

# Struma ovarii: Analysis of a single institution

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## ABSTRACT

**Objective:** The aim of this study was to evaluate the clinicopathological features and oncologic outcomes in patients with struma ovarii (SO) treated and followed up in our hospital.

**Material and Methods:** The presented study included 14 patients diagnosed with SO in a single institution for a period of 25 years.

**Results:** Histopathological diagnosis revealed benign SO in 13 patients and follicular carcinoma in 1 patient with malignant transformation in final pathology reports. The patient with malignant SO was follicular type and stage Ic2. This patient did not receive adjuvant therapy. The median follow-up time of the study cohort was 31 months and ranged between 3 and 134 months. No recurrence was detected in the patient with malignant SO during 44 months of follow-up.

**Conclusion:** Surgical intervention is adequate for treatment in patients with benign SO. For patients with malignant transformation, a conservative surgery may be suitable for fertility sparing. Additionally, staging surgery including retroperitoneal lymph node dissection is recommended for determining adjuvant therapy decisions. Due to the absence of well-defined and precise guidelines for treatment, a multidisciplinary approach is suitable for patients with malignant SO. Therapy modalities should be individualized according to intraoperative and postoperative findings in this patient group.

**Keywords:** Struma ovarii, follicular thyroid carcinoma, surgery, recurrence, thyroidectomy.

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## INTRODUCTION

Germ cell tumors constitute 15%–20% of all ovarian cancers, mature cystic teratomas being the most common type.<sup>[1]</sup> Struma ovarii (SO) is a specialized monodermal teratoma composed of at least 50% of mature thyroid tissue and represents approximately 5% of all ovarian teratomas.<sup>[2]</sup> This rare type of tumor was first described by Buttlin in 1888, and the presence of thyroid tissue was demonstrated by Pick.<sup>[3]</sup> Malignant transformation of SO occurs in 0.5%–5% of all cases.<sup>[4]</sup> The most common histologic subtypes are papillary and follicular carcinoma.<sup>[5]</sup> Recurrence rates were reported between 7.5% and 35%.<sup>[5,6]</sup> The most frequent symptoms are abdominal pain and distension, palpable abdominal mass, ascites, menstrual, and endocrine abnormalities. However, most SOs are detected incidentally during the pelvic examination as a unilateral abdominal mass.

SO can be seen in all age groups with a propensity to fifth and sixth decades of life.<sup>[7]</sup> Clinical and biochemical features of hyperthyroidism are present in approximately 8% of the patients with SO.<sup>[5,8]</sup> In patients with thyrotoxicosis, serum thyroid-stimulating hormone (TSH) level is low, and free thyroxine (fT4), thyroglobulin (TG), and/or triiodothyronine (T3) levels are elevated. Due to its rarity, the data are limited in terms of management and prognosis of SO with malignant transformation.

The aim of this study was to evaluate the clinicopathological features and oncologic outcomes in patients with SO treated and followed up in our hospital.

## MATERIAL AND METHODS

The data of patients who underwent surgery between January 1993 and December 2019 were obtained from retrospective research in

Gynecologic Oncology Clinic's electronic database system, patients' files, and pathology reports. Thirteen patients diagnosed as SO and 1 patient with a diagnosis of SO with malignant transformation were included. Patients with synchronized cancer, mixed ovarian germ cell tumors, and other histologic subtypes except SO were excluded. As a result, a study cohort composed of 14 patients was obtained.

The study group underwent unilateral or bilateral salpingo-oophorectomy±hysterectomy. The ovarian tumor was evaluated by intraoperative frozen section analysis. A fertility-sparing approach was preferred according to the patient's desire to maintain fertility. Thus, the uterus and contralateral ovary were preserved in this conservative surgical approach. For the patients who did not choose to maintain fertility, definitive surgery was performed. Staging surgeries were performed as unilateral or bilateral salpingo-oophorectomy±hysterectomy + omentectomy + bilateral pelvic±para-aortic lymphadenectomy + peritoneal cytologic sampling. The patients were assessed by the use of transvaginal and abdominal ultrasonography (USG), abdominal and pelvic magnetic resonance imaging (MRI), and/or computerized tomography (CT) before the initiation of treatment. Blood samples of all patients in the entire study cohort were collected for the assessment of thyroid gland functions. In this study, the patient with malignant SO was staged according to 2014 FIGO criteria. All operations were performed by gynecologic oncologists, and all pathology specimens were evaluated by gynecopathologists.

Histopathological evaluation was carried out according to 2014 World Health Organization criteria.<sup>[9]</sup> Tumor size was admitted as the largest diameter of tumor stated on the final pathology report. Adjuvant therapy decision was made by the tumor board.

