summarized in Table S2.

Median time until the first recurrence was 4.2 years (IQR: 2.5–7.1 years, range: 2 months– 32 years). After the first recurrence, a trend of an increasingly shorter RFS was seen, as shown in Fig. 1. The time interval between detection of recurrence on imaging and surgery for a recurrence increasingly prolonged with each consecutive recurrence (data not shown). In Figure S1 the

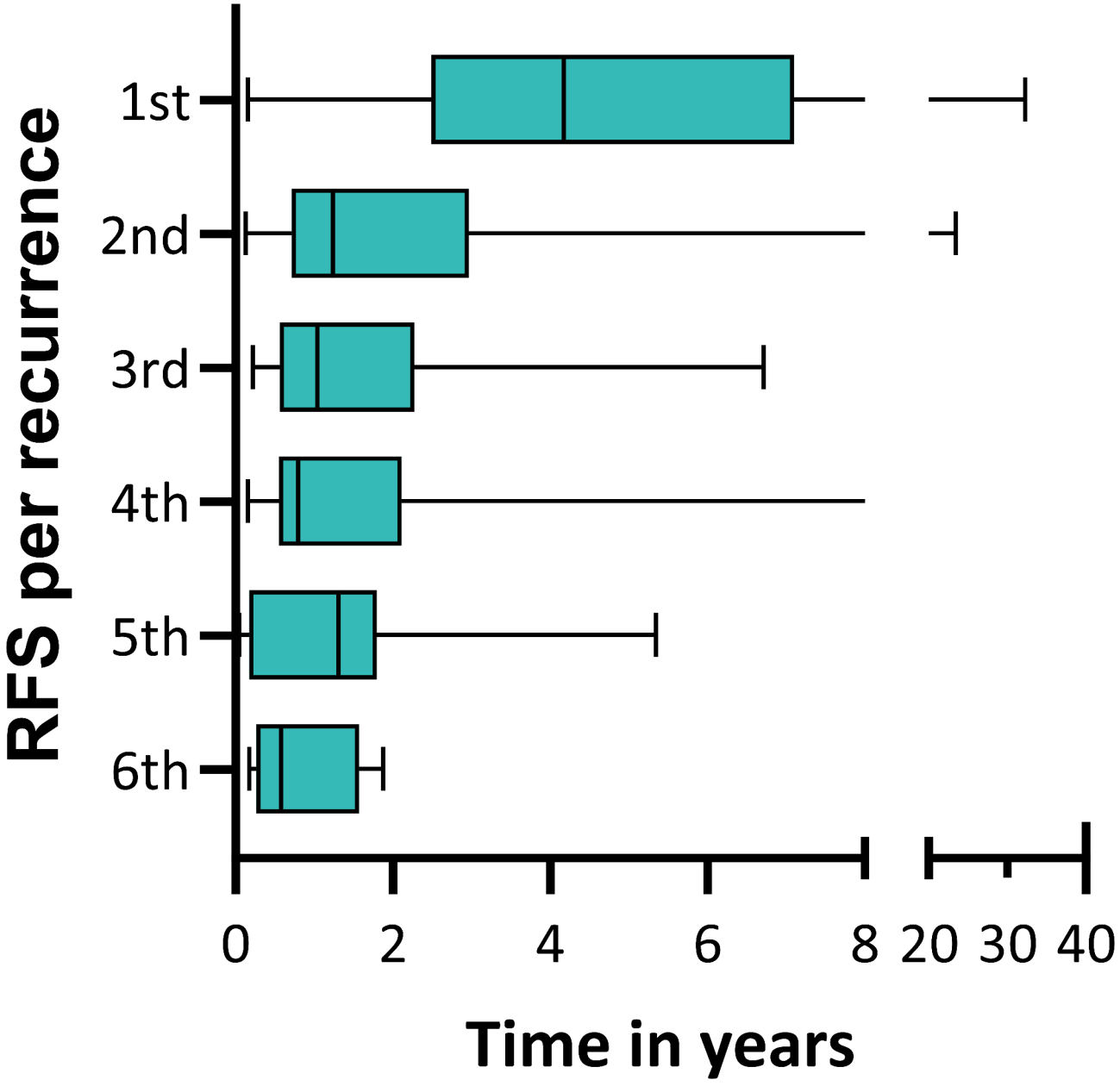

Fig. 1 Recurrence free survival per recurrence with the time in years. RFS: recurrence free survival

Kaplan-Meier curve for RFS for the first recurrence is shown per FIGO stage.

