Gynecologic Oncology Reports 26 (2018) 94–98

Contents lists available at ScienceDirect

Gynecologic Oncology Reports

journal homepage: www.elsevier.com/locate/gynor

Case series

Association between diabetes mellitus and progression free survival in women with ovarian granulosa cell tumors

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1. Introduction

Ovarian sex cord-stromal tumors are a heterogeneous group of rare neoplasms arising from the ovarian matrix, accounting for only 1.2% of all ovarian cancers. Granulosa cell tumors (GCTs), including adult and juvenile subtypes, comprise 70% of sex cord-stromal tumors (Colombo et al., 2007). The adult subtype is most commonly diagnosed after age 30, with a median age of 50 years. Adult GCTs are low-grade malignancies that typically demonstrate indolent growth. Approximately 70–90% are stage I at diagnosis and are associated with 90–95% 5-year survival (Colombo et al., 2007). However, late recurrences occur in up to 25% of stage I tumors and may recur 5 to 30 years after initial diagnosis (Malmstrom et al., 1994). Juvenile type GCTs, representing only 5% of all GCTs, demonstrate high proliferate rate and typically develop before puberty (Malmstrom et al., 1994). Similar to adult GCTs, 95% of juvenile GCTs are diagnosed as stage I cancers; however, lethal recurrences are more likely to develop within 3 years of diagnosis (Frausto et al., 2004).

The rarity of these tumors limits research opportunities to investigate the natural history of GCTs, treatment strategies, and prognosis. An extra-fascial hysterectomy with bilateral salpingo-oophorectomy is recommended for women who are done with childbearing. Though some authors suggest routine pelvic and para-aortic lymph node sampling may be omitted from surgical staging given the rarity of lymph node metastases, recent findings from a National Cancer Database study ($n = 2680$) found that incomplete surgical staging was associated with increased hazard of death (Miller et al., 1997; Brown et al., 2009; Seagle et al., 2017). A 2014 Cochrane review including five retrospective cohort studies ($n = 535$) deferred any conclusion regarding the safety of fertility-sparing surgery and the effectiveness of adjuvant treatment for GCTs (Gurumurthy and Shanbhag, 2014).

As late recurrences are common in women with ovarian GCTs, studies have sought to determine demographic and prognostic factors associated with disease. Suri et al. found diabetes to be a strong predictor of ovarian GCT recurrence (Suri et al., 2013). Given African Americans, Hispanics, and Asians are at increased risk of diabetes and Montefiore Medical Center serves a minority majority catchment population in Bronx, New York, we sought to further investigate the impact of clinical and pathologic covariates including diabetes mellitus on progression free survival in our unique patient cohort (Shai et al., 2006).

2. Methods

Approval to conduct this retrospective cohort study was obtained by the Institutional Review Board at Montefiore Medical Center. Our institutional gynecologic oncology tumor registry was queried to retrospectively identify all patients diagnosed with ovarian GCTs. Patients were considered eligible if they were diagnosed with ovarian GCTs, of both adult and juvenile subtypes, and received treatment at our institution from January 1, 2005 through December 31, 2015. The primary objective of our study was to evaluate the impact of clinicodemographic and prognostic factors on progression free survival in our unique patient cohort of a minority catchment population.

Inpatient and outpatient records were reviewed for collection of demographic data including clinical presentation, age at diagnosis, race, parity, menopausal status, BMI, personal and family history of malignancy, medical comorbidities, concurrent presence of endometrial abnormality, and smoking history. Clinicopathologic and treatment data including surgery performed, stage, tumor histology, and chemotherapy administration was abstracted from operative notes, ambulatory notes, and pathology reports. FIGO 1988 ovarian cancer staging guidelines were used. We defined complete surgical staging as extra-fascial hysterectomy with bilateral salpingo-oophorectomy, omental sampling, lymphadenectomy (pelvic and/or para-aortic), and pelvic washings. We defined fertility sparing surgery as any procedure with conservation of the uterus and one adnexa. Only pre-menopausal women under the age of 50 were eligible for analysis for fertility

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https://doi.org/10.1016/j.gore.2018.10.009
Received 31 August 2018; Received in revised form 22 October 2018; Accepted 23 October 2018
Available online 29 October 2018

sparing surgical procedures.

