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ORIGINAL RESEARCH

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Brenner tumors: single centre experience

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Abstract

The objective of this study was to assess the clinical and pathological characteristics, as well as the oncological outcomes, of Brenner tumors (BTs). The assessment was conducted on the information of 63 patients diagnosed with Brenner Tumor, which was obtained from both the oncology clinic database and pathology reports spanning the time period from 2002 to 2022. The patients' ages in the study had a median of 57 years, ranging from 43 to 83 years. Median (range) tumor size was 10 (0.75–165) mm. Out of the total number of patients, 60 individuals (95.2%) had benign tumors, while the remaining 3 (4.8%) were diagnosed with malign tumors. No borderline tumors were detected among the patients. A mixed tumor, comprising both a borderline tumor and other ovarian pathology, was found in 7 cases, accounting for 11.1%. Brenner tumors are infrequent and typically identified coincidentally. Malign Brenner Tumors (MBTs) receive similar management as epithelial neoplasms. Given the uncommon nature of these tumors, the appropriateness of lymphadenectomy and optimal chemotherapy protocols remains a subject of debate.

Keywords

Ovarian Brenner tumors; Rare tumors of ovary; Ovarian malignancies

1. Introduction

Brenner tumors (BTs) represent surface-epithelial stromal cell neoplasms, comprising 1–5% of epithelial ovarian cancers [1] and accounting for 1.4–2.5% of all ovarian malignancies [2, 3].

BT can be classified as benign, borderline, or malign according to the World Health Organization's (WHO) categorization of female genital tumors based on proliferation and invasiveness [4].

Since they typically manifest as tiny neoplasms, Benign Brenner tumors (BBT), which account for around 95% of occurrences, are frequently discovered by accident in asymptomatic females. Malign and borderline tumors affect 5 and 1% of BT patients, respectively, and are more frequently symptomatic due to their larger sizes [5].

Figs. 1,2 respectively illustrate the macroscopic and microscopic appearance of a Brenner tumor.

Less than 5% of BTs are borderline [6] and, as of 2019, fewer than 60 cases of borderline BTs had been reported [1].

The literature regarding Brenner tumors is composed mainly of case presentations and small retrospective studies due to the rarity of these tumors and the fact that the majority of them are benign.

This study's objectives were to present 63 cases of BTs of the ovary, characterize their medical and demographic characteristics, and examine their oncological prognosis.

2. Material and methods

Between 2002 and 2022, patients who were diagnosed with Brenner tumor and underwent treatment at our facility were retrospectively evaluated.

The clinical, operative, and pathological information regarding the patients was collected through the computerized database system utilized by the gynecologic oncology division, patient records, pathology summaries and surgical notes. Extracted from the hospital registry, the ensuing data encompassed: age, menopausal condition, tumor attributes (size, unilateral/bilateral), tumor markers ((Cancer Antigen 125 (CA-125)), surgical indications, surgical approach, simultaneous pathologies, malignancy classification and subsequent monitoring details.

The study comprised patients with BT that was Malign (MBT) and BT that was coexisting with another gynecological cancer.

A post-operative monitoring was conducted quarterly during the initial two years, biannually over the subsequent three years, and annually for the subsequent five years, while adhering to the 2014 guidelines provided by the International Federation of Gynecology and Obstetrics (FIGO).

Using the FIGO 2014 approach and surgical and pathological records, cancer staging was reevaluated for patients treated prior to 2014. Abdominal ultrasonography, a gynecological exam, and CA-125 measurements were all regularly performed at every follow-up consultation.

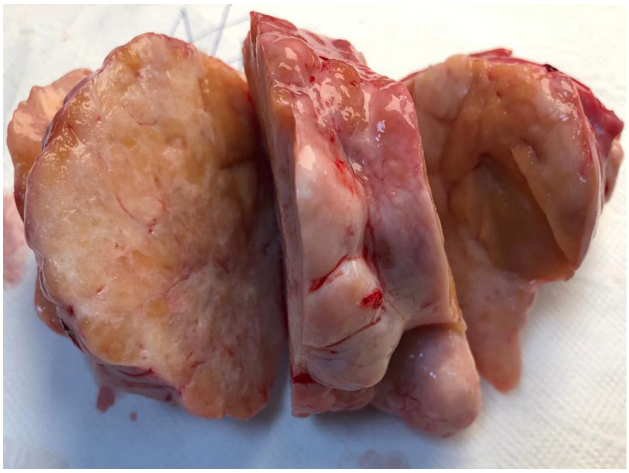

FIGURE 1. Macroscopic view of Brenner tumor.

