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Malignant Brenner tumors of the ovary; a population-based analysis

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HIGHLIGHTS

- Malignant Brenner Tumors of the ovary are extremely rare tumors with an unclear management.
- Patients usually present with disease confined to the ovary.
- Regional lymphatic spread is uncommon.
- Patients with tumors confined to the ovary have an excellent prognosis.

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ABSTRACT

Objective. Malignant Brenner Tumor (MBT) is a tumor with an extremely low incidence that morphologically resembles to urothelium. Given the paucity of evidence on the epidemiology and prognosis of MBT, the aim of this retrospective population-based study was to elucidate the demographic and clinico-pathological characteristics of patients with ovarian MBT.

Methods. A cohort of patients diagnosed between 1988 and 2012 was drawn from the National Cancer Institute Surveillance and Epidemiology End Results database. For surgically treated patients, Observed and Disease Specific Survival were calculated following generation of Kaplan-Meier curves. Comparisons were made using the log-rank test.

Results. A total of 207 patients were identified. Median patient age was 65 years and the majority presented with unilateral, high grade tumors with a median size of 10 cm. Stage I, II, III and IV disease was noted for 55.4%, 14.4%, 18%, and 12.2% of patients respectively. Only 5.1% had positive lymph nodes for metastatic disease. Five-year disease-specific survival (DSS) of patients with tumors confined to the ovary was 94.5% compared to 51.3% for those with extra-ovarian spread ($p < 0.001$). Lymphadenectomy was not associated with an improved DSS ($p = 0.2$).

Conclusions. MBTs are typically unilateral high grade tumors localized to the ovary. Regional lymphatic spread is uncommon and lymphadenectomy does not confer any improvement on survival. Patients with tumors confined to the ovary have an excellent prognosis while extra-ovarian spread is associated with a poor outcome.

1. Introduction

Ovarian cancer is a heterogeneous group of tumors each characterized by distinct histopathological and clinical features [1]. Information on the epidemiology and prognosis of each histological subtype will facilitate more appropriate treatments for affected women. However, for ovarian tumor subtypes with a low incidence, such as squamous ovarian carcinoma or granulosa cell tumors, only limited epidemiological data are available [2,3]. This lack of information remains a barrier to development of individualized treatment protocols. Benign, borderline and malignant Brenner tumors of the ovary microscopically resemble urothelium and its neoplasms [4]. According to the revised WHO ovarian tumor classification, they form a distinct histological subgroup of epithelial ovarian tumors, representing <1% of all ovarian neoplasms [4,5].

Morphologically benign Brenner tumors are biphasic, consisting of nests of epithelial cells resembling the urothelium, surrounded by dense fibromatous stroma [6]. Their origin from transitional-type metaplasia of ovarian surface epithelium is widely accepted, however, a tubal origin has also recently been proposed [6]. <5% of all Brenner tumors are malignant and microscopically they are characterized by destructive stromal invasion [5,7,8]. Concise guidelines on the management of these tumors are lacking due to their rarity and our current knowledge derives from single case-reports and small case-series [7,9,10]. The aim of this population-based study was to elucidate the epidemiology and prognosis of MBT.

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2. Material and methods

A cohort of patients was obtained from the National Cancer Institute's SEER database which incorporates high quality data from 18 cancer registries (Detroit, Iowa, Kentucky, Louisiana, Utah, Connecticut, New Jersey, Atlanta, Rural and Greater Georgia, Alaska, California, Hawaii, Los Angeles, New Mexico, San Francisco, San Jose, Seattle) that cover approximately 27.8% of the total US population based on the 2010 census [11]. All patient data are de-identified and available to the public for research purposes; an exemption was also granted from obtaining institutional review board approval. To identify all eligible cases the following criteria were applied: (i) tumor with malignant behavior located in the ovary (ICD-O-3/WHO 2008 site code C.569) [12], (ii) tumor of malignant Brenner histology (9000/3) [12], (iii) tumor diagnosis between January 1, 1988 and December 31, 2012, (iv) diagnosis not obtained from autopsy or death certificate.