Data analysis was performed using Stata version 14.2 (StataCorp. 2015. *Stata Statistical Software: Release 14*. College Station, TX: StataCorp LP). Continuous data was reported as medians with interquartile ranges. Categorical data was presented as the number of subjects with percentages. Bivariate analyses, including the Mann-Whitney *U* test and Fisher's exact tests, were performed to assess the association between clinical variables and diagnosis of disease recurrence or progression. Univariate logistic regression was performed to assess the association of individual variables with recurrence or progression. Odds ratios were reported with 95% confidence intervals. A Cox proportional hazards model was fit using both forwards and backwards stepwise elimination to accurately characterize the association of individual covariates with progression free survival (PFS). Log-rank testing was performed to compare experience of PFS by diagnosis of diabetes by groups and survivorship curves were generated using the Kaplan-Meier Method.

3. Results

Seventy-two cases of GCT were identified, of which histologically 96% ($n = 69$) were adult subtype and 4% ($n = 3$) were juvenile subtype. Although our study predominantly focused on the adult histologic subtype (96%, n = 69), we chose to also analyze the juvenile histologic subtype subtype (4%, n = 3) in our patient cohort. This was due to the fact that even though both manifest different pathologic behavior they are often similarly managed from a clinical standpoint. The median age of diagnosis and BMI were 55 years (IQR 43, 62) and 31 (IQR 26, 36), respectively (Table 1). While only 7% ($n = 5$) of patients were White, the remaining patients were Black ($n = 38$), Hispanic ($n = 15$), Asian ($n = 2$) and declined/unknown ($n = 12$). The most common presenting complaint was abnormal uterine or postmenopausal bleeding (28%). Other clinical presentations included: pain (26%), physical exam abnormality (14%), and incidental finding on imaging, intra-operative evaluation, or pathology (21%). The majority of patients (95%) presented with stage I disease. Twenty-one percent of patients (n = 15) had diabetes. Additionally, in our patient cohort 85% ($n = 61$) of patients underwent endometrial sampling pre-operatively, intra-operatively, or within 3 months of surgery. Of those, 31% ($n = 19$) were diagnosed with endometrial hyperplasia or carcinoma.

Seventy-two percent of patients underwent bilateral salpingo-oophorectomy. Of the remaining patients, 26% underwent unilateral salpingo-oophorectomy with conservation of the contralateral ovary and 1% underwent unilateral cystectomy with conservation of bilateral ovaries. The majority of patients (68%) also underwent hysterectomy. Complete surgical staging was performed in 36% ($n = 26$) of patients. Lymph node sampling was performed in 46% of patients and 1 patient was found to have nodal metastases. No patients that underwent omental sampling had microscopic omental disease. Fertility sparing surgery was performed in 22% ($n = 16$) patients, 38% of whom ($n = 6$) subsequently had a live birth without assisted reproductive technology (Table 2).

Only 10% of patients received adjuvant chemotherapy (Table 3). The most frequently prescribed chemotherapy regimen (43%) was bleomycin, etoposide, and cisplatin (BEP). Of those treated with adjuvant chemotherapy, 4 patients had stage IA, 1 had stage II, and 2 had stage IIIC disease. Of the four patients with early stage disease that received adjuvant chemotherapy, two of them had other synchronous cancers (one uterine carcinosarcoma and one uterine serous carcinoma), which dictated their need for chemotherapy and the prescribed regimen. Our records demonstrate incomplete documentation to explain why two of the stage IA patients initially received adjuvant treatment with BEP, limiting our ability to draw further conclusions about the decision-making process. However, one could infer that both of these patients had large tumor sizes (12 cm and 22 cm) and it has been previously described in the literature that large tumor size (> 5 cm) seems to be related to disease recurrence which may have prompted the provider to offer adjuvant chemotherapy (Suri et al., 2013). Of those who received adjuvant chemotherapy, there was one recurrence in a patient with stage IIIC disease in whom BEP was discontinued after one cycle due to anemia and bacteremia.