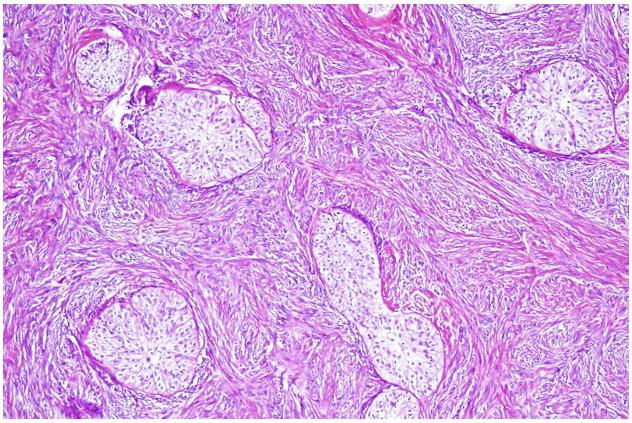

FIGURE 2. Microscopic view of Brenner tumor.

SPSS, version 24.0 software (SPSS Inc., Chicago, IL, USA) was used to statistically analyze the data gathered for the study. With descriptive statistics, the demographic information about the patients and the characteristics of the disease were assessed.

Continuous variables were presented as the median along with the range (minimum to maximum), while categorical variables were presented as counts and percentages (%).

3. Results

63 patients who showed up during the study period had evaluations done on them. The median (interquartile range) age of the patients was 57 (43–83). Tumor size was 10 (0.75–165) mm on average (interquartile range). The preoperative median (interquartile range) CA-125 level was 12.7 (2.7–286) IU/mL. Eight patients (12.7%) had bilateral tumors, 19 had unilateral tumors in their right ovary (30.1%), and 36 had unilateral tumors in their left ovary (57.1%). The postmenopausal patients numbered 45 (71.4%). 60 patients' tumors (95.2%) were benign, while 3 (4.8%) were malign. No patients on the edge were found. Adnexal mass (34.9%), irregular uterine hemorrhage (33.3%), and abdominal pain were the two conditions for which patients sought medical attention most frequently.

In 39 (61.9%) cases, tumors were discovered by chance during surgery for other reasons. These included cervical cancer (1 case), ovarian cancer (7 cases) (serous ovarian cancer (2 cases), mucinous ovarian cancer (3 cases), granulosa cell tumor of the ovary (2 cases)), myoma uteri (12 cases), endometrial cancer (7 cases), benign ovarian mass (5 cases) other gynecologic indications (n = 6) and borderline ovarian tumor (n = 1). In 13 (20.6%) cases, mixed tumors made up of BT and another ovarian disease were found. Mucinous cystadenoma coexisted with serous cystadenoma in 2 patients (3.1%), musinoz borderline ovarian tumor (BOT) in 1 patient (1.5%), endometrioid cystadenofibroma in 1 patient (1.5%), maturing cyctic teratoma in 1 patient (1.5%), and musinoz cystadenoma in 2 patients (3.1%).

Table 1 lists the patients' clinical and pathological characteristics. In instances with MBT, the age ranged from 53 to 66 years; in cases with benign conditions, it ranged from 43 to 83 years.

Three cases involving MBT were thoroughly reviewed in each case (Table 2).

The patient with the 61st diagnosis, classified as stage 3C, underwent debulking surgery (total abdominal hysterectomy, bilateral salpingo-oophorectomy, pelvic and para-aortic lymphadenectomy, excision of bulky mass from Douglas peritoneum and abdominal anterior wall peritoneum). Subsequently, they received 6 cycles of carboplatin and paclitaxel chemotherapy regimen. During remission follow-up, at the 22nd month, breast cancer was detected, and the patient underwent mastectomy performed by the General Surgery department. No recurrence was observed during clinical follow-ups for Brenner tumor. However, due to breast cancer recurrences, the patient received repeated chemotherapy treatments by the Medical Oncology department (23 cycles of cisplatin in the subsequent 34-month period, followed by 7 cycles of gemcitabine in 14 months, and then 4 cycles of doxorubicin and cyclophosphamide, and 4 cycles of liposomal doxorubicin). Unfortunately, the patient passed away at the 72nd month of follow-up due to breast cancer.