Among the patients who developed their first recurrence, 84 patients (90.3%) had a peritoneal recurrence, five patients (5.4%) had both peritoneal and nodal involvement, one patient (1.1%) experienced a hematogenous recurrence, and in three patients (3.2%), the site of recurrence was unknown. All staged patients ($n = 14$) developed a peritoneal recurrence.

In half of the patients, first recurrence was detected by an increase in the serum tumor markers, and in a third of patients recurrence was detected because the patient developed symptoms. Most common presenting symptom at the first recurrence was abdominal pain.

Of the patients who developed a recurrence, 69 patients (74%) were still in follow-up, 19 (20%) were no longer being followed, and the follow-up status of five patients (6%) was unknown.

During follow-up, most recurrences (73%) were asymptomatic and detected through elevated tumor markers and confirmed by imaging. All patients who were no longer in follow-up presented with symptoms, and no difference in OS was observed between these groups, as shown in Fig. 2A. RFS was significantly longer in patients not in

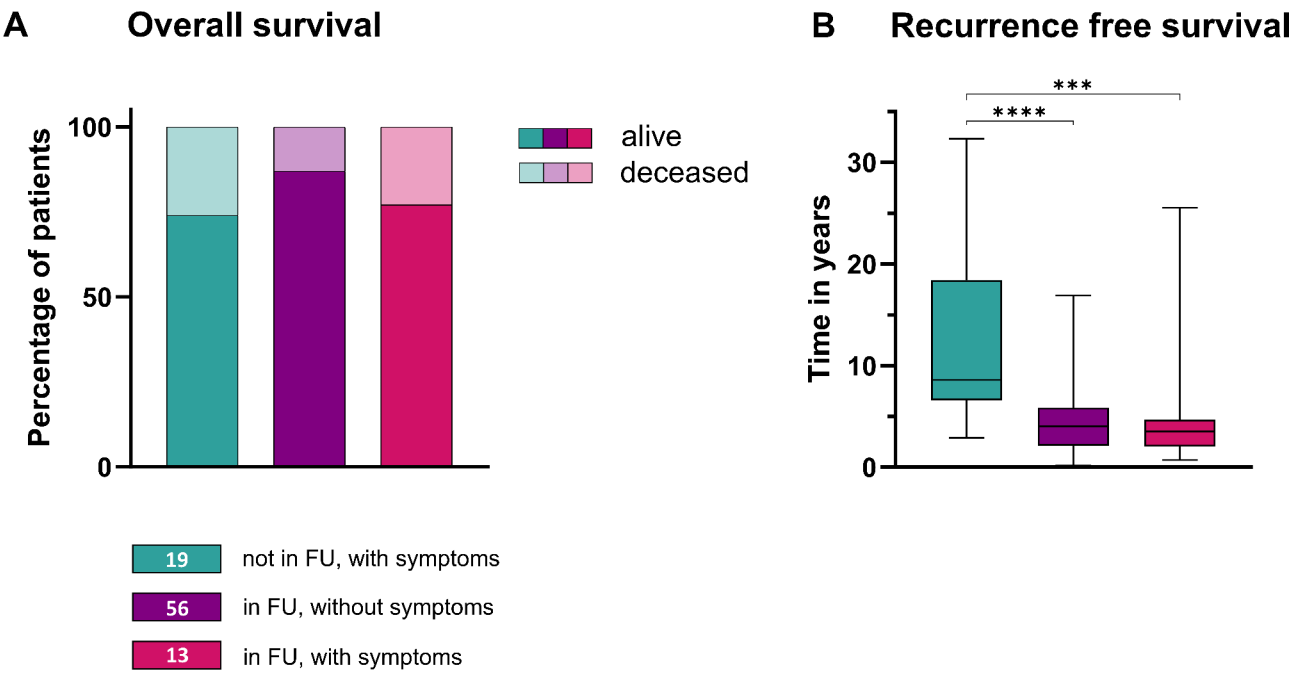

Fig. 2 Follow-up status and presentation of patients at the time of first recurrence. Follow-up status of 88 patients, presenting with or without symptoms, at the time of first recurrence. (**A**) Overall survival per subgroup of patients with recurrent disease. (**B**) The recurrence free survival until the first recurrence per subgroup

follow-up who presented with symptoms (8.6 years, IQR 6.6–18.4) compared to those still in follow-up without symptoms (4.0 years, IQR 2.1–5.8) or with symptoms (3.5 years, IQR 2.0–4.7), as shown in Fig. 2B.

