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REVIEW

Prognostic predictors in recurrent adult granulosa cell tumors of the ovary: a systematic review and meta-analysis

Frediano Inzani[1] · Angela Santoro[1] · Antonio Travaglino[2] · Nicoletta D'Alessandris[1] · Antonio Raffone[3] · Patrizia Straccia[1] · Giuseppe Angelico[1] · Damiano Arciuolo[1] · Giulia Scaglione[1] · Michele Valente[1] · Pietro Tralongo[1] · Valerio Gallotta[4] · Gian Franco Zannoni[1,5]

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Abstract

Background Ovarian adult granulosa cell tumours are low-grade malignant sex cord–stromal neoplasm with a low recurrence rate. Prognostic factors for recurrence include tumor stage, tumor rupture in Stage I neoplasms and the presence of residual tumors after surgery. However, in recurrent tumors, prognostic factors for overall survival (OS) are lacking. In the present paper, we conducted a systematic meta-analysis with the aim to assess prognostic factors for OS in patients with recurrent GCT.

Methods Electronic databases were searched for all studies assessing prognostic factors in recurrent adult granulosa cell tumor of the ovary. Student *T* test, Fisher's exact test and Kaplan–Meier survival analysis with long-rank test were used to assess differences among groups; a p value < 0.05 was considered significant.

Results Eleven studies analyzing 102 recurrent tumors were included in the systematic review. Tumor stage and localization of recurrent tumors were significantly associated with OS on Kaplan–Meier analysis; Cox regression analysis showed a HR of 0.879 for the stage II, of 3.052 for the stage III, and of 2.734 for stage IV tumor was significantly associated with OS ($p = 0.037$); observed HRs for abdominal and thoracic locations were of 2.405 and of 4.024, respectively.

Conclusions In conclusion, the present article emphasizes the prognostic significance of tumor stage > II and extrapelvic anatomic sites of recurrences in patients with recurrent granuolase cell tumors of the ovary.

Keywords Granuosa cell tumor · Prognosis · Tumor stage · Recurrence · Ovarian tumor · Sex cord tumors

Introduction

Granulosa cell tumors (GCT) of ovary originate from the ovarian mesenchyme and sex cords and account for 70% of all sex cord stromal tumors, and 5–8% of all ovarian neoplasms [1]. GCT can manifest in women of all age groups, is usually bilateral and has the ability to secrete [1–3].

There are two different histological types of GCT: adult-type GCTs (AGCTs) and juvenile-type GCTs (JGCTs) [1–4].

JGCTs is associated with abnormally high estrogen secretion and usually manifest with precocious puberty in about 75% of cases, [5]. Extremely rare examples of virilizing, testosterone-producing JGCT are reported in the literature (2–3% of GCTs) and manifest with hirsutism, amenorrhea, deepening of the voice, clitoral hypertrophy and acne [6]. In contrast, AGCTs usually present with menstrual irregularities, amenorrhea and endometrial hyperplasia [7, 8].

Frediano Inzani and Angela Santoro have equally contributed to the paper.

✉ Gian Franco Zannoni
gianfranco.zannoni@unicatt.it

1 Unità di Ginecopatologia e Patologia Mammaria, Dipartimento Scienze della Salute della Donna, del Bambino e di Sanità Pubblica, Fondazione Policlinico Universitario A. Gemelli IRCCS, Largo A. Gemelli 8, 00168 Roma, Italy

2 Department of Advanced Biomedical Sciences, Pathology Section, School of Medicine, University of Naples "Federico II", Via Sergio Pansini, 5, 80131 Naples, Italy

3 Department of Medical and Surgical Sciences (DIMEC), University of Bologna, Bologna, Italy

4 UOC Ginecologia Oncologica, Dipartimento per la salute della Donna e del Bambino e della Salute Pubblica, Fondazione Policlinico Universitario A. Gemelli, IRCCS, Largo Agostino Gemelli 8, 00168 Rome, Italy

