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Full Length Article

Retroperitoneal nodal metastasis in primary adult type granulosa cell tumor of the ovary: Can routine lymphadenectomy be omitted?

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ABSTRACT

Objective: To investigate the incidence of retroperitoneal lymph node metastasis among patients with primary adult type granulosa cell tumor (AGCT) of the ovary.
Study design: Between January 1982 and February 2017, patients with a pathological diagnosis of AGCT were identified. Clinical and pathological data were obtained from database records.
Results: A total of 151 patients with primary AGCT were identified with a mean age of 47.8 years (range, 17–91 years). 98 patients (64.9%) had stage IA, 24 (15.9%) had stage IC, 4 (2.6%) had stage IIB, 2 (1.3%) had stage IIIB, 6 (4.0%) had stage IIIC disease according to International Federation of Gynecology and Obstetrics (FIGO) 1988 criteria. In the remaining 17 patients (11.3%), primary stage was not detected. In 134 (88.7%) patients, pelvic and *para*-aortic lymphadenectomy was performed at primary staging surgery depending on the frozen section analysis or at re-staging surgery following initial diagnosis. In these patients, six (4.5%) of them had pelvic or paraaortic lymph node metastasis. The median number of lymph nodes removed was 43 (range, 10–96 lymph nodes).
Conclusion: Lymph node metastasis in initially staged AGCT is rare. Routine pelvic and paraaortic lymph node dissection may be omitted in these patients.

Introduction

Granulosa cell tumors (GCTs) are malign tumors of the ovarian stroma and account for about 5% of all ovarian malignancies [1]. These tumors are classified into 2 different sub-types based on clinical and pathological features. The adult granulosa cell tumor (AGCT), which occurs most commonly in *peri*-menopausal and post-menopausal women, comprises most of these (95%) neoplasms. The juvenile GCTs (JGCTs) are rare form of GCTs (5%), and mainly seen in prepubertal girls and young women.

In contrast with epithelial ovarian cancer (EOC), GCTs are diagnosed in early-stage disease; the tumors have a good prognosis with a long overall survival. But, even after decades of treatment, recurrences may occur even in early stage disease [2]. Because of this clinical nature, GCTs are accepted as low-grade malignancies.

After a diagnosis of GCT, surgical excision is the mainstay of the treatment [3]. Although the surgical procedure of GCT includes the same principles (cytology, peritoneal assessment/biopsies, omentectomy, surgical excision of the suspected lesions) suggested for the EOC, there are queries about the necessity of the lymph node dissection, as the incidence of nodal involvement in GCT is very low [3,4]. On the other hand, some believe in lymph node dissection at initial staging because of the literature reporting recurrences in the retroperitoneum [5]. Due to rarity and indolent course of the disease.

there are no randomized, prospective studies comparing different treatment modalities. In the present study, we aimed to determine the clinico-pathological characteristics of AGCT in newly diagnosed patients and analyze the frequency of nodal involvement among these tumors.

Materials and methods

After Institiutional Review Board approval was obtained for this study, records of the consecutive patients between January 1982 and February 2017 who underwent surgery at our clinic and whose final pathological diagnosis were AGCT were identified by using our database at the Department of Obstetrics and Gynecology, Gynecological Oncology Unit, Hacettepe University Hospital. All 6

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cases of JGCT were excluded from the study. Pathology and laboratory results were thoroughly reviewed. Collected data included patient's age, menopausal status, presenting symptom, serum CA 125 level, operative procedure, and final pathological report. Disease stage was determined according to International Federation of Obstetrics and Gynecology (FIGO) 1988, staging system. Staging procedure included cytology, peritoneal biopsies, infracolic omentectomy, pelvic and *para*-aortic lymph node dissecton (PPLND), surgical excision of the suspected ovarian mass. It was necessary to have all these surgical elements to be able to say complete surgical staging. Staging procedures were performed at initial operation depending on the frozen section analysis (primary staging) or at second operation (re-staging) following the initial diagnosis within one month. Fertility sparing surgery was defined as preservation of at least one ovary and the uterus. Non-conservative staging was defined as a staging procedure including hysterectomy and bilateral salpingo-oofor-ectomy (HBSO).

Statistical analyses were performed using Statistics Package for Social Sciences version 16.0 (SPSS,Chicago, IL, USA).

Results

A total of 151 patients with primary AGCT were identified with a mean age of 47.8 years (range, 17–91 years). Clinical and pathological characteristics of patients were shown in Table 1. Sixty-nine of the patients (45.7%) were postmenopausal. The main presenting symptom was abnormal uterine bleeding in 71 patients (47.0%), pelvic pain in 31 patients (20.5%), abdominal distention in 22 patients (14.5%), acute abdominal pain in 6 patients (4.0%), and asymptomatic in 21 patients (14.0%). A high serum CA 125 level (>35 U/ml) was detected in 28 women (18.5%).