An overview of the number of recurrences and all treatments per recurrence number is shown in Fig. 3. Almost all patients (95.7%) underwent surgery for their first recurrence. Four patients were treated with radiotherapy or anti-hormonal therapy alone, due to a localized recurrence, or the absence of symptoms. Surgery remained the most frequent treatment for subsequent recurrences, either as a single treatment or in combination with chemotherapy, anti-hormonal therapy or radiotherapy. Thirty-one patients (14.9%) received systemic treatments in adjuvant setting or as the only treatment for a recurrence. In total ten different types of chemotherapy were administered. Table S3 and S4 focus on the different types of systemic therapies administered per patient and their response according to RECIST criteria [19]. Due to the extensive variability in type of treatment and timing of treatment, no conclusions can be drawn on the effectiveness of the different regimens. Very few patients received radiotherapy and targeted therapy.

In the univariate Cox regression analysis, FIGO stage IC and FIGO stage II-III were associated with a significantly increased hazard ratio for recurrence. In the multivariate Cox regression analysis on recurrence, the hazard ratio for FIGO stage IC was 2.35 (95% CI 1.42–3.88, $p < 0.001$) and for FIGO stage II-III 2.81 (95% CI 1.28–6.16, $p = 0.010$), as shown in Fig. 4 and Table S5.

In the univariate Cox regression analysis for OS, age had a significantly increased HR, but in the multivariate Cox regression analysis for OS, no significant associations were found, see Table S6.

Median follow-up of all 208 aGCT patients was 5.5 years (IQR: 2.2–12.3 years). At the end of follow-up, 192 patients (92.4%) were alive, of whom 148 patients (71.2%) had NED, 44 patients were AWD (21.2%), 15 patients (7.2%) died from the consequences of aGCT and 1 patient (0.5%) died of another cause. Median time between diagnosis and death was 10 years (IQR: 5.9–19.1 years).

Discussion

In the multivariate Cox regression analysis, FIGO stage IC and FIGO stage II-III were associated with significantly increased odds of recurrence, whereas there was no evidence that staging surgery contributed to the prevention of recurrence. Of our 208 patients, 93 patients (44.7%) developed recurrent disease. The median time to the first recurrence was 4.2 years (IQR: 2.5–7.1 years). At the time of recurrence, 69 patients (74%) were still seen in follow-up, with recurrence detected primarily by rising tumor markers. Nineteen patients (20%), who were no longer in follow-up, presented with symptoms. The RFS was significantly shorter in patients still under follow-up