5 Istituto di Anatomia Patologica, Università Cattolica del Sacro Cuore, Largo A. Gemelli 8, 00168 Rome, Italy

The prognosis of JGCT is excellent, with tumour recurrence or metastasis being rare [4]. AGCT, on the other hand, is regarded as a low-grade malignant neoplasm since there is a significant propensity for recurrence or metastasis. Often the recurrent or metastatic tumour manifests itself many years after removal of the primary neoplasm with intervals in excess of 10 or even 20 years being not uncommon [1–3]. There is no standard management for recurrent GCT. Various treatment options include surgery with/without chemotherapy and/or radiotherapy [9]. Patients with peritoneal metastases are often considered inoperable with treatment largely directed at palliation of symptoms [9, 10].

To date, widely accepted prognostic factors for recurrence include tumor stage, tumor rupture in Stage I neoplasms and the presence of residual tumors after surgery [11, 12]. Up to date tumor size, morphological pattern of growth, cytological atypia and high mitotic count are not considered independent prognostic factors of patient survival [11, 12]. However, in recurrent tumors, prognostic factors for overall survival (OS) are lacking.

In the present paper, we conducted a systematic meta-analysis with the aim to assess prognostic factors for OS in patients with recurrent GCT.

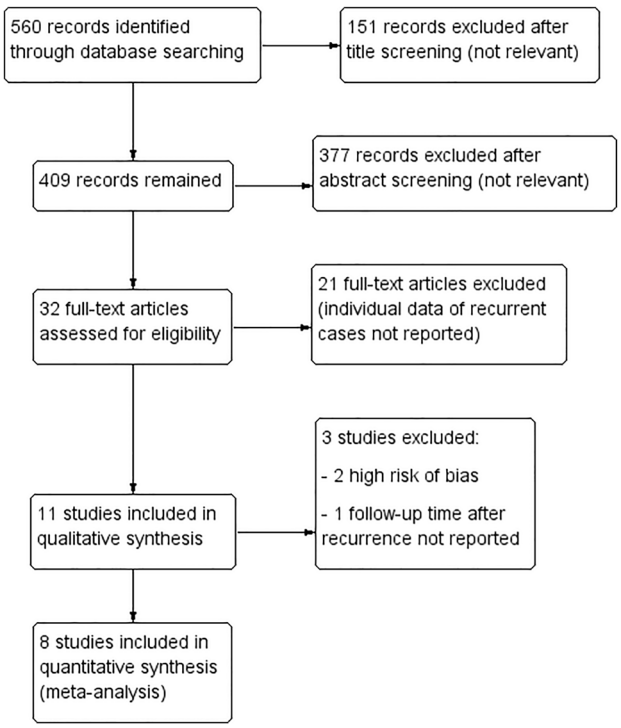

Fig. 1 Flow diagram of the study selection process

Materials and methods

This study was planned based on methods of previous systematic reviews [13–15]. Two independent authors performed all review stage; disagreements, if any, were resolved by consensus. The PRISMA statement [16] was followed to report this study.

Search strategy and study selection

Four electronic databases (i.e., MEDLINE, Scopus, ISI Web of Sciences and Google Scholar) were searched from their inception to May 2021. The following combination of text words was used: granulosa cell tumor AND prognosis. All studies reporting individual clinicopathological and survival data of series of women with GCT were included. Exclusion criteria were: sample size < 5; overlapping patient data; review. Relevant references from eligible studies were also assessed.

Flow diagram of the study selection process is reported in Fig. 1.

Data extraction

Main data extracted for analysis were follow-up time after recurrence, status at the last follow-up and each individual clinicopathological factor of recurrent cases (out of which patient age, tumor stage and localization of recurrent tumor were suitable for meta-analysis). Further data extracted were: country, period of enrollment, total sample size and number of recurrent cases, time to recurrence, total follow-up duration.

Risk of bias assessment

The risk of bias was assessed based on the QUADAS-2 [17], (Fig. 2). The four domains assessed were: patient selection (i.e., were inclusion criteria and period of recruitment reported?); index test (i.e., were clinicopathological variables clearly reported?); reference standard (i.e., were survival data clearly reported?); flow (were data reported for all eligible patients?). The risk of bias was categorized as "low", "unclear" or "high" following previously described criteria [16].

