

# Brenner tumors of the ovary: clinical features and outcomes in a single-center cohort

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## Abstract

**Objective:** The purpose of the present study was to evaluate the clinical and pathological features and oncological outcomes of Brenner tumors (BT).

**Material and Methods:** Evaluation was performed on the data of 46 patients with BTs retrieved from the oncology clinic database and pathology reports between 2005 and 2020.

**Results:** The median (range) age of the patients was 52 (22-75) years. Median (range) tumor size was 52.5 (5.0-300) mm. The tumor was benign in 37 (80.4%), borderline in one (2.2%), and malignant in the remaining eight (17.4%). Ten (21.7%) of the tumors were detected incidentally. Mixed tumor, BT plus another ovarian pathology, was found in 13 (28.2%). Recurrence developed in 2/8 (25%) with malignant BT (MBT). The stage of these patients was 3C, and both received chemotherapy after surgery.

**Conclusion:** BTs are rare and generally detected incidentally. MBTs are treated in the same way as epithelial tumors. Due to the rarity of these tumors, lymphadenectomy and optimal chemotherapy regimens are controversial issues. (J Turk Ger Gynecol Assoc 2022; 23: 22-7)

**Keywords:** Brenner tumors of the ovary, malignant Brenner tumors, mixed tumors, rare tumors

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## Introduction

Ovarian Brenner tumors (BTs) are a rare type of epithelial ovarian tumor and constitute only 2-3% of all ovarian tumors (1). They were first described and named by Fritz Brenner in 1907 (2). BTs occur incidentally and frequently with other epithelial neoplasms (3). Incidental BTs are more common in oophorectomy specimens although, as the diagnosis is difficult, true incidence cannot be assessed (4).

The aim of this study was to report 46 cases with BTs of the ovary and to analyze the clinical and demographic features, and oncological outcomes.

## Material and Methods

A retrospective evaluation was performed on patients with BT treated in our institution between 2005 and 2020. The clinical, surgical, and pathological data of the patients were collected from the gynecologic oncology department electronic database system, patient files, pathological reports, and operation notes. Data including age, menopausal status, tumoral features (tumor size, bilateral/unilateral), tumor markers (CA-125), surgical indications, type of surgical procedure, concomitant pathology, malignancy status, and follow-up information were obtained from the hospital registry. Written informed consent



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was obtained from all patients on admission for medical information to be used anonymously for academic purposes. Approval for the study was granted by the University of Health Sciences Turkey, Etilik Zübeyde Hanım Women's Health Care, Training and Research Hospital (approval number: 90057706-799/8, date: 30.10.2019).

Patients with malignant BT (MBT) and BT accompanied by another gynecological malignancy were included in the study, and post-surgical follow-up was performed every three months for the first two years, every six months for the following three years, and annually for the subsequent five years. The 2014 International Federation of Gynecology and Obstetrics (FIGO) staging criteria were considered. For patients treated before 2014, cancer staging was re-assessed using the FIGO 2014 system from surgical and pathological reports.

Gynaecological examination, abdominal ultrasonography, and measurements of CA-125 levels were routinely performed at each follow-up visit. Patients with borderline pathology were followed-up annually.

### Statistical analysis

Data obtained in the study were analyzed statistically using SPSS, version 17.0 software (SPSS Inc., Chicago, IL, USA). The demographic data of the patients and disease characteristics were evaluated with descriptive statistics, with continuous variables reported as median, minimum-maximum values, and categorical variables as number and percentage (%).

### Results

Evaluation was performed on 46 patients who presented during the study period. The patients had a median (range) age of 52 (22-75) years. The median (range) tumor size was 52.5 (5.0-300) mm. The median (range) preoperative CA-125 level was 19 (4.9-215) IU/mL.

Tumors were bilateral in 3 (6.5%) patients, unilateral in the right ovary in 21 (45.7%), and unilateral in the left ovary in 22 (47.8%). Twenty-five (54.3%) patients were postmenopausal. The tumor was benign in 37 patients (80.4%), borderline in 1 (2.2%) and malignant in 8 (17.4%).

The most frequent features leading to diagnosis were adnexal mass (71.7%), then myoma uteri (7%), followed by abdominal pain, abnormal uterine bleeding, and prolapse.