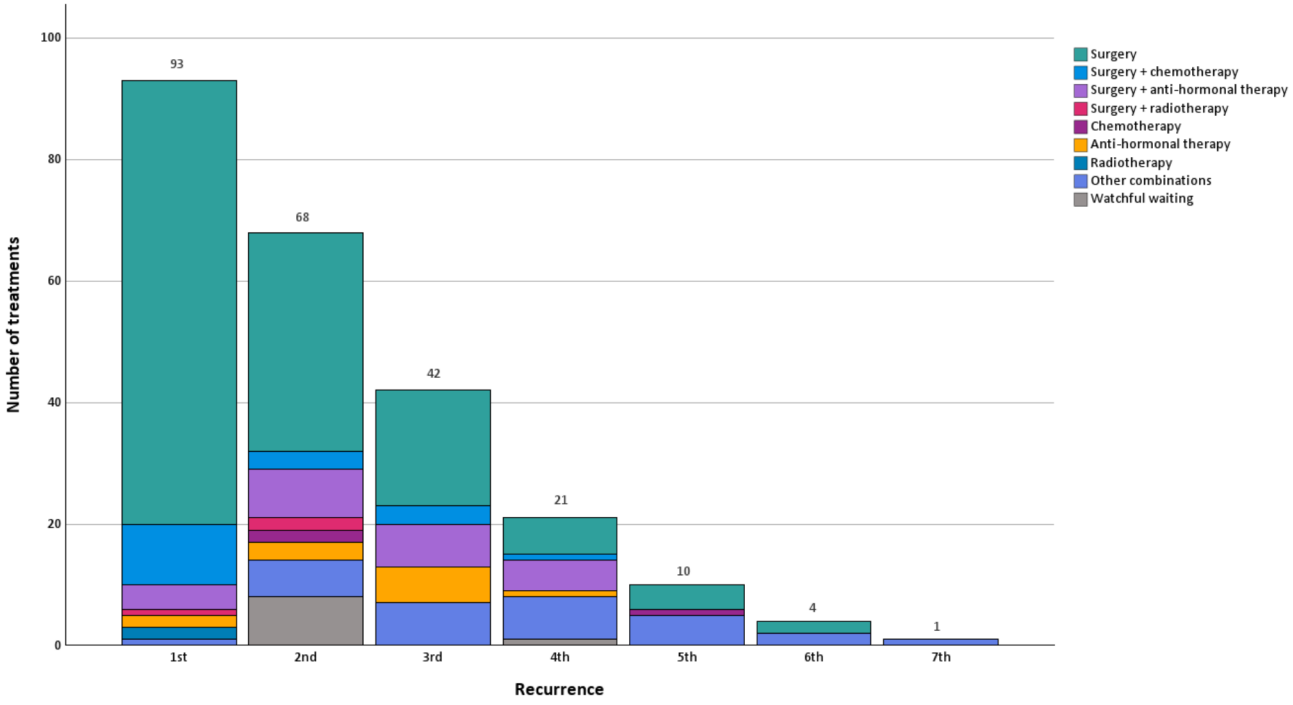

Fig. 3 Number of patients with a recurrence and the type of treatment per recurrence. Distribution of treatment modalities for first and subsequent recurrences. Different colors represent surgery alone and various treatment combinations (e.g., surgery + chemotherapy) using distinct colors for each combination

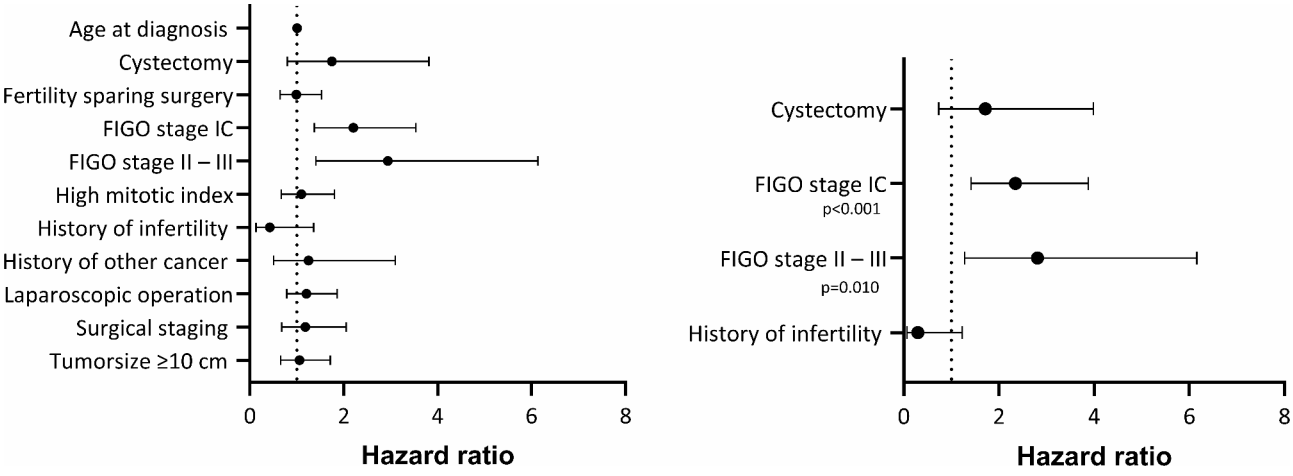

Fig. 4 Forrest plot of the uni- and multivariate Cox regression analysis for recurrence

compared to those not in follow-up who presented with symptoms.