Patients with benign SO were followed up annually; the patient with malignant SO was followed up at 3-month intervals in the first 2

**Table 1: Clinical and pathological features**

Patient no.	Age (years)	Symptom	Menopausal status	Ca125 (IU/ml)	TFT	Thyroid USG	Tumor size (mm)
1	72	Pelvic mass	Postmenopausal	17.5	N	NA	70
2	58	Pelvic mass	Postmenopausal	17	N	NA	70
3	66	Abdominal distension	Postmenopausal	15	N	NA	180
4	31	Pelvic pain	Premenopausal	49	N	NA	150
5	65	Pelvic pain	Postmenopausal	12	N	NA	70
6	34	Pelvic pain	Premenopausal	9	N	NA	150
7	71	Pelvic mass	Postmenopausal	33	N	NA	130
8	87	Pelvic mass	Postmenopausal	12	N	NA	50
9	70	Pelvic mass	Postmenopausal	4	N	NA	50
10	88	Postmenopausal bleeding	Postmenopausal	22	N	NA	180
11	45	Pelvic mass	Premenopausal	5	N	NA	50
12	73	Abdominal distension	Postmenopausal	1815	N	NA	150
13	55	Abdominal distension	Postmenopausal	NA	N	NA	70
14	42	Pelvic pain	Premenopausal	225	N	N	60

USG: Ultrasonography; NA: Not available; N: Normal; TFT: Thyroid function tests.

Table 2: Details of treatment procedures

Patient no.	Surgery type	Surgical treatment	Ascites volume (mL)	Adjuvant therapy	Stage	Recurrence	Follow-up time (months)
1	Definitive	TAH + BSO + cytology	0	Negative	Benign	Negative	3
2	Definitive	TAH + BSO + BPPLND + cytology	0	Negative	Benign	Negative	88
3	Definitive	TAH + BSO + cytology	0	Negative	Benign	Negative	10
4	Conservative	USO + cytology	0	Negative	Benign	Negative	115
5	Definitive	TAH + BSO + appendectomy + cytology	0	Negative	Benign	Negative	11
6	Conservative	USO + cytology	0	Negative	Benign	Negative	130
7	Definitive	TAH + BSO + cytology	0	Negative	Benign	Negative	11
8	Definitive	TAH + BSO + BPPLND + omentectomy + cytology	0	Negative	Benign	Negative	3
9	Definitive	TAH + BSO + cytology	0	Negative	Benign	Negative	134
10	Definitive	TAH + BSO + cytology	0	Negative	Benign	Negative	6
11	Definitive	TAH + USO + cytology	0	Negative	Benign	Negative	122
12	Definitive	TAH + BSO + cytology	8600	Negative	Benign	Negative	18
13	Definitive	TAH + BSO + cytology	0	Negative	Benign	Negative	104
14	Definitive	TAH + BSO + BPPLND + omentectomy + appendectomy + cytology	60	Negative	Ic2	Negative	44

TAH: Total abdominal hysterectomy; BSO: Bilateral salpingo-oophorectomy; BPPLND: Bilateral pelvic-para-aortic lymph node dissection; USO: Unilateral salpingo-oophorectomy.

years, 6-month intervals in the next 3 years, and 1-year intervals after 5 years after the completion of therapy. On outpatient clinical controls, the patients were questioned systematically about possible symptoms, got physical and pelvic examination, complete blood count, serum tumor markers, renal function tests, and transvaginal or abdominal USG. Advanced imaging techniques (MRI, CT, and positron emission tomography) were applied in case of a suspicion of recurrence. Local ethics committee approval was obtained before the study.

SPSS 20.0 (SPSS, Inc., Chicago, IL, USA) was used for data management and statistical analysis. Descriptive statistics were expressed as mean±standard deviation or median (min–max) for continuous variables and number/percentage for categorical variables. Variables with a p-value less than 0.05 were considered significant.

## RESULTS

The mean age of the study cohort was 61 years (range 31–88). Histopathological diagnosis revealed benign SO in 13 patients and follicular carcinoma in 1 patient with malignant transformation in final pathology reports. The main presenting symptom was pelvic mass; six patients (43%) were admitted to our clinic with a pelvic mass. Four (29%) patients had pelvic pain, 3 patients (21%) had abdominal distension, and one patient (7%) had postmenopausal bleeding. The median preoperative serum Ca125 level was 17 IU/mL (range 4–1815). Thyroid function tests (TSH, fT4, and T3) were in normal range in the entire cohort. The patient with malignant SO (patient

#14) underwent a scintiscanning study and thyroid USG. The results revealed no pathological features, and this patient did not get any further adjuvant therapy with the gynecologic oncology council's decision. The median tumor size was 70 mm and ranged between 50 and 180 mm. Four patients were premenopausal (patients #4, #6, #11, and #14) in our study group. The clinical and pathological features of the study population are summarized in Table 1.