Tumours were detected incidentally during surgery for other indications in 10 (21.7%) cases. These were: cervical cancer (n=2); ovarian cancer (n=2); serous ovarian cancer (n=1); endometrioid type of ovarian cancer (n=1); myoma uteri (n=3); prolapse (n=1); high-grade cervical intraepithelial lesion (n=1); and endometrial cancer (n=1).

The patient with borderline BT accompanied by hyperplasia was found to have endometrial atypia, which was determined in

preoperative endometrial biopsy and postoperative pathology. Mixed tumors consisting of BT and another ovarian pathology were detected in 13 (28.2%) cases. Mucinous cystadenoma were concomitant in 7 (15.2%) patients, serous cystadenoma in 2 (4.3%), endometrioma in 2 (4.3%), struma ovarii in 1 (2.1%) and mature cystic teratoma in 1 (2.1%). The clinical and pathological features of the patients are presented in Table 1.

The median age was 52 years (range, 36-57 years) in cases with MBT and 52 years (range, 22-74 years) in benign cases.

Eight cases with MBT were examined separately in detail. Stage IIIC was identified in 4 patients, IA in 1 patient, IIA in 1 patient, IC1 in 1 patient, and IC3 in 1 patient. The median (range) follow-up time was 75 (36-75) months. In this period, recurrence was observed in 2/8 (25%). The patient with recurrence at stage 3C, case no: 43, underwent a total abdominal hysterectomy, bilateral salpingo-oophorectomy, bilateral pelvic lymph node dissection, appendectomy, and omentectomy, followed by six cycles of paclitaxel and carboplatin treatment, and had a recurrence in paraaortic + pelvic lymph node regions and the liver 86 months later. The other patient with recurrence (case no: 46) underwent a total abdominal hysterectomy, bilateral salpingo-oophorectomy, bilateral pelvic-paraaortic lymphadenectomy, and total omentectomy due to adnexal mass. After six cycles of chemotherapy (cisplatin + paclitaxel), the patient showed pulmonary + liver + pelvic recurrence in the 13<sup>th</sup> month. The patient underwent bleomycin + etoposide + cisplatin chemotherapy and pelvic radiotherapy (RT), but died after 53 months due to progressive disease. The clinical and oncological characteristics of the cases with MBT are given in Table 2. The recurrences were detected by imaging.

### Discussion

Tumors originating from the surface epithelium of the ovary are the most common ovarian neoplasms. BTs are a rare subtype of epithelial ovarian tumors. The WHO categorizes BTs into three types - benign, borderline, and malignant. BTs are known as transitional cell tumors because of their histological similarity to the urothelium resembling epithelial components (5).

BTs usually present in the fifth to sixth decades of life. In a series of 13 cases reported by Gezginç et al. (6), 61.5% of patients were post-menopausal and the median age was 55.6 years. Green et al. (7) also reported the mean age to be 58 years in 22 patients. Of the 46 patients in the current series, 54.3% were postmenopausal, and the median age was 52 years. The vast majority of reported cases of BT consist of small tumors and are detected incidentally when oophorectomy is performed for some other indication. In these cases tumor size is small, usually <2 cm and most patients are asymptomatic (4).