According to the Dutch Cancer Registry, 520 primary cases of aGCT were registered in the period from 1989 till 2022 [20]. Our study includes patients diagnosed from 1976 till 2024, this implies that our study is a relevant representation of the Dutch aGCT population.

The most striking finding of our study is that all patients who were no longer under routine follow-up, showed symptoms when recurrence occurred. The RFS in these patients was significantly longer than in those who remained under follow-up care while no influence on OS was observed. Although the majority of patients still in follow-up had their recurrence detected through elevated markers, discharging patients from follow-up after five years appears to be safe, as OS does not differ between the two groups. This finding also highlights the prognostic value of tumor markers, as RFS is shorter due to earlier detection of recurrence by these markers [21]. Our results indicate that a follow-up period of five years may be sufficient for aGCT patients, after which they can be safely discharged from routine follow-up, provided

they are given thorough counseling on recognizing potential symptoms of recurrence. Recurrences that occur after five years are often symptomatic, and patients who present with symptoms can still receive timely treatment without compromising survival. This approach could not only reduce healthcare costs but also improve patients' quality of life by avoiding the burden of long-term follow-up. Long-standing follow-up periods can greatly impact quality of life, and follow-up practices vary significantly between countries, as reported by aGCT patients themselves, and will benefit from uniform policies [22]. Although over half of recurrences occurs within five years, our findings show that the RFS of patients who were discharged from follow-up and presented with symptoms was significantly longer than for those still under follow-up, without affecting overall survival. These findings align with similar studies in ovarian cancer, where hospital-based follow-up has not been proven to detect recurrences earlier or improve survival rates [23, 24]. Therefore, we propose that a patient-initiated follow-up, where follow-up is limited to five years, with proper patient education on symptom awareness for the period after follow-up. This approach may optimize healthcare resources and reduce unnecessary patient burden.

The finding of capsule rupture (FIGO IC) as a risk factor is consistent with other research in aGCT, showing it to be a main prognostic factor [12, 13]. More awareness for the spill-free removal of adnexal masses is necessary, especially in case of a preoperative suspicion of aGCT. In our study, only 27.9% of patients were suspected of having an aGCT preoperatively. This implies that the majority of patients will not undergo primary surgery by a gynecologic oncologist, but by a general gynecologist. The general gynecologist is preoperatively not aware of a malignancy and may mistakenly accept spill. Efforts should be made to minimize surgical spill by removing all adnexal masses using an endobag, even in case of intended fertility sparing surgery, to prevent the risk of recurrence and thus enhance outcome.

We found more than 50% of patients with aGCT to present with vaginal bleeding and abdominal pain. This is significantly different from patients who present with epithelial ovarian cancer who usually present with much vaguer symptoms such as abdominal discomfort and abdominal distention.

As current guidelines are inconclusive regarding peritoneal staging for aGCT, this results in varying interpretations in clinical practice. Staging was performed in only 46 patients (22.1%) of our cohort. Peritoneal staging had no significant effect on the risk of recurrence or site of recurrence or on OS. Therefore we suggest that if aGCT is diagnosed postoperatively, no additional peritoneal surgical staging needs to be conducted if no other lesions were seen during the first surgery. This avoids unnecessary additional surgical procedures which may be especially important considering the numerous procedures that may follow in case of recurrences, where minimizing adhesions is particularly valuable.

Our cohort is biased due to the retrospective identification of patients with recurrent disease, as shown in Fig. 1. As a result, it is difficult to compare our recurrence rate with other studies that report lower recurrence rates when compared to the percentage of patients with recurrent disease in our study [1, 9–11, 13].

We can however compare the time until the occurrence of a first recurrence and found a median time until first recurrence of 4.2 years (range 2 months– 32 years), which is similar to the findings of Mangili, Ottolina [10] and Bryk, Färkkilä [9] who reported a median of 4.4 years (range 9 months– 27.6 years) and 7.0 years (range 1.0–32.5 years) respectively. This underscores that aGCT can recur even after a very long period of time. The few prospective cohort studies currently published have a mean follow-up time of 60 months, which might be too short to detect recurrences in most patients.