Patient number 62, diagnosed with stage 1C, underwent total abdominal hysterectomy, bilateral salpingo-oophorectomy, bilateral pelvic, and para-aortic lymphadenectomy, as well as infracolic omentectomy. After the surgery, the patient was placed under observation without any treatment. With a total follow-up period of 130 months, the patient experienced intra-abdominal recurrence during the 102nd month of follow-up. Debulking surgery was performed, followed by 6 cycles of carboplatin and paclitaxel chemotherapy regimen. The patient has been in remission for 1 year during the follow-up.

Patient number 63, evaluated as stage 3C, underwent debulking surgery (total abdominal hysterectomy, bilateral salpingo-oophorectomy, pelvic and para-aortic lymphadenectomy. Afterward, 6 cycles of carboplatin and paclitaxel chemotherapy were administered. The patient was followed up in remission and chemotherapy was started again with 6 courses of carboplatin and gemcitabine protocol in the 10th month of follow-up upon the detection of multiple implants and metastasis in the liver. After 4 months, the CA-125 levels of the patient who went into remission were elevated and intra-abdominal implants were observed on imaging. The patient was started on liposomal doxorubicin. However, she died in the 31st month of patient follow-up.

TABLE 1. Characteristics of patients: clinical and pathological findings.

No	Age	M	Side	Size/mm	Presenting Sympyom	Ovarıan Concomitan Pathology	Endometrial Pathology	Surgery	Histology
1	67	+	L	10	Pain	Left ovarian endometrioid cystadenofibroma	endometrial hyperplasia without atypia + adenomyosis	tah + bso	Benign
2	55	+	L	8	Bleeding	-	endometrial polip	tah + bso	Benign
3	65	+	L	15	Bleeding	-	Cervical ca	radical hysterectomy	Benign
4	48	−	R	60	Bleeding	-	myom + endometrial hyperplasia without atypia	omentectomy + tah + bso	Benign
5	60	+	L	2	Bleeding	Granulosa cell tumor	myom	pplnd + tah + bso + omentectomy	Benign
6	49	−	B	30/30	Pain	-	chronic cervicitis	tah + bso	Benign
7	58	+	R	45	Bleeding	-	-	l/s right uso	Benign
8	57	+	L	4	Pain	-	myom + polip	tah + bso	Benign
9	61	+	R	3	Bleeding	-	endometrial karsinosarkam	pplnd + tah + bso + omentectomy	Benign
10	49	−	B	5.0/2	Bleeding	-	endometrium ca	tah + bso	Benign
11	49	−	L	6	Pain	-	myom + adenomyosis	tah + bso	Benign
12	49	−	L	7	Pain	-	myom	tah + bso	Benign
13	59	+	L	140	Pain + mass	-	Irreguler proliferative endometrium	tah + bso	Benign
14	57	+	L	7	Pain + mass	Mucinous cystadenoma		tah + bso	Benign
15	80	+	L	140	Bleeding	-	endo ca	pelvic lnd + tah + bso + omentectomy	Benign
16	45	−	R	60	Pain	Serous cystadenoma		left uso	Benign
17	59	+	L	70	Pain + mass	Mucinous cystadenoma		left uso	Benign
18	83	+	L	10	Mass	Overca mucinous ca		omentectomy + tah + bso	Benign
19	48	−	L	10	Mass	-	atrophic end + myom	tlh + bso	Benign
20	60	+	L	100	Mass	Mucinous cystadenofibroma		l/s bso	Benign
21	51	+	L	10	Bleeding	-	end ca	pplnd + tah + bso	Benign
22	76	+	L	150	Mass	-	Irreguler proliferative endometrium + adenomyosis	tah + bso	Benign

TABLE 1. Continued.

