

May Lymphadenectomy be Omitted in Granulosa Cell Tumors of the Ovary?

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Abstract

Granulosa cell tumors (GCTs) of the ovary are rare tumors and they are generally detected in early stages with a favorable prognosis. However, the controversies over the extend of surgery are still judging the surgical management. We retrospectively evaluated demographic and clinical variables of granulosa cell tumors of the ovary with probable prognostic factors to identify the clinicopathological features. Women with adult type granulosa cell tumor pathology result between March 2007 and April 2013 were evaluated retrospectively using computerized database of the institution. Age, stage, menopausal status, parity, clinical presentation, surgical procedures, histopathologic results, preoperative tumor markers, tumor diameter and laterality were the reviewed parameters. Patients were staged according to the International Federation of Gynecology and Obstetrics (FIGO) staging system for ovarian tumors that was revised in 2014. A total of 40 patients were retrospectively evaluated. We further categorized patients as stage 1A and more advanced stage disease. Twenty-seven patients (67.5%) were within Stage 1A disease and 13 (32.5%) patients had more advanced stage of disease. Only one patient had retroperitoneal lymph node involvement and recurred 2 years after the completion of the chemotherapy, and died of disease after 2 years from recurrence. Since the risk of unintended complications and morbidity, which is related with lymph node dissection, the rare incidence of lymph node involvement should be kept on mind. So that omitting lymphadenectomy could be an option for GCTs if a low mitotic index ($<5/10\text{HPF}$), negative LVSI or mild atypia with a mass not larger than 10 cm.

Keywords: Granulosa cell tumors, lymph node dissection, staging surgery

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Introduction

Granulosa cell tumors (GCTs) of the ovary are rare tumors that represent less than 5% of all ovarian carcinomas. However, more than 70% of all sex-cord stromal tumors are comprised of granulosa cell tumors [1]. They originate from the granulosa cells, which secrete mainly estradiol and have two distinct forms; adult (95%) and juvenile (5%). By the effect of estrogen; abnormal uterine bleeding or precox puberty can be the presenting symptom for these patients [2]. Unlike epithelial ovarian cancer, they are generally detected in early stages with a favorable prognosis [3]. The slow growing nature of these tumors with late recurrences and prolonged survival disclose the need for the individualization of the management and it is mainly based on the slow growing nature of the tumor [4]. Despite the importance of surgical evaluation and staging, the residual disease after the initial surgery decreases overall survival (OS) [5]. The controversies over the extend of the surgery are still judging the surgical management. By the rarity of these tumors, much of the studies are with limited patient groups. We retrospectively evaluated demographic and clinical variables of granulosa cell tumors of the ovary with probable prognostic factors to identify the clinicopathological features.

Materials and Methods

Women with adult type granulosa cell tumor pathology result between March 2007 and April 2013 were evaluated retrospectively using computerized database of the institution. All the patients had undergone exploratory laparotomy with proper surgical staging except two patients who refused further surgical intervention after hysterectomy with bilateral salpingo-oophorectomy for benign indications. After approval of local institutional ethical board, we retrieved the medical records of patients from the computerized database of Gynecologic Oncology Department at Zekai Tahir Burak Women's Health Education and Research Hospital. Age, stage, menopausal status, parity, clinical presentation, surgical procedures, histopathological results, preoperative tumor markers, tumor diameter and laterality were the reviewed parameters. Patients were staged according to the International Federation of Gynecology and Obstetrics (FIGO) staging system for ovarian tumors that was revised in 2014. Initial surgical procedure was total abdominal hysterectomy, bilateral salpingo-oophorectomy, pelvic-paraaortic lymph node dissection and omentectomy with peritoneal

washings on the other hand fertility sparing surgery as a conservative management was composed of unilateral salpingo-oophorectomy, pelvic-paraaortic lymph node dissection and omentectomy with peritoneal washings. BEP (bleomycin, etoposide, cisplatin) and CP (carboplatin, paclitaxel) were the administered chemotherapy protocols.

Statistical analyses were performed with the SPSS (version 21 for Macintosh; SPSS, Chicago, IL). Normal distribution of the continuous variables was evaluated by Kolmogorov-Smirnov test. Non-parametric Mann Whitney-U test was used for the comparison of continuous variables without normal distribution. Pearson-Chi square test was used to compare the categorical variables. p value <0.05 was set for statistical significance.