**Table 1. The Clinical and pathological features of the patients**

N	A	M	Side	Size/mm	Presenting symptom	Concomitant pathology	Surgery	CA-125	Histology
1	57	+	R	33	Adnexal mass-ovarian cancer	Serous ovarian carcinoma	Tah + Bso + Bpplnd + App. + Omm.	215	Benign
2	55	+	R	N/A	Cervical cancer	Cervical cancer	Type 3 hysterectomy + Bso + Bpplnd	N/A	Benign
3	55	+	R	50	AUB	-	Tlh + Bso	6.2	Benign
4	42	-	L	N/A	Recurrent cervical cancer	Cervical cancer	Pelvic exenteration	N/A	Benign
5	46	-	L	N/A	Endometrial cancer	Endometrial cancer	Tlh + Bso	N/A	Benign
6	43	-	L	150	Adnexal mass + Abd. pain	Mucinous cystadenoma	Left uso	10.9	Benign
7	65	+	L	120	Adnexal mass + Abd. pain	-	Tah + Bso	N/A	Benign
8	54	+	R	20	HSIL surgical margin +	HSIL surgical margin +	Tlh + Bso	N/A	Benign
9	49	-	L	150	Adnexal mass + AUB	Mucinous cystadenoma	Tah + Bso + App.	13	Benign
10	53	+	L	20	Adnexal mass-ovarian cancer	Endometrioid ovarian carcinoma	Type 2 hysterectomy + Bso + Bpplnd + App. + Omm.	32	Benign
11	52	+	L	50	Adnexal mass	-	Tah + Bso	16	Benign
12	57	+	B	50	Adnexal mass	-	Tlh + Bso	30	Benign
13	69	+	L	200	Adnexal mass	-	Tah + Bso	28	Benign
14	56	+	R	55	Adnexal mass	Struma ovarii	Tah + Bso	5	Benign
15	63	+	R	80	Adnexal mass	-	Tah + Bso	N/A	Benign
16	38	-	R	56	Adnexal mass	-	Right uso	9.4	Benign
17	74	+	R	40	Adnexal mass	Endometrioma	Tah + Bso	19	Benign
18	73	+	L	100	Adnexal mass + AUB	Mucinous cystadenoma	Tah + Bso	40	Benign
19	50	-	L	200	Adnexal mass	Mucinous cystadenoma	Right uso + Left salpingectomy + App.	100	Benign
20	43	-	L	55	Adnexal mass	Mature cystic teratoma	Left uso	77	Benign
21	47	-	R	85	Adnexal mass	Mucinous cystadenoma	Right uso	12	Benign
22	48	-	R	40	Adnexal mass	Endometrioma	Tah + Bso	37	Benign
23	48	-	R	45	Myoma uteri	-	Tah + Bso	N/A	Benign
24	54	+	R	6	Myoma uteri + uterine prolapse	-	Tah + Bso	N/A	Benign
25	34	-	L	60	Adnexal mass	Mucinous cystadenoma	Cystectomy	9.2	Benign
26	54	+	R	15	Adnexal mass	-	Tah + Bso	13	Benign
27	60	+	R	5	Uterine prolapse	-	Tah + Bso	6	Benign
28	53	+	L	30	Myoma uteri	-	Tah + Bso	N/A	Benign
29	52	+	L	65	Adnexal mass	Mucinous cystadenoma	Left uso	4.9	Benign
30	50	+	L	10	Myoma uteri	-	Tah + Bso	6.3	Benign
31	46	-	R	40	Adnexal mass	-	Right uso	8.4	Benign
32	52	-	R	25	Myoma uteri	Serous cystadenoma	Tah + Bso	N/A	Benign
33	52	-	R	25	Myoma uteri	-	Tlh + Bso	24	Benign
34	39	-	L	40	Adnexal mass	Serous cystadenoma	Left uso	24.4	Benign
35	22	-	L	45	Adnexal mass	-	Cystectomy	9.5	Benign
36	59	+	R	8	Myoma uteri	-	Tah + Bso	N/A	Benign
37	50	-	L	270	Adnexal mass	-	Tah + Bso	152	Benign

**Table 1. Continued**

N	A	M	Side	Size/mm	Presenting symptom	Concomitant pathology	Surgery	CA-125	Histology
38	70	+	L	100	Adnexal mass + AUB	Atypical hyperplasia	Tah + Bso	38	Borderline
39	75	+	B	36	Adnexal mass	Breast cancer history	Tah + Bso + Bpplnd + App. + Omm.	20	Malignant
40	57	+	L	55	Adnexal mass	-	Tah + Bso + Omm.	N/A	Malignant
41	48	-	L	200	Adnexal mass	-	Tah + Bso + Bpplnd + App. + Omm.	9.6	Malignant
42	37	-	R	300	Adnexal mass	-	Tah + Bso + Bpplnd + App. + Omm.	12	Malignant
43	49	-	R	N/A	Adnexal mass	Mucinous cystadenoma	Tah + Bso + Bplnd + App. + Omm.	N/A	Malignant
44	75	+	R	N/A	Adnexal mass	-	Tah + Bso + Bpplnd + App. + Omm.	95	Malignant
45	36	-	R	180	Adnexal mass	-	Tah + Bso + Bpplnd + App. + Omm.	209	Malignant
46	55	+	B	150	Adnexal mass + Abd. pain	-	Tah + Bso + Bpplnd + App. + Omm.	64	Malignant