Eleven recurrences were diagnosed over a median follow up 58.5 months (IQR 26.8, 94.0). The majority of recurrences (91%) occurred among women with early stage disease at initial diagnosis. Among the three juvenile subtypes in our patient cohort there was one recurrence of disease. Complete surgical staging was performed in 55% ($n = 6$) of patients that had recurrent disease and there was one recurrence among those that underwent fertility sparing surgery. Of those patients that were not lost to follow up and accepted treatment for their first recurrence, the majority underwent secondary debulking and one patient received bleomycin, etoposide, and cisplatin. Three patients were treated with aromatase inhibitors and three received Megestrol acetate. Though no deaths were attributable to disease, one patient died secondary to bleomycin pulmonary toxicity.

Patients contributed a total of 4143 person-months of analysis time over the course of the study. The incidence rate of disease recurrence or progression was 0.3% with a median time to recurrence of 140 months. In simple logistic regression, no significant association was found between age, BMI, race, parity, menopausal status, family history of cancer, histologic subtype, tumor size, stage, extent of lymph node sampling, complete surgical staging, laterality of adnexectomy, and fertility sparing surgery and disease recurrence/persistence. Similarly, there was no association between hypertension, hyperlipidemia, obesity, and smoking status, and risk of disease recurrence/progression. Of the 15 women with diabetes, 33% ($n = 5$) had recurrent/persistent disease and all 5 were alive at last evaluable encounter. Although simple logistic regression did not identify an association between diabetes and disease recurrence, Cox proportional hazards modeling revealed that diabetes was significantly associated with PFS when controlling for other covariates. Women with diabetes had a median PFS of 116 months compared to 140 months in women without diabetes (HR 5.72, 95% CI 1.52–21.56). Covariates were selected for inclusion in the model if they achieved a pre-determined p value cutoff of < 0.25 in univariate survival analysis. These covariates included hyperlipidemia, BMI, smoking status, menopausal status and receipt of adjuvant chemotherapy. In stepwise elimination, all covariates with the exception of diabetes exited the model, as they were not significantly associated with disease recurrence. Log-rank testing for stratified experience of PFS by diagnosis of diabetes was also significant ($p < .01$). Kaplan Meier survival curves for PFS are shown in Fig. 1.

4. Discussion

Our study describes a large and well-characterized unique patient cohort of a minority catchment population with ovarian GCTs. In this group of women, diagnosis of diabetes mellitus was associated with worse progression free survival. Additionally, we found no difference in progression free survival among those women that did and did not undergo lymphadenectomy and complete surgical staging. Lastly, we identified no patients in our cohort that died of recurrent granulosa cell tumor. However, one patient in the cohort did die from chemotherapy related complications.

Our study shares several similarities to those findings previously reported in the literature. We identified an association between diabetes mellitus and worse progression free survival. To the best of our knowledge, the association between diabetes mellitus and increased risk of recurrence in women with early stage GCT has been reported only once in the literature, by Suri et al. where in univariate analysis diabetes mellitus showed the strongest association with recurrence (HR 3.37, 95% CI 1.38–8.20) and in multivariate analysis diabetes was associated with a HR of 3.19 (95% CI 1.08–9.44) (Suri et al., 2013). One reason for the difference in outcomes on univariate analysis between

Table 1
Bivariate analysis examining association of individual covariates with disease recurrence or progression in patients with granulosa cell tumors[a]