Most of the patients (n = 118, 78.1%) underwent primary staging surgery, of which 13 patients (8.6%) had fertility preserving procedure. All of the re-staged patients (n = 16, 10.6%) did not maintain fertility. Totally, in 134 (88.7%) patients, staging procedure including PPLND was performed. In these patients, six (4.5%) of them had pelvic or paraaortic lymph node metastasis. The median number of lymph nodes removed was 43 (range, 10–96 lymph nodes).

According to final pathological diagnosis, tumor was bilateral in only 4 (2.6%) patients. There was no endometrial pathology in 92 (60.9%) patients. Co-existing endometrial pathologies were endometrial hyperplasia in 58 patients (38.4%), and carcinoma in one patient (0.7%). Following the review of pathological results, the final stages were found to be IA (64.9%) in 98 patients, IC (15.9%) in 24 patients, IIB (2.6%) in 4 patients, IIIB (1.3%) in 2 patients, and IIIC (4.0%) in 6 patients. None of the patients had stage IV disease. In the remaining 17 patients (11.3%), primary stage was not detected,

Table 1
Clinical and pathological characteristics of patients.

Characteristics	n (%)
Age, year	
<60	118 (78.1)
≥60	33 (21.9)
Menopausal status	
Premenopausal	82 (54.3)
Postmenopausal	69 (45.7)
Symptoms	
Abnormal uterine bleeding	71 (47.0)
Pelvic pain	31 (20.5)
Abdominal distension	22 (14.5)
Acute abdominal pain	6 (4.0)
Asymptomatic adnexal mass	21 (14.0)
CA-125 level	
Elevated	28 (18.5)
Norma	55 (36.4)
Not assessed	68 (45.0)
Ovarian tumor	
Unilateral	147 (97.4)
Bilateral	4 (2.6)
Surgical Procedure	
Primary fertility sparing staging	13 (8.6)
Primary non-conservative staging	105 (69.5)
Re-staging	16 (10.6)
Not staged (only tah + bso)	17 (11.3)
Surgical Stage	
I	122 (80.8)
II	4 (2.6)
III	8 (5.3)
Not staged	17 (11.3)
Endometrial Pathology	
Normal	92 (60.9)
Hyperplasia	58 (38.4)
Carcinoma	1 (0.7)
Lymph Node Involvement	
Yes	6 (4.5)
No	128 (95.5)
Not dissected	17

Comment

AGCTs are the most common sex cord stromal tumors (SCSTs) of the ovary and constitute less than 5% of all ovarian malignancies [6]. Due to granulosa cells forming the tumor and accompanying stromal component, patients usually present with complaints of hormone (especially estrogen) production, such as abnormal uterine bleeding or endometrial hyperplasia. In our study, as in the literature, the most common symptom was abnormal uterine bleeding [5,6]. Ottolina et al. investigated the issue of routine endometrial sampling in patients with AGCT. At the time of surgery, hyperplasia was found in 29.2% of the patients, whereas endometrial cancer occurred in 7.5% of patients. They concluded that endometrial sampling should be performed in symptomatic women at least 40 years of age [7]. In our study, the rate of endometrial hyperplasia was in accord with the literature, whereas endometrial cancer ratio (0.7%) was found to be low compared to the literature [7,8].

It is necessary to know which methods have been used in the diagnosis of GCT. Mutation of FOXL2 seen in 97% of AGCT may be pathognomonic for AGCT. In the study of Bryk et al., the original diagnosis of AGCT was confirmed in 68% of the patients when the samples were re-evaluated by genetic analysis [9,10]. In our study, FOXL2 analysis was used in few difficult cases for differential diagnosis.

The rare incidence of the disease and the insidious nature as late recurrences can be seen even after cured early-stage disease make it impossible to design prospective, randomized trials. Therefore, the disease related approaches mimic the more common EOCs which were staged according to FIGO criteria. Although various clinical and pathological factors have been shown to affect survival of patients with GCT, only the stage was consistently shown as prognostic factor in different studies [11,12]. But there is some debate about the retroperitoneal lymph node dissection as a part of staging procedure. In the study of Brown et al., the risk of nodal metastasis in SCSTs of the ovary was determined [4]. Of the 262 patients with ovarian SCSTs, 178 had AGCT. Of the 58 patients with lymph nodes removed during staging, none had positive nodes. But