Demographic and clinicopathological parameters were extracted using the "case listing" option. Registries were grouped geographically as follows: central (Detroit, Iowa, Kentucky, Louisiana, Utah), eastern (Connecticut, New Jersey, Atlanta, Rural and Greater Georgia) and western (Alaska, California, Hawaii, Los Angeles, New Mexico, San Francisco, San Jose, Seattle). Staging information was based on the derived 7th edition of the AJCC staging system for patients diagnosed in 2010–2012, the derived 6th edition of the AJCC staging for 2004–2009 and the SEER-modified 3rd edition of AJCC staging for patients diagnosed between 1988 and 2003. SEER-historic stage was categorized as localized/regional/distant; localized stage includes cancer limited to the organ in which it began, regional stage includes cancer that has spread to nearby lymph nodes or tissues while distant stage includes cases that have spread to distant lymph nodes or tissues. Marital status was grouped as single, married and unknown. Tumor grade when available was recoded into a 3-tier grading system; grade 1 (well differentiated tumor), grade 2 (moderately differentiated tumor), and grade 3 which included both poorly differentiated and undifferentiated tumors. Cases for which the exact number of removed and examined lymph nodes was available were categorized in two groups: 1 to 10 nodes (limited lymphadenectomy) and >10 nodes (extended lymphadenectomy).

Observed survival (OS) and disease-specific survival (DSS) were estimated only for surgically treated patients. The survival variable in SEER database represents the number of months from cancer diagnosis to the date of death. Patients were presumed alive at the time of study cut-off (December 31st, 2012) and those that were alive at the last follow-up were censored. For the estimation of DSS, only patients with one tumor or the first of multiple primary malignant tumors were included; patients who died from causes other than ovarian cancer were censored. Kaplan-Meier curves were generated to determine median and 5-year survival rates and the log-rank test was employed to perform comparisons of survival between different groups A Cox hazard regression analysis was conducted to identify independent predictors of survival of patients with MBT; patients with missing information for one or more variables were excluded from the multivariate analysis. All statistical analyses were performed with the SPSS v.22 statistical package. The alpha level of statistical significance was set at 0.05 and all p-values were two-sided.

3. Results

In total, we identified 207 patients that met the inclusion criteria of this study. Demographic and clinicopathological characteristics of the cohort are summarized in Table 1. Median patient age was 65 years (range 34–95). The majority of patients presented with unilateral (84.1%) high grade (57% were grade 3) tumors that had spread locoregionally (71%). According to SEER historic stage, 58% of the patients had localized disease, while 13% had regional spread, and 28% had distant disease. AJCC staging information was available for 139 (67%) of the patients, from which 55.4% had stage I, 14.4% stage II, 18% stage III

Table 1
Demographic and clinico-pathological characteristics of patients with malignant Brenner tumor (MBT).

Variable	
Age (median, range)	65 (34–94)
Age	
<50	31 (15%)
50–64	68 (32.9)
65–74	48 (23.2%)
≥75	60 (29%)
Race	
White	168 (81.2%)
Black	19 (9.2%)
Other	20 (9.7%)
Marital status	
Married	101 (48.8%)
Single	94 (45.4%)
Unknown	12 (5.8%)
SEER registry	
Eastern	42 (20.3%)
Western	122 (58.9%)
Central	43 (20.8%)
Year of diagnosis	
1988–1992	15 (7.2%)
1993–1997	34 (16.4%)
1998–2002	62 (30%)
2003–2007	55 (26.6%)
2008–2012	41 (19.8%)
Laterality	
Unilateral	174 (84.1%)
Bilateral	26 (12.6%)
Unknown	7 (3.3%)
Grade	
Unavailable	100 (48.3%)
Available	107 (51.7%)
Grade 1	14 (13.1%)
Grade 2	32 (29.9%)
Grade 3	61 (57%)
Tumor size mm	100 (5–450)
(median, range)	(n = 143)[a]
AJCC stage	
Stage I	77 (55.4%)
IA	57
IB	3
IC	7
INOS	10
Stage II	20 (14.4%)
IIA	6
IIB	9
IIC	4
IINOS	1
Stage III	25 (18%)
IIIA	2
IIIB	4
IIIC	13
IIINOS	6
Stage IV	17 (12.2%)
SEER stage	
Localized	120 (58%)
Regional	27 (13%)
Distant	58 (28%)
Unstaged	2 (1%)
Surgery	
Yes	202 (97.6%)
No	5 (2.4%)
Lymphadenectomy	
Yes	99 (47.8%)
No	108 (52.2%)
1–10 LN removed	48 (54.4%)
>10 LN removed	40 (45.5%)
LN status	
Positive	5 (5.1%)
Negative	94 (94.9%)
Radiotherapy	5 (2.4%)

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