Characteristics	Total cohort (*N* = 72)	No recurrence or progression (*N* = 60)	Recurrence or progression (*N* = 12)	OR	95% CI	*P* value
Age (years)	55 (43, 62)	55 (42, 62)	56 (49, 64)	–	–	0.50
Body mass index (kg/m^2)	31 (26, 36)	31 (26, 36)	31 (29, 38)	–	–	0.60
Parity	2 (1, 3)	2 (0,3)	2 (1,3)	–	–	0.61
Medical co-morbidities						
Diabetes	15 (21)	10 (17)	5 (42)	3.50	0.92–13.29	0.11
Hypertension	47 (66)	38 (64)	9 (75)	1.66	0.40–6.80	0.74
Hyperlipidemia	29 (41)	22 (37)	7 (58)	2.35	0.67–8.33	0.21
Obesity	43 (60)	36 (60)	7 (58)	0.93	0.27–3.29	< 0.99
Current or former smoker	19 (26)	18 (30)	1 (8)	0.21	0.03–1.77	0.16
Postmenopausal	42 (58)	33 (55)	9 (75)	2.45	0.60–9.98	0.20
Family history of cancer	18 (25)	15 (25)	3 (25)	0.98	0.23–4.09	< 0.99
Received chemotherapy	11 (15)	6 (10)	5 (42)	6.43	1.55–26.71	0.02
Race						
White	5 (7)	3 (5)	2 (5)	REF	REF	0.07
Black	38 (53)	33 (55)	5 (55)	0.23	0.03–1.72	
Hispanic	15 (21)	11 (18)	4 (18)	0.55	0.07–4.56	
Asian	2 (3)	1 (2)	1 (2)	1.50	0.06–40.63	
Unknown/declined	12 (17)	12 (20)	0 (20)	N/A	N/A	
Non-white race	67 (93)	57 (95)	10 (83)	0.26	0.04–1.78	0.20
Nulliparity	18 (25)	16 (27)	2 (17)	0.55	0.11–2.79	0.72
Histologic subtype						
Adult	69 (96)	58 (97)	11 (92)	REF	REF	0.43
Juvenile	3 (4)	2 (3)	1 (8)	2.64	0.22–31.65	
Tumor size (cm)[b]	9 (5, 14)	8 (5, 13)	11 (6, 17)	–	–	0.17
Cancer stage						
IA	51 (71)	45 (75)	6 (50)	REF	REF	0.19
IB	2 (3)	1 (2)	1 (8)	7.50	0.41–136.27	
IC	15 (21)	11 (18)	4 (33)	2.72	0.65–11.36	
II	1 (1)	1 (2)	0 (0)	N/A	N/A	
IIIC	3 (4)	2 (3)	1 (8)	3.75	0.29–47.89	
> Stage I disease	4 (5.6)	3 (5)	1 (8)	1.73	0.16–18.17	0.53
Surgical Approach						
Abdominal	47 (66)	36 (60)	11 (100)	N/A	N/A	0.01
Laparoscopic/robotic	24 (34)	24 (40)	0 (0)	N/A	N/A	
Adnexal surgery						
BSO	52 (72)	40 (67)	11 (92)	REF	REF	0.39
USO	19 (26)	19 (32)	1 (8)	0.21	0.03–1.79	
Unilateral cystectomy	1 (1)	1 (1)	0 (0)	N/A	N/A	
Hysterectomy	49 (68)	37 (62)	11 (92)	6.84	0.83–56.53	0.05
Pelvic lymph node dissection	32 (46)	25 (42)	7 (70)	3.27	0.77–13.88	0.17
Para-aortic lymph node dissection	25 (35)	19 (32)	6 (60)	3.24	0.82–12.83	0.15
Complete staging	26 (36)	19 (32)	7 (58)	3.02	0.85–10.76	0.10
Partial staging	40 (56)	32 (53)	8 (67)	1.75	0.48–6.44	0.53
Fertility sparing[c]	16 (62)	15 (65)	1 (33)	0.27	0.02–3.41	0.54

[a] Continuous data reported as median (interquartile range). Categorical data are presented as N (%) associated with odds ratios and 95% confidence intervals.
[b] Tumor size observations missing for two patients with recurrent or progressive disease.
[c] Based on the 26 patients who were eligible for fertility sparing surgery (< 50 years old and pre-menopausal).

Table 2
Pregnancy outcomes in patients undergoing fertility sparing surgery for ovarian granulosa cell tumors (N = 16).