Results

A total of 40 patients were retrospectively evaluated. Mean age of patients was 51.13 ± 15.09 (range: 24-82) and mean parity number was 3.1 ± 1.9 . Abdomino-pelvic pain (n=19, 47.5%) was the most common presenting symptom and totally 16 (40%) patients were postmenopausal.

Mean CA-125, Ca-15.3, CA-19.9 levels were found within normal limits; 17.5 ± 13.7 , 11 ± 9 and 15.6 ± 8.7 IU/mL respectively. Mean tumor diameter was 6.8 ± 3.9 cm. None of the ovarian masses were bilateral. Mean dissected pelvic and paraaortic lymph node number was 43.5 ± 21.2 and 22.9 ± 10.9 respectively.

We further categorized patients as stage 1A and more advanced stage disease. Twenty-seven patients (67.5%) were within Stage 1A disease and 13 (32.5%) patients had more advanced stage of disease. Stage 1A patients were significantly younger than the other group; mean age of groups was 47.6 ± 12.7 and 58.5 ± 17.3 respectively. Moreover stage 1A patients were significantly premenopausal; 19 (47.5%) versus (vs.) 5 (12.5%) patients. On the other hand we did not detect a significant difference between parity, serum CA-125, Ca-15.3, CA-19.9 and CEA levels, Histo-pathologic evaluation revealed no significant difference between mitotic figures per 10 HPF (4 ± 4.5 vs. 3.7 ± 2) and presence of nuclear atypia (mild or moderate; 21 (52.5%) vs 6 (15%) and 6 (15%) vs. 7 (17.5%) respectively). Number of patients with lymphovascular space invasion (LVSI) was also not significantly different

between the groups (Table 1). BEP protocol was the most commonly applied chemotherapy regimen (12 patients-30% received BEP, one patient-2.5% received CP).

Table 1. Demographic, clinical and histopathologic characteristics of patients

	Stage 1A	Stage 1B-3B	Total	P
Age (years; mean $\pm$ SD, Number of patients)	47.6 $\pm$ 12.7	58.5 $\pm$ 17.3	51.1 $\pm$ 15	<0.05 ¹
21-30 years	2 (5%)	1 (2.5%)	3 (7.5%)	
31-40 years	7 (17.5%)	1 (2.5%)	8 (20%)	
41-50 years	8 (20%)	2 (5%)	10 (25%)	
51-60 years	6 (15%)	3 (7.5%)	9 (22.5%)	
61-70 years	2 (5%)	1 (2.5%)	3 (7.5%)	
71-80 years	2 (5%)	3 (7.5%)	5 (12.5%)	
81-90 years	0	2 (5%)	2 (5%)	
Menopausal status (Number of patients)				<0.05 ¹
Premenopausal	19 (47.5%)	5 (12.5%)	24 (60%)	
Postmenopausal	8 (20%)	8 (20%)	16 (40%)	
Parity (mean $\pm$ SD)	2.59 $\pm$ 1.7	4.15 $\pm$ 2	3.1 $\pm$ 1.9	0.19 ²
Serum Ca-125 levels (U/ml; mean $\pm$ SD)	14.6 $\pm$ 10.6	23.5 $\pm$ 17.6	17.5 $\pm$ 1.7	.078 ²
Serum Ca-15.3 levels (U/ml; mean $\pm$ SD)	16.6 $\pm$ 9	13.4 $\pm$ 7.9	15.6 $\pm$ 8.7	.177 ²
Serum Ca-19.9 levels (U/ml; mean $\pm$ SD)	9.7 $\pm$ 7.4	13.8 $\pm$ 11.5	11 $\pm$ 9	.264 ²
Serum CEA levels (ng/ml; mean $\pm$ SD)	1.1 $\pm$ 0.6	0.9 $\pm$ 0.4	1.08 $\pm$.059	1 ²
Number of mitotic figures per 10 HPF (mean $\pm$ SD)	4.0 $\pm$ 4.5	3.7 $\pm$ 2	3.9 $\pm$ 3.9	.549 ²
LVSI (Number of patients)				.056 ¹
Present	1 (2.5%)	3 (7.5%)	4 (10%)	
Not-present	26 (65%)	10 (25%)	36 (90%)	
Presence of nuclear atypia (Number of patients)				.261 ¹
Mild	21 (52.5%)	6 (15%)	27 (67.5%)	
Moderate	6 (15%)	7 (17.5%)	13 (32.5%)	