No	Age	M	Side	Size/mm	Presenting Sympyom	Ovarıan Concomitan Pathology	Endometrial Pathology	Surgery	Histology
23	49	−	R	90	Mass	Mature teratoma	Irreguler proliferative endometrium + myom + adenomyosis	tah + bso	Benign
24	71	+	B	120/50	Mass	-	Irreguler proliferative endometrium + myom + adenomyosis	tah + bso	Benign
25	64	+	L	2	Bleeding	-	endo ca g1	tlh + bso	Benign
26	62	+	L	18	Mass	mucinous borderline tumor		left uso	Benign
27	56	+	R	50	Mass	-		tah + bso	Benign
28	45	−	L	5	Pain	-	myom + adenomyosis	tah + bso	Benign
29	58	+	L	100	Mass	-	adenomyosis	tah + bso	Benign
30	54	+	B	1.0/1.0	Mass	Serous/mucinous cystadenoma		tah + bso	Benign
31	44	−	L	10	Pain	-	myom + adenomyosis	tah + bso	Benign
32	56	+	R	4	Mass	Serous bot	endometrial hyperplasia without atypia + polip + myom	omentectomy + tah + bso + pplnd	Benign
33	54	+	L	7	Bleeding	-	endometrial hyperplasia without atypia + myom + polip	tah + bso	Benign
34	74	+	L	1	Mass	Granulosa cell tumor (right)		pplnd + tah + bso + omentectomy	Benign
35	57	+	L	55	Pain	-	endometrial hyperplasia without atypia	tah + bso	Benign
36	53	+	L	5	Bleeding	-	end ca g2	tah + bso + plnd	Benign
37	63	+	L	5	Bleeding	-	polip + myom	tah + bso	Benign
38	49	+	R	165	Mass	-		tah + bso	Benign
39	55	+	R	5	Mass	High grade serous tumor		pplnd + tah + bso + omentectomy	Benign
40	48	−	R	4	Pain	-	myom	tlh + bso	Benign
41	73	+	B	0.5/1	Bleeding	-	endometrial hyperplasia without atypia + polip + adenomyosis	tah + bso	Benign
42	49	−	L	3	Pain	-	Irreguler proliferative endometrium + myom	tah + left uso	Benign
43	49	−	R	4	Mass	High grade serous peritoneal tumor		pplnd + tah + bso + omentectomy	Benign

TABLE 1. Continued.

No	Age	M	Side	Size/mm	Presenting Sympyom	Ovarıan Concomitan Pathology	Endometrial Pathology	Surgery	Histology
44	68	+	L	150	Bleeding	-	endometrial hyperplasia without atypia + adenomyosis	tah + bso	Benign
45	53	−	R	50	Pain	-	adenomyosis	tah + bso	Benign
46	59	+	L	50	Mass	Mucinous adeno ca	endometrial hyperplasia without atypia	pplnd + tah + bso + omentectomy	Benign
47	57	+	L	50	Mass	-	myom + adenomyos	tlh + bso	Benign
48	55	+	L	80	Mass	-	adenomyosis	pplnd + tah + bso + omentectomy	Benign
49	51	+	L	50	Mass	Mucinous adeno ca	Irreguler proliferative endometrium	pplnd + tah + bso + omentectomy	Benign
50	59	+	R	10	Bleeding	-	end stromal sarkom	pplnd + tah + bso + omentectomy	Benign
51	52	+	B	1.5/1	Pain	-	myom	tah + bso	Benign
52	62	+	L	6	Bleeding	-	myom + polip	tah + bso	Benign
53	46	−	L	15	Bleeding	-	polip + endometrial hyperplasia without atypia	tlh + bso	Benign
54	54	+	L	5	Bleeding	-	endo ca g2	pplnd + tah + bso + omentectomy	Benign
55	60	+	R	110	Mass	-	adenomyosis	tah + bso	Benign
56	71	+	R	6	Mass	Left benign mucinous cystadenoma	inaktif rndo	tah + bso	Benign
57	69	+	R	15	Pain	Left serous cystadenoma	atrophic end	tah + bso	Benign
58	50	−	B	3.0/3	Pain	-	adenomyosis	tah + bso	Benign
59	43	−	R	40	Pain	-	myom	right uso + myomektomi + omentectomy + plnd	Benign
60	63	−	R	4	Bleeding	-	endometrial carcinosarcoma	pplnd + tah + bso + omentectomy	Benign
61	53	+	B	50/120	Bleeding	-	myom + endometrial hyperplasia without atypia	pplnd + tah + bso + omentectomy	Malign
62	66	+	L	100	Pain + mass	-	myom	pplnd + tah + bso + omentectomy	Malign
63	64	+	R	70	Mass	-		pplnd + tah + bso + omentectomy	Malign

R: right; L: left; B: bilateral; tah: total abdominal hysterectomy; bso: bilaterally salphingooferectomy; pplnd: pelvic and para-aortic lymphadenectomy; lnd: lymphadecetomy; tlh: total laparoscopically hysterctomy; ca: Cancer.