Patient #	Age	Surgery performed	# Pregnancy	# Live birth	Recurrence
1	30	LSC USO	2	2	No
2	41	LSC USO	Unavailable	Unavailable	No
3	31	LSC USO	0	0	No
4	43	LSC USO	Unavailable	Unavailable	No
5	35	Exlap, USO, PPALND	0	0	No
6	40	LSC USO	Unavailable	Unavailable	No
7	26	LSC USO, PPALND	0	0	No
8	32	RA USO, contralateral ovarian cystectomy	1	1	No
9	43	LSC USO	0	0	No
10	24	LSC ovarian cystectomy	Unavailable	Unavailable	No
11	38	LSC USO	0	0	Yes
12	25	RA USO, PLND, peritoneal biopsy, omental biopsy	0	0	No
13	21	Exlap, USO, omental biopsy	1	1	No
14	38	Exlap, USO, omental biopsy	1	1	No
15	34	LSC USO	1	1	No
16	35	Exlap, USO	1	1	No

Please note the following abbreviations listed: LSC- laparoscopic, USO- unilateral salpingoophorectomy, Exlap- exploratory laparotomy, PPALND-pelvic and para-ortic lymph node dissection, RA- robotic assisted, PLND- pelvic lymph node dissection.

Table 3
Chemotherapy regimens used for adjuvant treatment of recurrent or advanced stage granulosa cell tumors (N = 7).

Patient #	Stage	Complete surgical resection	Adjuvant treatment received	Recurrence	Time to recurrence (months)	Other synchronous cancer
1	IIIC	Yes	BEP	Yes	4	No
2	II	Yes	Carbo/taxol, RT	No	–	No
3	IA	Yes	Ifosfamide	No	–	Uterine carcinosarcoma
4	IA	Yes	Carbo/taxol, RT	No	–	Uterine serous carcinoma
5	IA	Yes	BEP	No	–	No
6	IA	Yes	BEP	No	–	No
7	IIIC	Yes	Cisplatin/paclitaxel x1 then Carbo/taxol due to neuropathy	No	–	No

Please note the following abbreviations listed: BEP-bleomycin, etoposide, cisplatin, Carbo/taxol-carboplatin, paclitaxel, RT-radiation therapy, n/a-not applicable.

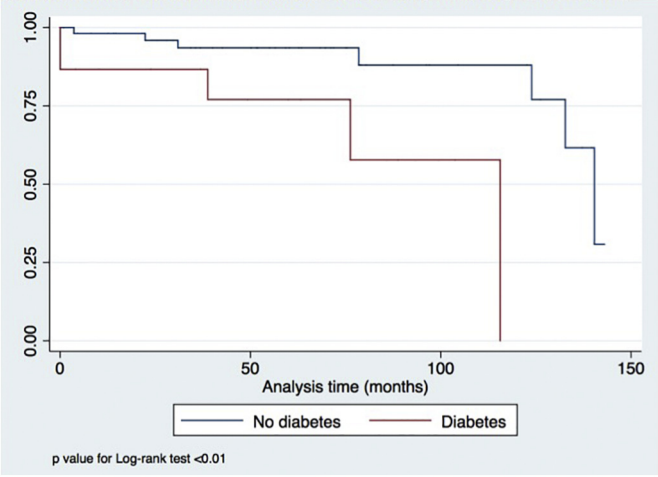

Fig. 1. Kaplan Meier survival curve examining progression-free survival stratified by diagnosis of diabetes.

our findings and that reported by Suri et al., could be that the later study focused on early stage disease in their analysis whereas our analysis included both early and late stage disease. Additionally, one could infer that perhaps the difference could be a result of the distinction in racial profile of the two patient cohorts with 76% of the patients in our cohort being non-white and 41% of the patients in the later study.

In our study, fertility sparing surgery was performed in 22% of patients, 1 of whom has had multiple disease recurrences, which have been successfully salvaged with cytotoxic chemotherapy and surgical debulking. These findings support the data reported by a SEER study, which demonstrated equivalent survival outcomes for women with stage I-II ovarian GCT who underwent fertility sparing surgery compared with those who underwent definitive surgery with hysterectomy (Brown et al., 2009). In our cohort, 26% of patients had concurrent endometrial hyperplasia/carcinoma and 5 patients had breast cancer. This is consistent with prior literature, which reports concurrent endometrial pathology in 25–30% of patients and increased risk of breast cancer in women with GCTs (Hammer et al., 2013; Meisel et al., 2015; van Meurs et al., 2013). Authors have proposed that a hyperestrogenic state develops secondary to upregulation of aromatase by a mutant FOXL2 gene (C134W) found in > 90% of adult-type GCTs, resulting in endometrial and breast pathology (Shah et al., 2010; Fleming et al., 2010).