Data analysis

Kaplan–Meier survival analysis with Log-rank test was used to assess the impact of clinicopathological variables on OS; Kaplan–Meier curves were used to graphically report the results. Cox regression survival analysis was used to calculate hazard ratio (HR) with 95% confidence interval for each

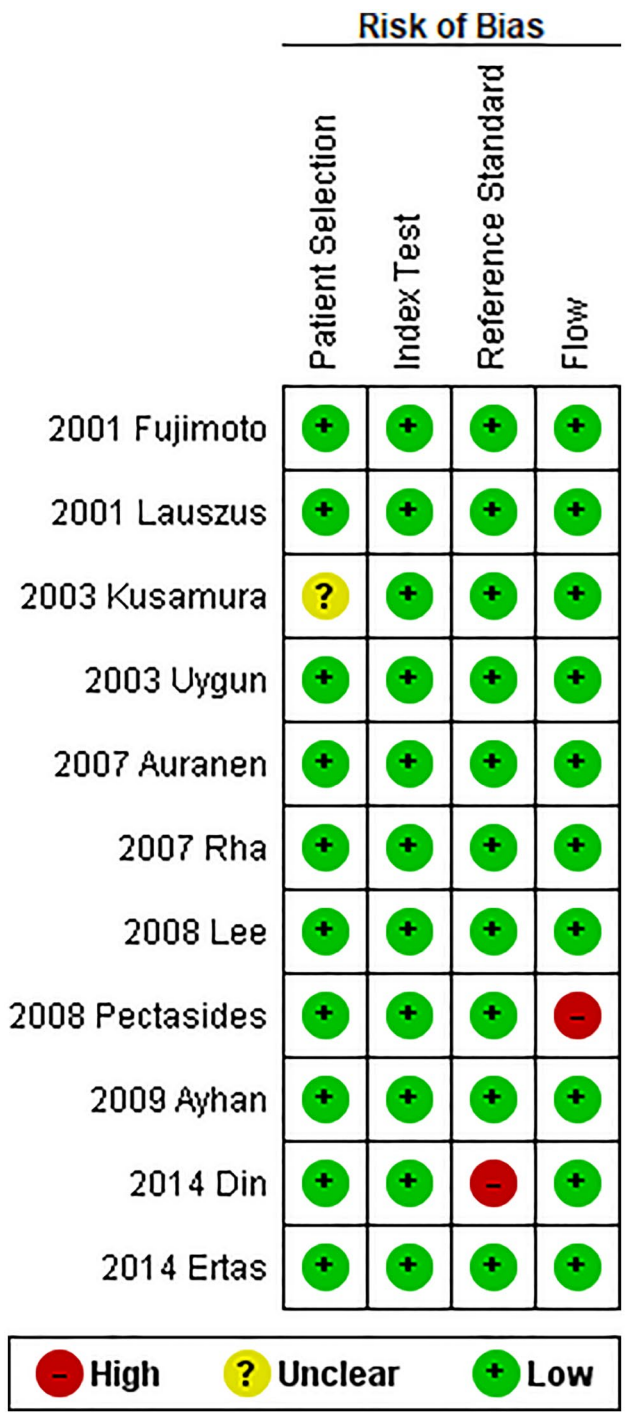

Fig. 2 Risk of bias assessment

clinicopathological variable. A p value < 0.05 was considered significant.

Statistical analyses were carried out using Statistical Package for Social Science (SPSS) 18.0 package (SPSS Inc., Chicago, IL, USA).

Results

Study selection and characteristics

Eleven studies [18–28] with 102 recurrent GCT were included in the systematic review. The process of study selection is summarized in Supplementary Fig. 1. Characteristics of the included studies are listed in Table 1.