Three (21%) patients (patients #2, #8, and #14) underwent staging surgeries including retroperitoneal lymphadenectomy. Only one of them (patient #14) was diagnosed with SO with malignant transformation by intraoperative frozen section analysis. Lymphadenectomy was carried out because of the presence of suspicious lymph nodes in the remaining two patients. In one of them (patient #2), retroperitoneal lymphadenectomy was abandoned after the completion of pelvic lymph node dissection. Two premenopausal patients (patients #4 and #6) underwent unilateral salpingo-oophorectomy for fertility sparing. Ascites was present in 1 patient (patient #12). According to FIGO 2014 criteria, the patient with malignant SO was follicular type and stage Ic2. Pelvic and para-aortic lymph nodes, omentum, appendix, pelvic peritoneum, uterus, ipsilateral salpinx, contralateral ovary, and salpinx were free of tumors. Also, peritoneal cytologic sampling was negative. Lymphovascular space invasion and ovarian capsular invasion were positive. Immunohistochemical analysis was not offered. This patient (patient #14) did not receive adjuvant therapy.

The median follow-up time of the study cohort was 31 months and ranged between 3 and 134 months. Malignant SO patient was

followed up with 3-month intervals on gynecologic oncology out-patient clinical controls for 24 months and 6-month intervals for 20 months. After a period of 44 months, the patient was lost to follow-up. However, no recurrence was detected, and the patient was alive with no evidence of disease. The details of the surgical procedures are shown in Table 2.

## DISCUSSION

SO is a rare and specialized form of ovarian teratomas. Due to its rarity, no randomized controlled trials are available, and data from the literature is limited to retrospective case reports, case series, and review articles. They usually occur in older women, but there are reports of younger age groups even in a 10-year-old girl with a malignant SO.<sup>[10–12]</sup> The median age was 61 years in our cohort and ranged between 31 and 88 years. There are different studies reporting that the same age groups were diagnosed as SO.<sup>[2,7,13]</sup> Although the majority of patients were asymptomatic, the most common symptoms were stated as abdominal pain, palpable abdominal and/or pelvic mass, ascites, and abnormal vaginal bleeding at the time of diagnosis.<sup>[14]</sup> In our study, the most frequent presenting symptom was abdominal mass with a ratio of 42%. Ascites was present in one patient with a benign SO in our study group (7%). However, it was reported in the literature that ascites up to 15%–20% was present in patients with SO.<sup>[5,14]</sup> Ascites may be associated with pleural effusion called Pseudo-Meigs' syndrome. This situation can be misdiagnosed as malignant epithelial ovarian cancer preoperatively. The combination of thyroid scintigraphy and FDG PET was suggested for successful preoperative diagnosis.<sup>[15]</sup> SO can be accompanied by hyperthyroidism in approximately 8% of patients.<sup>[2,8]</sup> Thyroid hormone production from ectopic thyroid tissue within SO is uncommon. Patients generally present with nonspecific symptoms caused by abdominal mass. Several reports are available establishing hormonally active SO cases.<sup>[10,16]</sup> None of the patients in our study group had abnormal thyroid hormone levels.

Thyroid tissue within SO lesions is classified mainly into three types: normal thyroid tissue similar to the thyroid gland, proliferative or cellular lesions with hyperplastic or adenomatous components, and thyroid-type carcinomas.<sup>[17,18]</sup> Malignant transformation of SO is rare; approximately 5% of cases are diagnosed as thyroid carcinoma arising in SO.<sup>[5,19]</sup> This term is more appropriate for thyroid-type carcinomas of the ovary because they originate from four different precursor lesions: mature cystic teratoma or SO, strumal carcinoid, metastasis from thyroid gland, or unidentified lesions.<sup>[11,20]</sup> The most common histologic subtype is papillary thyroid carcinoma (PTC), and the second most frequent histologic subtype is follicular carcinoma.<sup>[11,17]</sup> Our patient with malign transformation also had follicular carcinoma. In addition, some investigators reported rarer histological variants such as insular carcinoma (poorly differentiated carcinoma) arising from SO.<sup>[21,22]</sup> In a recent review, Ayhan et al.<sup>[23]</sup> found that the presence of a histological type other than PTC was an independent adverse prognostic factor. Differential diagnosis between benign and malignant SO cases can be challenging especially in follicular thyroid carcinoma because of the rarity of the disease. However, the same diagnostic pathological criteria used for cervical thyroid carcinoma have been suggested by Devaney et al.<sup>[17]</sup> for malignant SO. Histopathological features such as mitotic activity, vascular invasion, and presence of

irregular, ground-glass cores are included in the diagnostic criteria for papillary carcinoma within SO lesions and cervical thyroid gland.