As demonstrated in our previous systematic review, a wide range of systemic therapies are administered to aGCT patients [15]. Similarly, in our current study, we observed a diverse array of therapies being used. However, the considerable variation in therapies and the retrospective character of this study meant that we could not draw conclusions on the measured responses. More unanimity of treatment choices, based on clinical data, should be implemented in order to better evaluate treatment responses.

Strengths of this study include its national multicenter set-up, by which we aim to include as many aGCT patients as possible. Furthermore, the data was not collected from a registry, but retrieved from patient medical records, providing more exact and more detailed information. A limitation of this study is the inclusion bias towards patients with recurrent disease who are still under follow-up and thus are more likely to be included in the study. Conversely, a substantial portion of the sample, mainly consisting of patients diagnosed with primary disease over the last four years, may exhibit more favorable outcomes.

Our results suggest that aGCT patients can be discharged from follow-up for aGCT after five years with thorough instructions to return when symptoms of a possible recurrence arise. This could implicate lower health care costs and more importantly, a lower disease burden for aGCT patients. Furthermore, no additional peritoneal staging is recommended after a postoperative aGCT diagnosis. Future research should focus on increasing the knowledge of this potential diagnosis in case of an adnexal mass and on finding the most effective systemic treatment for recurrent aGCT.

Conclusions

To conclude, for aGCT specifically it is not necessary to perform an additional staging surgery and a regular follow-up period of five years is advised. In addition, it is important to identify adnexal masses that are suspicious for granulosa cell tumor preoperatively. More awareness of the presenting symptoms such as vaginal bleeding and abdominal pain as well as aiming for spill-free removal of adnexal masses are needed.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13048-025-01622-5.

Supplementary Material 1

Acknowledgements
This research was carried out with support of the Granulosa Foundation Philine van Esch.

Author contributions
Overall conceptualization of this study was done by GB, JG, PW, and RZ. Patients were recruited by HN, LL, CL, JP, ER, CK, WH, GJ, PW, and RZ. Data collection was performed by GB and AS, data analysis by GB and JG, and data visualization by GB. GB and JG wrote the main manuscript text under the supervision of EG, PW, and RZ. All authors reviewed the manuscript.

Funding
This study received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Data availability
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethical approval and consent to participate
A national multicenter prospective study was conducted and approved by the Medical Ethics Committee of the University Medical Centre Utrecht (UMCU METC 17–868) and by the institutional review boards of all participating centers. All patients provided written informed consent. The study was registered in the Dutch Trial Register under trial number NL63786.041.17, first registered on April 17, 2018 (https://onderzoekmetmensen.nl/en/trial/54607). The study was conducted in accordance with the ethical principles of the Declaration of Helsinki.

Consent for publication
All patients provided written informed consent.

Competing interests
J.M.J. Piek received grants of the Dutch Cancer society, the Catharina research fund and the INNOsign/OPZuid grant. C.D. de Kroon received grants from ZonMW, KWF, and ZorgInstituut, and occupies chair roles for the guideline committee on endometrial cancer and the working party gynecological oncology from the NVOG. The other authors declare no conflicts of interest.

Author details
[1]Department of Gynecologic Oncology, University Medical Center Utrecht, Heidelberglaan 100, Utrecht 3584 CX, The Netherlands
[2]Department of Obstetrics and Gynecology, University Medical Center Groningen, Groningen, The Netherlands
[3]Department of Gynecological Oncology, Amsterdam University Medical Center, Amsterdam, The Netherlands
[4]Department of Gynecological Oncology, Center of Gynecologic Oncology, Amsterdam, The Netherlands
[5]Department of Obstetrics and Gynecology, Catharina Hospital, Eindhoven, The Netherlands
[6]Department of Gynecologic Oncology, Erasmus MC Cancer Institute, Rotterdam, the Netherlands
[7]Department of Gynecology, Leiden University Medical Center, Leiden, the Netherlands
[8]Department of Obstetrics and Gynecology, Franciscus Gasthuis en Vlietland, Rotterdam, The Netherlands
[9]Department of Pathology, University Medical Center Utrecht, Utrecht, the Netherlands
[10]Department of Medical Oncology, University Medical Center Utrecht, Utrecht, the Netherlands