Our data differs from the existing literature as our patient cohort is enriched with racial minorities. Seventy-six percent of our cohort was non-white. In comparison, 57% and 72% of patients in a 2014 Cochrane review (n = 535) and a National Cancer Database study (n = 2680), respectively, were white (Seagle et al., 2017; Gurumurthy and Shanbhag, 2014). To the best of our knowledge, no other authors have reported the impact of diabetes mellitus on progression free survival in such a minority catchment patient population; 58.5% of patients reported by Suri et al. were Caucasian (Suri et al., 2013). Additionally, in a study of 58 women with sex cord-stromal tumors that underwent lymph node sampling, Brown et al. found no cases of nodal metastases (Brown et al., 2009). In our cohort, 1 of 32 patients that underwent lymph node sampling had nodal metastases. On review of that patient's pre-operative imaging, there was no pre-operative concern for nodal spread. However, we did not find an association between complete surgical staging and survival. This differs from the results of a recent retrospective study of 2680 women with ovarian GCTs, which reported an increased risk of death (HR 1.77, 95% CI 1.30–2.41) in those that underwent incomplete surgical staging (Seagle et al., 2017). These authors report robust survival, surgical staging, and chemotherapy data and performed matched cohort analyses and propensity scores to reduce the effects of confounding factors, including chemotherapy exposure. However, they define incomplete surgical staging as surgery without bilateral salpingo-oophorectomy and hysterectomy whereas we also required lymphadenectomy and omental sampling to define complete surgical staging.

One shortcoming of this study is the retrospective study design. Additionally, due to the rare nature of ovarian GCTs, as well as low rate and late onset of recurrent disease, our study is limited by small numbers and few recurrences, which prevents multivariate modeling to evaluate the impact of clinicopathologic variables on the risk of recurrence. In a 10-year study period, we identified only 72 patients with GCT and observed only 11 recurrences. In comparison, the largest cohort of GCTs reported 240 cases over a 56-year study period (Bryk et al., 2015). Moreover, as failure in our cohort was defined as disease progression or recurrence and was calculated from date of surgery to documented date of failure. Patients were censored at date of last follow-up or death unrelated to disease. As no patients died from disease in the cohort, we are unable to make any conclusions regarding overall or disease specific survival and thus unable to demonstrate a clear association between diabetes and survival outcomes.

In conclusion, we found that diabetes mellitus is associated with worse progression free survival in women with ovarian granulosa cell tumors. These findings are worthy of further investigation in multi-institutional studies or meta-analyses to investigate how lifestyle and behavioral modification may impact progression free survival in women with GCTs (Suri et al., 2013). Although the association between endometrial cancer and granulosa cell tumors is well described, we identified higher than expected rates of breast cancer in our cohort. Providers should be diligent about breast cancer screening in GCT survivors. Finally, while we observed no deaths related to disease, we did observe one death secondary to bleomycin-induced pulmonary toxicity. Given the lack of definitive data demonstrating a survival benefit with adjuvant therapy, providers should strongly consider the risks of chemotherapy related adverse events.

Author contributions

Dr. Tymon-Rosario, Dr. Miller, and Dr. Nevadunsky conceived of the presented ideas and designed the study. Dr. Tymon-Rosario and Dr. Miller abstracted the data from the medical records and wrote the manuscript in consultation with Dr. Gressel and Dr. Nevadunsky. Dr. Gressel aided with the statistical analysis. Input from all of the authors was used for the final editions to the manuscript.

Acknowledgements

The research described was supported by NIH/National Center for Advancing Translational Science (NCATS) Einstein- Montefiore CTSA Grant Number UL1 TR001073.