N: Patient no, A: Age, M: Menopausal status, AUB: Abnormal uterine bleeding, Abd.pain: Abdominal pain, Uso: Unilateral salpingo-oophorectomy, Tah: Total abdominal hysterectomy, Bso: Bilateral salpingo-oophorectomy, Tlh: Total laparoscopic hysterectomy, App: Appendectomy, Bpplnd: Bilateral pelvic-paraaortic lymph node dissection, HSIL: High grade squamous intraepithelial lesion, L: Left, R: Right

**Table 2. The clinical and oncological characteristics of cases with malignant Brenner tumors**

Case no	Age	Stage	Chemotherapy	Recurrence (time/site/treatment)	Follow-up time (m)	Outcome
39	75	IIIC	C + PTx (6 cyc.)	No	47 m	Ned/Alive
40	57	IIA	C + PTx + RT (7 cyc.)	No	12 m	NA
41	48	IA	-	No	96 m	Ned/Alive
42	37	IC1	C + PTx (6 cyc.)	No	115 m	Ned/Alive
43	49	IIIC	C + PTx (6 cyc.)	86 m (paraaortic + pelvic lymph node and liver) Surgery + 6 cyc. C + PTx	96 m	Ned/Alive
44	75	IIIC	C + PTx (6 cyc.)	No	12 m	DOD
45	36	IC3	C + PTx (6 cyc.)	No	125 m	Ned/Alive
46	55	IIIC	Cis + PTx (6 cyc.)	13 m (pulmonary + liver + pelvic side) BEP + pelvic RT	53 m Progressive disease	DOD

Cyc: Cycle, C: Carboplatin, PTx: Paclitaxel, Cis: Cisplatin, RT: Radiotherapy, BEP: Bleomycin + Etoposid + Cisplatin, Ned: No evidence of disease, DOD: Dead of Disease, NA: Not available, m: Month

In the current study, 10 cases were detected incidentally after surgery for other indications. In these cases, the size of the tumor varied from 5 mm to 45 mm (Table 1).

BTs can be accompanied by mucinous cystadenoma, serous cystadenoma, benign cystic teratoma, or struma ovarii in approximately 20% of cases (8). Similarly, in the current study, coexistence with benign ovarian tumors was detected in 13

(28%) cases. Roma and Masand (9) reported that up to 27% of BTs were associated with mucinous tumors. The coexistence of struma ovarii and BT is rare. According to the current literature, only seven cases have been reported (10). The origin of the BT and the struma ovarii association may be the germ-cell, as described in various studies, or due to the metaplastic features of the BT (10,11).

BTs might be accompanied by other ovarian tumors and be associated with endometrial pathologies in 4-14% of patients. The stromal component of the BT, resembling the theca cells of the ovary, produces estrogen, which may be related to estrogen-related pathologies (3). In the current cohort, BTs were seen to coexist with atypical endometrial hyperplasia in one patient and endometrioid-type endometrial cancer in another.

Synchronous tumors of the female genital tract account for only 1-6% of all genital neoplasms (12). Similarly, in this study, one case was diagnosed incidentally in a case of serous ovarian carcinoma and one case in an endometrioid ovarian tumor. Coexistence with the endometrioid ovarian tumor and the history of breast cancer in one patient also supports estrogen-related events. These findings also explain the vaginal bleeding complaint in these patients. Although no data exist about the coexistence of cervical cancer and BTs in the literature, two (4.3%) patients had cervical cancer in the current study. This might have resulted from the fact that the study was conducted in a gynecological oncology clinic.