Risk of bias assessment

For the "patient selection" domain, one study was considered at unclear risk of bias (period of recruitment not specified), while the other studies were considered at low risk. For the "index test" domain, all studies were considered at low risk. For the "reference standard" domain, one studies were considered at high risk (no clear report of survival data), while the other studies were considered at low risk. For the "flow" domain, one study was considered at high risk (inconsistent data reporting) and the remaining studies at low risk.

Survival analysis

The two studies at high risk of bias were excluded from the meta-analysis. A further study [c] was excluded because it reported the total follow-up duration of patients with GCT but not the follow-up time after recurrence.

Patient age was not significantly associated with OS ($p = 0.098$) on Kaplan–Meier analysis (Fig. 3); Cox regression analysis showed a HR of 0.460 (95% CI 0.188–1.125; $p = 0.089$) for the age range 40–49, of 0.690 (95% CI 0.289–1.644; $p = 0.402$) for the age range 50–59, and or 1.398 (95% CI 0.568–3.437; $p = 0.466$) for an age ≥ 60, using an age < 40 as reference.

Tumor stage was significantly associated with OS ($p = 0.007$) on Kaplan–Meier analysis (Fig. 4); Cox regression analysis showed a HR of 0.879 (95% CI 0.200–3.856; $p = 0.864$) for the stage II, of 3.052 (95% CI 1.498–6.221; $p = 0.002$) for the stage III, and of 2.734 (95% CI 0.768–9.742; $p = 0.121$) for stage IV, using stage I as reference.

Localization of recurrent tumor was significantly associated with OS ($p = 0.037$) on Kaplan–Meier analysis (Fig. 5); Cox regression analysis showed a HR of 2.405 (95% CI 1.078–5.365; $p = 0.032$) for an abdominal localization, and of 4.024 (95% CI 1.054–15.369; $p = 0.042$) for a thoracic localization, using pelvic localization as a reference.

Table 1 Characteristics of selecting studies on recurrent GCT

Study	Country	Period of enrollment	Sample size		Follow-up after recurrence median (range)
			Recurrent	Total	
Fujimoto [18]	Japan	1968–1999	7	27	15 (5–79) m
Lauszus [19]	Denmark	1962–1996	13	42	19 (3–164) m
Kusamura [20]	Brazil	12 years	5	18	Only total follow-up reported
Uygun [21]	Turkey	1979–1999	11	45	26 (5–73) m
Auranen [22]	Finland	1970–2003	7	35	128 (61–236) m
Rha [23]	South Korea	1992–2003	12	34	72 (1–228) m
Lee [24]	South Korea	1987–2005	8	35	58 (12–132) m
Pectasides [25]	Greece	1983–2007	5	34	Unclear
Ayhan [26]	Turkey	1982–2006	9	80	13 (8–20) m
Din [27]	Pakistan	1992–2012	8	156	Not reported
Ertas [28]	Turkey	1991–2010	18	108	30 (8–128) m