SD: Standard Deviation; HPF: High Power Field; LVSI: Lympho-vascular space invasion

¹Chi-square test, ² Mann-Whitney-U Test

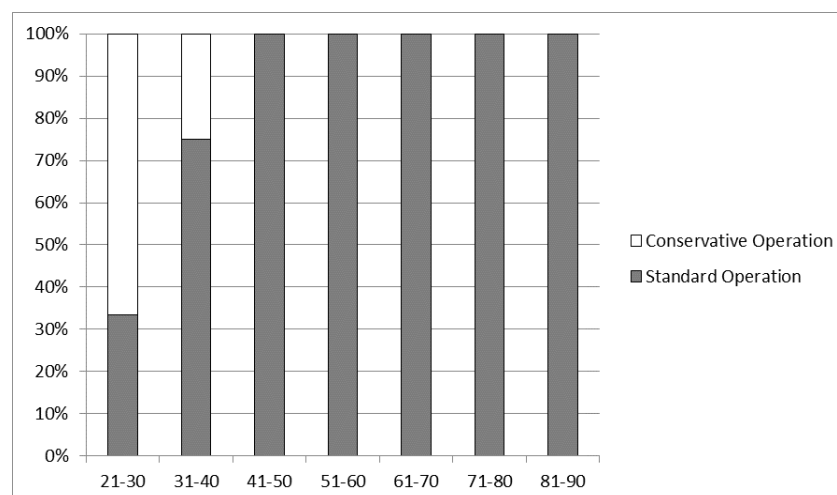


Figure 1. Distribution of surgery type by age; Gray column: Standard operation, white column: conservative operation. (standard + conservative operation = 100%)

Fertility sparing surgery as a conservative management was the performed surgical procedure only for stage 1A patients, predominantly between 21-30 years of age (Figure 1). We performed a complementary surgical staging procedure for 9 patients after postoperative histological diagnosis of unilateral adnexectomy or ovarian cystectomy. We did not detect any lymphatic dissemination within these patients; mean mitotic count was 3.7/10 HPF; there were not any LVSI and two patients were with moderate atypia. Only one patient was having a mass of 11cm in diameter and the mean mass diameter was 5cm. All of our patients had a complete debulking surgery without any residual disease and we did not detect any recurrence or death during the follow up period; in 6 years time.

Eight patients showed endometrial hyperplasia without atypia, whereas 2 patients had complex endometrial hyperplasia with atypia in the pathological sections of the endometrium.

2 patients died during the follow-up period. Only one patient had retroperitoneal lymph node involvement and recurred 2 years after the completion of the chemotherapy, and died of disease after 2 years from recurrence. The other patient died three months after the initial surgery, during the chemotherapy period because of febrile neutropenia.

Discussion

There is not a consensus regarding the optimal management and follow-up of GCTs because of the rare prevalence of these tumors. These low-grade, relatively good prognostic tumors are generally seen in the perimenopausal period especially in the fifth decade. Abdominal pain and vaginal bleeding are the most common presenting symptoms. Although most of the patients in the premenopausal period are symptomatic; the symptom incidence in the postmenopausal period is fewer [6, 7]. Nevertheless in symptomatic postmenopausal patients, bleeding is the most common symptom [3]. These tumors characteristically secrete estrogen and endometrial pathologies should be kept on mind for these patients. So that a concurrent endometrial pathology; hyperplasia or carcinoma could be detected by the effect of estrogen. Any type of hyperplasia could be detected in 25-50% of cases and also endometrial adenocarcinoma in 5-10% of cases; these endometrial carcinomas are generally well-differentiated, early stage carcinomas [8]. For our patient group no endometrial carcinoma had been detected. We found similar results with the described data in the literature; that the

mean age was 51.13 ± 15.09 , abdominopelvic pain was the most common symptom and most of the patients were in stage 1A disease with a low malignant potential.

For GCTs we found tumor marker levels in normal range. This was previously declared in the literature. Lee et al. [6] found elevated CA-125 levels in 9.8% of patients. Huang et al. [9] also found similar results for preoperative CA-125 levels, on the other hand in the follow-up period of these tumors CA-125 might be important. They reported elevated CA-125 levels for patients with a recurrent disease. The tendency towards bleeding in GCTs because of the vascular nature might cause peritoneal irritation thus elevated CA-125 levels could be detected. Despite the hormonally active structure of these tumors, they did not find a correlation with preoperative estrogen levels and prognosis. Inhibin is mainly formed in granulosa cells and it is within elevated levels, and serum levels are correlated with both preoperative tumor size and recurrent diseases [10].