Received: 20 December 2024 / Accepted: 10 February 2025
Published online: 22 February 2025

References

1. Sun H-D, et al. A long-term follow-up study of 176 cases with adult-type ovarian granulosa cell tumors. Gynecol Oncol. 2012;124(2):244–9.
2. Schumer ST, Cannistra SA. Granulosa cell tumor of the ovary. J Clin Oncol. 2003;21(6):1180–9.
3. Ferlay J, Lam EM, Laversanne F, Colombet M, Mery M, Piñeros L, Znaor M, Soerjomataram A, Bray I. F. Global Cancer Observatory: Cancer Today.. 2024 11 June 2024]; Available from: https://gco.iarc.who.int/today
4. Ray-Coquard I, et al. Non-epithelial ovarian cancer: ESMO Clinical Practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2018;29:iv1–18.
5. Integraal K, Nederland WOG. Niet epitheliale maligniteiten van het ovarium. Landelijke richtlijn, versie: 2.0. 2016; Available from: https://richtlijnendatabase.nl/richtlijn/niet_epitheliale_maligniteiten_ovarium/algemeen.html
6. van Meurs HS, et al. The incidence of endometrial hyperplasia and cancer in 1031 patients with a granulosa cell tumor of the ovary: long-term follow-up in a population-based cohort study. Int J Gynecol Cancer. 2013;23(8):1417–22.
7. Park JY, et al. Surgical staging and adjuvant chemotherapy in the management of patients with adult granulosa cell tumors of the ovary. Gynecol Oncol. 2012;125(1):80–6.
8. Kleppe M, et al. Lymph-node metastasis in stage I and II sex cord stromal and malignant germ cell tumours of the ovary: a systematic review. Gynecol Oncol. 2014;133(1):124–7.
9. Bryk S, et al. Clinical characteristics and survival of patients with an adult-type ovarian granulosa cell tumor: a 56-Year single-center experience. Int J Gynecologic Cancer. 2015;25(1):33–41.
10. Mangili G, et al. Long-term follow-up is crucial after treatment for granulosa cell tumours of the ovary. Br J Cancer. 2013;109(1):29–34.
11. McConechy MK et al. Molecularly Defined Adult Granulosa Cell Tumor of the Ovary: The Clinical Phenotype. JNCI: Journal of the National Cancer Institute, 2016. 108(11).
12. Wilson MK, et al. Stage I granulosa cell tumours: a management conundrum? Results of long-term follow up. Gynecol Oncol. 2015;138(2):285–91.
13. Plett H et al. Adult ovarian granulosa cell tumors: analysis of outcomes and risk factors for recurrence. Int J Gynecologic Cancer, 2023;33(5).
14. Teoh D, Freedman R, Soliman PT. Nearly 30 years of treatment for recurrent Granulosa Cell Tumor of the Ovary: a Case Report and Review of the literature. Case Rep Oncol. 2010;3(1):14–8.
15. Brink GJ, et al. Response to systemic therapies in ovarian adult granulosa cell tumors: a literature review. Cancers. 2022;14(12):2998.
16. Castor EDC. Castor Electronic Data Capture. 2019 August 28, 2019]; Available from: https://castoredc.com
17. Julius. Clinical. Available from: https://www.juliusclinical.com/
18. GraphPad P. 2023, GraphPad Software, Boston, Massachusetts USA.
19. Eisenhauer EA, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45(2):228–47.
20. Dutch Cancer Registry I. Available from: nkr-cijfers.iknl.nl.
21. Portuesi R et al. Role of inhibin B in detecting recurrence of granulosa cell tumors of the ovary in postmenopausal patients. Int J Gynecologic Cancer, 2021;31(6).
22. White VM, et al. How social media can help to understand treatment experiences of survivors of rare cancers: findings from the Granulosa Cell Tumor Survivor Sisters Facebook group member survey. Cancer. 2023;129(14):2224–34.

23. Newton C et al. British Gynaecological Cancer Society recommendations and guidance on patient-initiated follow-up (PIFU). Int J Gynecologic Cancer, 2020;30(5).
24. Luk HM, et al. Patient-initiated Follow-Up in Ovarian Cancer. Curr Oncol. 2023;30(4):3627–36.

Publisher's note