References

Brown, J., Sood, A.K., Deavers, M.T., Milojevic, L., Gershenson, D.M., 2009 Apr. Patterns of metastasis in sex cord-stromal tumors of the ovary: can routine staging lymphadenectomy be omitted? Gynecol. Oncol. 113 (1), 86–90.

Bryk, S., Färkkilä, A., Bützow, R., Leminen, A., Heikinheimo, M., Anttonen, M., Riska, A., Unkila-Kallio, L., 2015. Clinical Characteristics and Survival of patients with an Adult-Type Ovarian Granulosa Cell Tumor. Int. J. Gynecol. Cancer 25 (1), 33–41.

Colombo, N., Parma, G., Zanagnolo, V., et al., 2007. Management of ovarian stromal cell tumors. J. Clin. Oncol. 25, 2944.

Fleming, N.I., Knower, K.C., Lazarus, K.A., Fuller, P.J., Simpson, E.R., Clyne, C.D., 2010. Aromatase is a direct target of FOXL2: C134W in granulosa cell tumors via a single highly conserved binding site in the ovarian specific promoter. PLoS ONE 5.

Frausto, S.D., Geisler, J.P., Fletcher, M.S., et al., 2004. Late recurrence of juvenile granulosa cell tumor of the ovary. Am. J. Obstet. Gynecol. (1), 366.

Gurumurthy, M., Shanbhag, Bryant A., 2014 Apr. Effectiveness of different treatment modalities for the management of adult-onset granulosa cell tumours of the ovary (primary and recurrent). In: Cochrane Database of Systematic Review.

Hammer, A., Lauszuz, F.F., Peterson, A.C., 2013 Dec. Ovarian granulosa cell tumor and increased risk of breast cancer. Acta Obstet. Gynecol. Scand. 92 (12), 1422–1425.

Malmstrom, H., Hogberg, T., Risberg, B., et al., 1994. Granulosa cell tumors of the ovary: prognostic factors and outcome. Gynecol. Oncol. 52, 50–55.

Meisel, J.L., Hyman, D.M., Jotwani, A., Zhou, Q., Abu-Rustum, N.R., Iasonos, A., Pike, M.C., Aghajanian, C., 2015. The role of systemic chemotherapy in the management of Granulosa cell tumors. Gynecol. Oncol. 136 (3), 505–511.

Miller, B.E., Barron, B.A., Wan, J.Y., et al., 1997. Prognostic factors in adult granulosa cell tumor of the ovary. Cancer 79, 1951.

Seagle, B.L., Ann, P., Butler, S., Shahabi, S., 2017 Aug. Ovarian granulosa cell tumor: A National cancer database study. Gynecol. Oncol. 146 (2), 285–291.

Shah, S.P., Köbel, M., Senz, J., Morin, R.D., Clarke, B.A., Wiegand, K.C., Leung, G., Zayed, A., Mehl, E., Kalloger, S.E., Sun, M., Giuliany, R., Yorida, E., Jones, S., Varhol, R., Swenerton, K.D., Miller, D., Clement, P.B., Crane, C., Madore, J., Provencher, D., Leung, P., Defazio, A., Khattra, J., Turashvili, G., Zhao, Y., Zeng, T., Glover, J.N., Vanderhyden, B., Zhao, C., Parkinson, C.A., Jimenez-Linan, M., Bowtell, D.D., Mes-Masson, A.M., Brenton, J.D., Aparicio, S.A., Boyd, N., Hirst, M., Gilks, C.B., Marra, M., Huntsman, D.G., 2010. Mutation of FOXL2 in granulosa –cell tumors of the ovary. N. Engl. J. Med. 360 (260), 2279–2719.

Shai, I., Jiang, R., Manson, J.E., et al., 2006. Ethnicity, obesity, and risk of type 2 diabetes in women: a 20-year follow up study. Diabetes Care 29, 1585.

Suri, A., Carter, E.B., Horowitz, N., Denslow, S., Gehrig, P.A., 2013. Factors Associated with an increased risk of Recurrence in Women with Ovarian Granulosa Cell Tumors. Gynecol. Oncol. 131 (2), 321–324.

van Meurs, H.S., Bleeker, M.C., van der Velden, J., et al., 2013. 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 23 (8), 1417.