Most studies state stage at diagnosis, age, nuclear atypia, mitotic index and residual disease after initial surgery as the most important prognostic factors in univariate analysis [3, 11, 12]. Khosla et al. [13] found stage as the most significant predictor of prognosis. Patients with early stages especially stage 1 had better overall survival when compared to more advanced stages. We categorized patients as stage 1A and higher than stage 1A disease. 27 patients were within stage 1A. Age and menopausal status was the only significant parameters between groups. Tumor marker levels, number of mitotic figures per 10 HPF, LVSI status and presence of nuclear atypia was not significantly different between the groups. Mangili et al. [11] found older age at diagnosis (>50 years), advanced stage disease and residual tumor after surgery in association with poor prognosis. Lee et al. [14] found early stage disease and residual tumor after surgery as the important and significant predictors of prognosis.

Suri et al. [12] did not find any difference between tumor size (>5 cm), mitotic rate ($>4/10$ hpf) and intraoperative tumor rupture for the risk of recurrence even though these were mostly stage 1 patients. Many studies showed greater tumor size with the increased risk of recurrence. Sun et al. [15] reported the cut off limit of tumor diameter for tumor recurrence as 13.5cm. Chan et al. [16] reported tumor size >10 cm as an important prognostic finding for recurrence. Most of our patients were with a tumor diameter of ≤ 5 cm ($n=22, 55\%$); only 6 (15%) patients were having a mass between 11-15cm. The risk of recurrence for a mitotic

index $<5/10\text{HPF}$ was not significant [13], in our study we found the mean mitotic index for stage 1A and higher than 1A group, 4 ± 4.5 and 3.7 ± 2 respectively; there were not any significant difference between the groups. Additionally atypia more than mild form increases the risk of recurrence moreover a positive LVSI should also arise the risk; our patient group was generally with mild atypia ($n=27$, 67.5%) and there were not any difference between the groups for mild and moderate atypia. Detected rate of LVSI for our patients was also low; one patient in stage 1A and 3 patients in higher than stage 1A group. Any significant difference for LVSI between the groups was not detected. We did not detect any recurrence or death during the follow up period; in 6 years time.

The prognostic value of systematic surgical staging in GCTs is controversial. Shim et al. [7] did not find an association between disease free survival and lymphadenectomy. However they offered the importance of omentectomy and performing multiple peritoneal biopsies to detect extra-pelvic disease. The low incidence of detecting lymph node metastasis in GCTs directed many gynecological oncologists to omit lymphadenectomy procedure [17, 18]. Nevertheless the metastatic disease would have different ways of tumor dissemination thus a multivisceral operative approach with extensive peritonectomy, intestinal and diaphragmatic resection, splenectomy and partial hepatectomy/pancreatectomy in addition to lymphadenectomy should be performed if needed [19]. Since the disease related mortality rate is more than 40% if an extra-ovarian spread is present [20] and the recurrence rate for stage 1 disease and advanced stage disease is 5% and 33% respectively [21]; a surgical debulking without a residual disease could improve survival rates. We detected only one patient (2.5%) with a lymph node metastasis and one patient with an omental metastasis. For GCTs the low detection rate of lymphatic dissemination might prevent gynecological oncologists from unnecessary surgical procedures since the most common stage was 1A. We performed a complementary surgical staging procedure to 9 patients after unilateral adnexal removal. We did not detect any lymphatic dissemination within these patients; mean mitotic count was $3.7/10\text{HPF}$; there were not any LVSI and two patients were with moderate atypia. Only one patient had a mass of 11cm in diameter and the mean mass diameter was 5cm for these patients. So that the role of lymphadenectomy as a complementary surgery or during the initial cytoreductive surgery is debated.

Conclusion

GCTs are rare neoplasms of ovarian stroma with a low recurrence rate and long overall survival. They are generally detected in early stages without extra-pelvic metastasis. Younger age during the surgery should be a predictor of early stage disease. Since the risk of unintended complications and morbidity, which is related with lymph node dissection, the rare incidence of lymph node involvement should be kept on mind. So that omitting lymphadenectomy could be an option for GCTs if a low mitotic index ($<5/10\text{HPF}$), negative LVSI or mild atypia with a mass not larger than 10 cm.

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