TABLE 2. Profile of patients with malign Brenner tumors: clinical and oncological attributes.

No	Age	Stage	Chemotherapy	Recurrence (time/site/treatment)	Follow-up time (m)	Outcome
61	53	IIIC	C + PTx (6 cyc.)	No	72 m	died due to breast ca
62	66	1C	-	102 m/intra-abdominal recurrence/surgery + C + PTx (6 cyc.)	130 m	alive
63	64	IIIC	C + PTx (6 cyc.)	10 m/intra-abdominal and liver recurrens/C + gms (6 cyc.) 14 m/second intra-abdominal rec/liposomal doxorubicin	31 m	dead of disease

cyc: Cycle; C: Carboplatin; PTx: Paclitaxel; gms: gemsitabin; m: Month; ca: Cancer.

4. Discussion

The most frequent ovarian tumors are those that develop from the surface epithelium of the ovary.

Brenner tumors (BTs) of the ovary constitute around 5% of all epithelial ovarian neoplasms [7]. The three categories of BTs that the WHO classifies are benign, borderline and malign. Because of their histological resemblance to the components of the urothelium that resemble epithelial tissue, BTs are also known as transitional cell tumors [8].

The majority of ovarian BTs are unilateral. In several case studies, the percentage of bilateral cancers varies between 3.7% and 8% [9–12]. In our patient series, this bilateral rate was determined as 12.7%. This rate was seen as somewhat high according to the literature. 19% were unilateral in the right and 36% were unilateral in the left ovary.

Normal BT onset occurs between the fifth and sixth decades of life. Green and colleagues [13] also found that the average age was 58 years among 22 patients. In the series of 46 patients, Yüksel *et al.* [12] had a median age of 52 and 54.3% were in the postmenopausal group. Similarly, in our series, the median age was 57 years, while the postmenopausal group had a high rate of 71.4%.

Benign ovarian tumors are generally solid and well-defined grey-white nodules, usually measuring less than 2 cm in size in the majority of cases. Nevertheless, large tumors have been documented, with the largest tumor reported in the literature measuring 39 cm in its maximum dimension [14].

In our patient group, 58% of the patients had tumors below 2 cm in diameter, with the largest tumor measuring 16.5 cm. Tumors smaller than 2 cm were all benign, and 88% of them were incidentally detected. Borderline and malign tumors are larger with median sizes of 12 cm and 10 cm, respectively [15, 16]. In our series, no borderline BTs were identified, while in malign cases, the median tumor size was determined to be 85 mm.

There are studies in the literature reporting the coexistence of Brenner tumors with mucinous ovarian tumors, particularly mucinous cystadenomas [17–20]. In a literature review that included 460 Brenner tumors, Waxman *et al.* [18] reported that in 14.3% of cases, there was an associated ipsilateral mucinous tumor. Alloush and colleagues, on the other hand, reported this rate as 11%. This relationship has been attributed to the presence of mucinous metaplastic areas within Brenner tumors [21]. Wang and colleagues' study on BTs connected to mucinous neoplasms showed that the two components in each case shared a similar X-chromosome inactivation pattern, pointing to a common clonal origin for the two lesions [22]. In our series, while mucinous cystadenomas were present in 3.3% of the benign group, a combination of mucinous tumors (mucinous cystadenoma + mucinous adenocarcinoma) was identified in 10% of cases alongside benign Brenner tumors. We consider this relationship to be noteworthy during pathological examination.

The stromal component of Brenner tumors, resembling ovarian theca cells, produces estrogen, which may contribute to estrogen-related pathologies [23]. In our patient series, 9 patients exhibited non-atypical endometrial hyperplasia. Among these 9 patients, 4 had Brenner tumors with sizes exceeding 5 cm, with one of them being malign, while the others were smaller than 2 cm. Additionally, 8 patients had endometrioid-type endometrial cancer, with only one tumor measuring 14 cm, while the rest were below 1 cm. This trend might be attributed to an increasing hormonal effect with larger tumor sizes. However, the limited number of cases in our study was a weakness in establishing a conclusive hormonal relationship.