The presence of residual disease should be confirmed by the use of total body scintiscanning with radioactive iodine ( $I^{131}$ ) in malignant SO postoperatively. In the presented study, no residual lesion could be detected in a patient with malignant SO after surgical intervention. At the time of diagnosis, the overall incidence of metastasis was reported between 5% and 27%.<sup>[5,8]</sup> The sites of metastasis are adjacent pelvic structures, pelvic and para-aortic lymph nodes, and distant organs including lungs, bones, liver, and brain.<sup>[17–19]</sup> Dissemination of rare structures such as omentum was reported in the literature.<sup>[24]</sup> On the other hand, recurrence rates were reported between 7.5% and 35% in malignant SO cases.<sup>[4–6]</sup> The malignant SO patient in our cohort remained disease-free during 44 months of follow-up. Our patient was alive with no evidence of disease at the time of the last contact. During the follow-up period, serum TG level measurement enables early detection of recurrence.<sup>[19]</sup> Serum TG levels were normal in our patient in the follow-up period.

The recommended treatment modality for benign lesions is surgical resection. In malignant SO, there are no consistent guidelines for the management of the disease. For patients who desire to maintain fertility, a conservative approach (unilateral salpingo-oophorectomy) may be suitable. However, the absence of extra-ovarian disease should be confirmed by intraoperative evaluation and by the use of imaging techniques in this patient group.<sup>[13,25]</sup> Total hysterectomy and bilateral salpingo-oophorectomy is the treatment option for postmenopausal patients and patients with the extra-ovarian disease. Complete surgical staging is generally recommended independently of fertility desire for malignant SO.<sup>[4,5,8]</sup> After the completion of debulking surgery, all patients should undergo total body scintiscanning with  $I^{131}$  for the detection of metastatic disease. For patients with metastatic lesions, some authors recommend total thyroidectomy with radioactive  $I^{131}$  thyroid ablation following primary surgery.<sup>[5]</sup> However, thyroidectomy has some remarkable risks such as iatrogenic parathyroidectomy, thyroxine replacement, and laryngeal nerve damage.<sup>[21]</sup> In addition, some investigators suggest that malignant SO with a tumor size >2 cm, disease with extra-ovarian extent, and tumor with aggressive histopathological features should also be treated with total thyroidectomy and  $I^{131}$  ablation.<sup>[26]</sup> While thyroid suppression with thyroxine is suggested for low-risk patients with a lesion less than 2 cm, well-differentiated histology and confined to the ovary.<sup>[4]</sup> On the other hand, surgical removal of the ovarian tumor is considered sufficient treatment modality for malignant SO cases without extra-ovarian spread and recurrence by different investigators.<sup>[27]</sup> For management of malignant SO with metastatic and recurrent disease, thyroidectomy, radioactive iodine therapy, chemotherapy, and radiotherapy following the surgical intervention of the ovarian tumor are admitted as adjuvant therapy modalities. No consensus on optimal treatment modality has been reached. Thus, all patients with malignant SO should be evaluated by a multidisciplinary team including gynecologic oncology, endocrinology, head and neck surgery, radiation oncology, medical oncology, and pathology.

The most important limitation of this study are its retrospective design and low number of patients. On the other hand, given the rarity of the disease, this study group reflects the experience of a tertiary center for approximately 25 years.

## CONCLUSION

Surgical intervention is adequate for treatment in patients with benign SO. For patients with malignant transformation, a conservative surgery may be suitable for fertility sparing. Additionally, staging surgery including retroperitoneal lymph node dissection is recommended for determining adjuvant therapy decision. Due to the absence of well-defined and precise guidelines for treatment, a multidisciplinary approach is suitable for patients with malignant SO. Therapy modalities should be individualized according to intraoperative and postoperative findings in this patient group.

## Statement

**Ethics Committee Approval:** The Etik Zübeyde Hanım Training and Research Hospital Ethics Committee granted approval for this study (date: 28.11.2019, number: 90057706-799-18).

**Informed Consent:** Written informed consent was obtained from patients who participated in this study.

**Peer-review:** Externally peer-reviewed.

**Author Contributions:** Concept – ÇK, DY, NB; Design – ÇK, VK, SK, YÜ; Supervision – NB, YÜ, FK; Data Collection and/or Processing – ÇK, DY, CÇ, RD, VK; Analysis and/or Interpretation – ÇK, RD, SK, VK; Literature Search – ÇK, CÇ, SK, FK; Writing – ÇK, DY, CÇ, RD; Critical Reviews – FK, SK, YÜ, NB.

**Conflict of Interest:** The authors have no conflict of interest to declare.

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