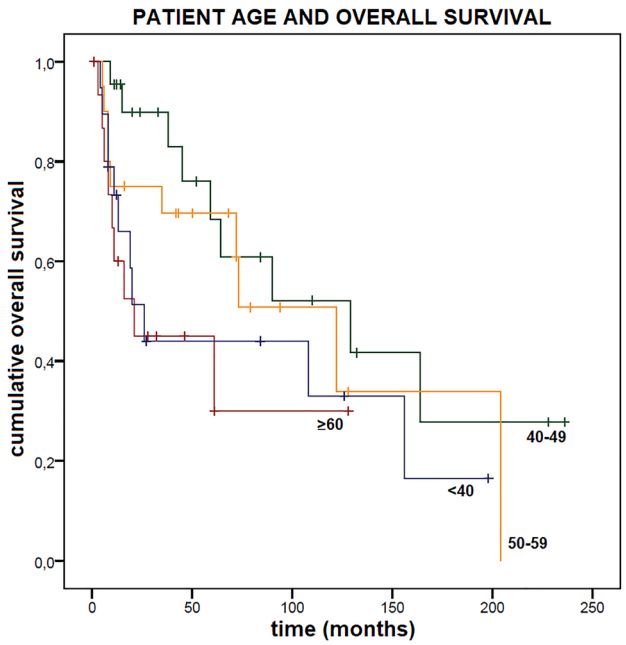

Fig. 3 Kaplan–Meier analysis illustrating patient age and OS

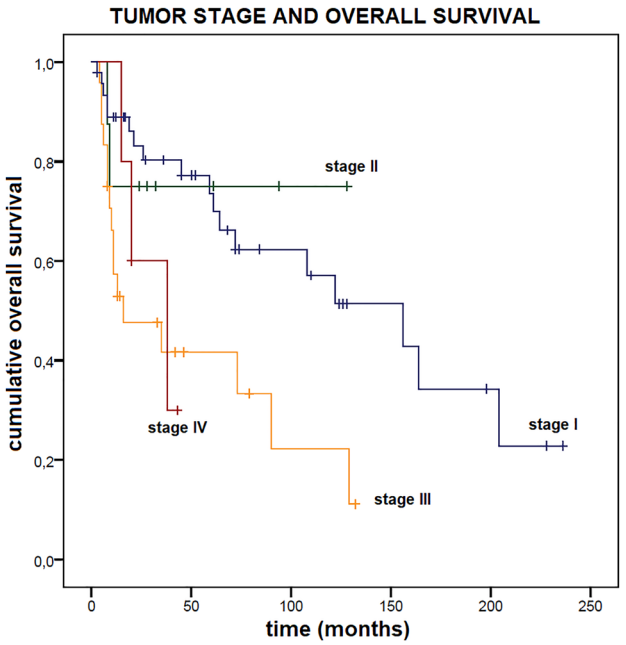

Fig. 4 Kaplan–Meier analysis illustrating tumor stage and OS

Discussion

Ovarian adult granulosa cell tumours are regarded as low-grade malignant sex cord–stromal neoplasms with a low recurrence rate and long overall survival, generally detected in early stages without extra-pelvic metastasis [1–3]. Recurrent or metastatic GCT can manifests many years after initial surgery and the 10-year survival for GCT ranges from 60 to 90% [1–3].

To date, different studies attempted to individuate the most relevant prognostic factors that might predict tumor recurrences and metastases to select the most appropriate candidates for adjuvant therapy after surgical removal.

The most widely reported clinicopathological factors related to prognosis in GCT include: tumour stage, tumor rupture, size, mitotic activity, nuclear atypia more than mild, histological pattern, patient age, p53 immunohistochemistry, Ki-67 proliferative index and DNA ploidy analysis [11, 12, 18, 20].

Unfortunately, literature data regarding the above-mentioned parameters are conflicting and no single prognostic factor is sufficiently reliable for predicting GCT prognosis.

To date, following many studies, tumors stage represents the only universally accepted prognostic factor in GCT and

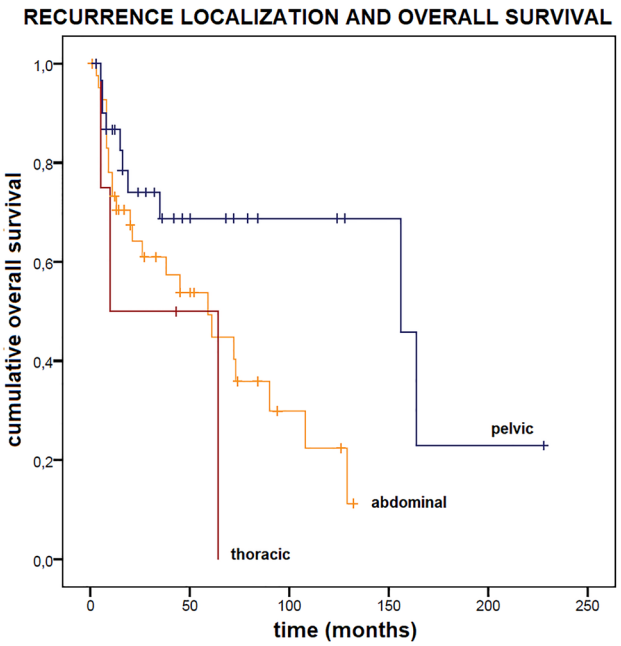

Fig. 5 Kaplan–Meier analysis illustrating recurrence location and OS

advanced-stage (II–IV) tumors are believed to benefit from adjuvant therapy. Capsular rupture in low-stage tumors may also represent an important adverse prognostic factor in GCT; although not extensively investigated, few studies showed a significant relation between capsular rupture and tumor recurrences [11, 12, 18].