Concurrent tumors within the female reproductive system make up merely 1–6% of all genital neoplasms [24]. In our patient group, 2 patients (3.17%) were diagnosed with granulosa cell tumor in the contralateral ovary, 2 patients (3.17%) with serous ovarian carcinoma, and one patient with cervical carcinoma. The coexistence of these malignancies with the identified benign Brenner tumors, which were of 2 mm in size, was observed. There is no available data in the literature regarding the association of these tumors with Brenner tumors. We considered these 5 cases as incidental findings, which might be attributed to the fact that our study was carried out at a gynecologic oncology clinic.

Less than 5% of Brenner tumors are malignant [25]. In our patient group, there were 3 cases of Malign Brenner tumors with ages of 53, 64 and 66, respectively. All of these patients were postmenopausal, which aligns with the most commonly observed age range for malign Brenner tumors, typically occurring in the fifth and sixth decades of life [13, 26].

Surgical resection is used to treat BTs of all types, including

benign, borderline, and malign ones, at least in part. Any symptoms they may produce can usually be treated with resection, which also aids in making a pathologic diagnosis. The FIGO staging system can then be used to stage borderline and malign BTs [1, 16].

Information regarding the treatment of malign Brenner tumors is limited due to their rarity, and the management of adjuvant therapy remains unclear. Similar to epithelial ovarian cancers, the primary treatment is surgery. In the literature, there are studies reporting favorable outcomes with the use of adjuvant chemotherapy, specifically carboplatin and paclitaxel, as seen in other epithelial ovarian tumors [8, 27].

Lymph node dissection in Brenner tumor surgery is a debated topic. There are series in the literature that report no disease-specific survival (DSS) benefit from lymphatic spread and lymph node dissection in these patients. Approximately half of the patients underwent lymphadenectomy during surgery, and only 5% of them showed evidence of lymphatic spread [28]. In our series, pelvic and para-aortic lymphadenectomy was performed in three patients. Lymph node involvement was absent in the early-stage patient (patient 62, stage 1C). Only one patient (patient 61) had lymph node involvement, and during follow-up, a single intra-abdominal recurrence occurred at the 130th month. The other two patients were in advanced stages (stage 3C).

Out of our 3 patients with Malign Brenner tumors (MBT), two in advanced stages (patients 61 and 63) received carboplatin + paclitaxel chemotherapy after primary surgery, while the patient in the early stage (patient 62) received the same regimen after recurrence surgery. All three patients achieved complete chemotherapy responses. Gezginç *et al.* [26] reported a complete response rate in 9 out of 10 patients with a recurrence rate of 7/10. These results underline the significance of both cytoreductive surgery and chemotherapy. In our study, recurrence occurred in 2 out of 3 patients with MBT. One of the recurrent patients (patient 62) received chemotherapy after recurrence surgery and is currently disease-free. The other patient (patient 63), after primary adjuvant chemotherapy, experienced recurrence and received carboplatin, gemcitabine, and subsequently liposomal doxorubicin. This patient succumbed to the disease at the 31st month. Notably, this patient had no lymph node involvement. Interestingly, another advanced-stage patient (patient 61) with lymph node involvement did not experience recurrence during the 72 months of follow-up. We attribute this to the chemotherapy the patient received for breast cancer.

The absence of any borderline Brenner tumor cases and the limited number of malignant cases in our series, which is due to the rarity of these tumors, represent limitations of our study, restricting us from drawing more definitive conclusions. Nevertheless, sharing oncological outcomes in the management of these extremely rare tumors is still valuable.

5. Conclusions

The tumors known as Brenner tumors (BTs), particularly their malign varieties, are relatively uncommon. It's important to note that these tumors have the potential to influence hormones and trigger endometrial conditions. Multicenter studies are required to determine the best course of treatment and surgery, particularly for malign types.

AVAILABILITY OF DATA AND MATERIALS

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

AUTHOR CONTRIBUTIONS

ÖE—conceptualization, data curation, formal analysis, investigation, methodology, project administration resources, writing-original draft; CA—conceptualization, data curation, resources; AGB—formal analysis, methodology, project administration; EDÖ—investigation, resources, software; SK—methodology, resources, software; DA—supervision, validation, writing-review & editing; EK—data curation, methodology; MS—project administration, supervision, validation, writing-review & editing.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study titled "Brenner tumors: single centre experience" has been conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Health Sciences University Izmir Tepecik Training and Research Hospital with the approval number 2022/09-14.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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