BTs are known to range from benign to malignant. In the current study, 1 patient had borderline and eight patients had MBT. Borderline BTs are rare and defined as “epithelial proliferation without stromal invasion” and only 60 cases have been published in the English literature to date (13). Most of the cases in the literature were reported as older than 50 years. Presenting with postmenopausal bleeding indicates that some of the borderline BTs may contain hormone-secreting elements. The case in the current study with borderline BT was 70 years old and the main complaint was postmenopausal bleeding. Histopathological examination showed concomitant atypical endometrial hyperplasia. Similar to the cases in literature, this finding indicates that endometrial hyperplasia may have developed due to the hormonal effects of borderline BT.

Whereas the vast majority of BTs are benign and often found incidentally, MBT, accounting for <5% of all BTs, are extremely rare (5). The clinical and oncological features of the eight patients with MBT are summarized in Table 2. The median age of the MBT cases was 52 years, similar to the study of Han et al. (14). A small number of studies provide the only available information about the treatment of these patients, and the optimal adjuvant management remains unclear. Surgery is the main treatment, as in the case of other epithelial ovarian carcinomas. In the reported case series carboplatin and paclitaxel had been used for adjuvant chemotherapy, as in other epithelial ovarian tumors (6,14). In the presented series, all patients, except one case (stage 1A), received paclitaxel-carboplatin as adjuvant therapy in line with previous reports. A recent large retrospective study reported the median tumor size as 10 cm for MBT and most of these were unilateral (15). In this case series, the median

tumor size was 16.5 cm and the majority of the tumors (6/8) were unilateral.

Lymph node dissection is a controversial issue in MBT. Nasioudis et al. (15) reported that lymphatic spread and lymph node dissection did not confer any disease-specific survival (DSS) benefit to these patients. Approximately 50% of patients with surgical tumor excision had concomitant lymph node dissection, but only 5% of these patients had evidence of lymphatic spread. In that study, no DFS difference was found between the lymphadenectomy group and non-lymphadenectomy group (15). In the current study, lymph node dissection was performed in all except two patients (stage 1A and IIA). No recurrence was observed in these early stage patients.

Complete chemotherapy response was obtained from 7/7 patients who received carboplatin + paclitaxel chemotherapy in this series. Similarly, Gezginç et al. (6) reported a complete response rate in 9/10 patients, and the recurrence rate was 7/10. These results support the importance of complete cytoreductive surgery before chemotherapy. In the current study recurrence was seen only in 2/8 MBT patients. One of the patients with recurrence was given chemotherapy following surgery for recurrence, and that patient is currently alive without disease. The second patient, who had recurrence after primary adjuvant chemotherapy was given bleomycin, etoposide, and cisplatin. Palliative RT was given for progressive disease and the control of pelvic recurrence. The patient died from the disease in the 53<sup>rd</sup> month. NCCN guidelines on epithelial ovarian cancers do not include RT as a primary treatment recommendation, but reference palliative RT for local symptom control (16).

Although specific tumor markers for MBT have not been identified, CA-125 can be used to monitor the effectiveness of therapy and to detect recurrence during follow-up (17). In the current study, 3/8 patients (38%) had CA-125 levels >35 IU/mL. Roth et al. (18) reported that MBTs are associated with better survival compared to other epithelial ovarian tumors. In the current study, 4/8 patients were diagnosed at stage IIIC and the others were stage IA, IIA, IC1, and IC3. Two reported recurrences were seen at stage IIIC. In the early stages, no recurrence was observed. These findings support the suggestion that DSS is better in the early stages, in agreement with the findings of Nasioudis et al. (15).

This report presents a single-center experience over fifteen years. Due to the relatively low number of cases, the cohort provides information about benign, borderline, and malignant MBTs of the ovary. This study can be considered to provide valuable information in terms of oncological results about MBTs, as rare case reports and a limited number of case series in many reports are presented together.



## Conclusion

BTs are rare and mostly incidental findings. It should be remembered that these tumors can secrete hormones and can cause endometrial pathologies. Especially for malignant forms, multicenter studies are needed to be able to establish the optimal treatment regimen and surgery.

**Ethics Committee Approval:** *This study was approved by the University of Health Sciences Turkey, Etlik Zübeyde Hanım Women's Health Care, Training and Research Hospital, approved the study (approval number: 90057706-799/8, date: 30.10.2019).*

**Informed Consent:** *Written informed consent was obtained from all patients on admission for medical information to be used anonymously for academic purposes.*

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