Different cut off limits of tumor diameter for tumor recurrence have been also reported [11, 12, 18].

The prognostic impact in stage I GCTs of mitotic activity and Ki-67 proliferative index has also been demonstrated by several studies. However, the available results need to be furtherly validated since they suffer from significant variations in methodology between studies [11, 20].

The prognostic significance of lymphovascular invasion (LVSI) has also been taken into account by some authors; in detail, a moderate/prominent LVSI has been related to worse survival in GCT patients. However, its role as independent prognostic factor is still not clear and precise criteria to define lymphatic and blood vessel invasion are still lacking [11, 12, 18, 20].

Despite many studies have investigated the prognostic predictors of GCTs, limited and conflicting results are currently available in the literature regarding the biologic behavior and prognosis of recurrent tumors. Therefore, the main aim of the present study was to assess the most relevant prognostic factors capable of affecting OS in patients with recurrent GCTs.

Starting from 11 studies analyzing 102 recurrent GCTs [18–28], we observed that tumor stage and tumor location represented reliable prognostic predictors for OS. In detail, advanced tumor stages of II or more were significantly associated with worse prognosis both on Kaplan–Meier analysis and Cox regression analysis, with observed HRs of 0.879, 3.052 and 2.734 for stage II, III and IV, respectively.

The anatomic location of tumor recurrences was also significantly related to OS on survival analysis; in fact, worse prognoses were recorded for patients showing tumor recurrences outside the pelvis with observed HR values of 2.405 and 4.024 for abdominal and thoracic localizations, respectively.

This study showed that a tumor stage > II and a localization outside pelvis were significant unfavorable prognostic factors in recurrent GCT; on the other hand, patient age was not significantly associated with OS.

In our study, the median time until recurrence was 42 months and this observation is in line with previous reports. As distant metastases are not infrequent in recurrent tumors, patients at high-risk for recurrence should receive adjuvant systemic chemotherapy. There is no consensus regarding the adequate management and no standard treatment for recurrent GCT, and multiple approaches including surgery, chemotherapy, radiotherapy, and hormone therapies have been proposed [10].

The controversies over the extend of surgery are still matter of debate, with many gynecological oncologists in favour of omitting lymphadenectomy procedure, in particular in tumors without unfavourable clinical-pathological prognostic characteristics and since the high risk of complications and morbidity, and others considering as a valid option a multivisceral surgical debulking in addition to lymphadenectomy [10, 21, 27, 28].

The first-line standard chemotherapy has been suggested to be BEP, which is a combination of bleomycin, etoposide, and cisplatin; CAP, which comprises of cyclophosphamide, adriamycin, and cisplatin, is also used [29, 30].

Etiological relationship between ovarian stimulation and granulosa cell tumorigenesis has also been speculated and a proportion of these tumors express steroid hormone receptors [31]. Therefore, hormonal treatment using gestagen or GnRH agonist may be expected to exert anti-tumor activity for AGCTs [31]. However, the number of reports regarding this issue is still limited and further investigations are needed to verify the role of gestagen and GnRH in treatment of AGCTs.

In conclusion, the present article emphasizes the prognostic significance of tumor stage and anatomic site of recurrences in patients with relapsed GCT. However, scientific articles on this topic are still limited and multicentric studies on larger series are still needed to elucidate the prognostic impact of clinicopathological factors in GCTs.

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Availability of data and material All presented data are available from corresponding author upon reasonable request.

Code availability Not applicable.

Declarations

Conflict of interest All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

Ethical approval Not applicable.

Consent to participate Not applicable.

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