Clinicopathological profile of adnexal masses presenting to a tertiary-care hospital in Bhutan

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Abstract

Context: Adnexal masses of ovarian origin are of growing concern due to high fatality associated with ovarian malignancy because they are diagnosed at advanced stage due to vague symptoms and absence of recommended screening tests. **Aims:** The aim was to study the prevalence of histopathologic types of adnexal masses in different age groups and to analyze the accuracy of preoperative evaluation in diagnosing ovarian malignancy. **Settings and Design:** This was a cross-sectional study carried out in the Department of Obstetrics and Gynecology of a tertiary care hospital in Bhutan with gynecologic-oncology services, from January to December 2017. **Subjects and Methods:** Women presenting with adnexal mass were evaluated and those meeting criteria were enrolled. They were evaluated preoperatively with complete history, examination, ultrasound, and tumor markers. Risk of malignancy index (RMI) was calculated for all patients. Following surgery, histopathology results were compared with preoperative evaluation. **Statistical Analysis Used:** Chi-square test, t-test, Cohen's Kappa, and receiver operating characteristic curve analysis were used for statistical analysis. **Results:** Of 165 patients evaluated, 127 fulfilling criteria were enrolled. Adnexal masses of ovarian origin were most common ($n = 102, 80.3\%$), of which 12.7% were malignant. Epithelial ovarian malignancy was the most common malignant ovarian tumor, serous cystadenocarcinoma being the most common. Malignancy was significantly more in older, postmenopausal women with high RMI. Seven out of 11 women with high RMI were diagnosed in Stage 3 or 4. RMI score at cutoff of 200 was 54.6% sensitive and 85.7% specific. **Conclusions:** Adnexal mass of ovarian origin was the most common. Malignancy was significantly more in older, postmenopausal women with high RMI. RMI showed moderate correlation in diagnosing epithelial ovarian malignancies.

Key words: Adnexal mass, ovarian cancer, risk of malignancy index

Introduction

Adnexal masses are a commonly encountered gynecological problem.[1,2] Of them, malignant epithelial ovarian tumors are associated with the highest mortality of all gynecological cancers.[3] Most ovarian cancers are diagnosed at advanced stages, with 5-year survival as low as 10%. Early diagnosis provides 5-year survival rate up to 90%.[4]

Appropriate preoperative evaluation to discriminate between benign and malignant adnexal masses helps guide gynecologists refer women with suspected malignancies to a gynecologic-oncologist for appropriate therapy and optimal debulking, which is known to improve survival rate.[2]

This study aimed to determine the prevalence of different histopathologic types of adnexal masses among women presenting to our hospital and the proportion of ovarian malignancies among them. We also aimed to describe known risk factors of epithelial ovarian cancer and compare the preoperative evaluation and histopathologic diagnosis of epithelial ovarian cancer.

Subjects and Methods

We conducted this cross-sectional study from January 15, 2017, to January 15, 2018, in the Department of Obstetrics and Gynecology of a tertiary care hospital in Bhutan. We obtained ethical clearance from the Research Ethics Board of Health under the Ministry of Health (approval number REBH/Approval/2016/051 dated January 16, 2017).

We enrolled all premenopausal women with adnexal mass ≥ 8 cm, pregnant women with adnexal mass who underwent surgery, and postmenopausal women with adnexal mass of any size. Women with nongynecologic abdominal or pelvic masses, with known history of ovarian malignancy, with a history of

other established gynecological cancers, and diagnosed cases of ectopic pregnancy were excluded. Patients in whom surgery was not done, tumor markers were not available, who did not have adnexal mass intraoperatively, whom tissue was not sent for histopathology, or died before surgery were excluded from the study.

We obtained informed, written voluntary consent from all patients before enrolment. We used a structured interviewer-administered proforma to collect demographic data and gynecological anamnesis and performed thorough general and perabdominal examination.

We performed gray-scale ultrasound examination (transabdominal or transvaginal) for each patient before surgery and following data points were recorded – location, bilateralism, multiloculated or not, nature of mass, size of the mass, presence of solid areas, ascites, and presence of intra-abdominal metastasis. Adnexal mass size was measured based on transverse and longitudinal diameters in centimeters. Color Doppler study was not done for any patient.

We sent blood samples for tumor markers relevant to different age groups. Risk of malignancy index (RMI) was calculated using the formula: $RMI = U \times M \times CA\text{-}125$. Ultrasound score (U) was calculated based on five features – one point each for multilocular tumor, bilateral tumor, presence of solid parts in the tumor, presence of metastasis, and ascites; U = "1" if none or one feature is present, U = "2" if two or more than two features are present. Menopausal status (M) was marked "1" for premenopausal and "3" for postmenopausal women. Patients with amenorrhea more than a year or who had hysterectomy and older than 50 years were described as postmenopausal women. Value of CA-125 was calculated directly into the equation.

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Based on RMI, the patients were stratified into three groups (RMI <25 = low risk; RMI 25–200 = intermediate risk; RMI >200 = high risk). All patients with RMI >200 were considered highly suspicious for malignancy, and they were operated by the gynecologic-oncologist.

We noted the intraoperative findings of each patient and sent tissue specimen for histopathology. Histopathologic findings were analyzed to make the final diagnosis and stage of the disease. International FIGO staging criteria (2014) was used for final staging of the disease. All the histopathologic examinations of the specimens were done by pathologists to whom the ultrasonographic findings, tumor markers, and intra-operative findings were not revealed. Histopathologic diagnosis was regarded as a gold standard for evaluation of results to classify malignant and benign mass.

We cleaned the data for inconsistencies and coded data were entered twice using Epidata Version 3.1, and we used Epidata Analysis Version 2.2.2.183 (Epidata Association, Odense, Denmark; free online versions) and STATA Version 15 (University Licence, StataCorp) for data management, processing, and analysis.

We expressed descriptive statistics in terms of frequencies and percentages and summarized using means (standard deviation) or medians (interquartile range) where applicable. To test the significance of association between various risk factors of epithelial ovarian malignancies, we used Chi-square test and *t*-test with a significance level of 0.05.

We performed a diagnostic test evaluation between different RMI score cutoffs in predicting malignancy. We also compared the agreement between RMI score and results of HPE assuming HPE as the gold standard test using Cohen's Kappa statistics. Optimal value of RMI for our study population was calculated by receiver operating characteristic (ROC) curve analysis.

Results

Of 793 gynecologic patients admitted in the study period, 165 were evaluated for suspected adnexal mass and 127 were recruited for the study. Thus, 16% of gynecology in-patients were operated for adnexal mass.

The demographic characteristics of the study participants are given in Table 1. The mean age of the participants was 36.6 ± 14.1 years (range 12–84 years). Most of the patients (78.7%) were in the reproductive age group of 20–49 years.

The distribution of histologic types of adnexal masses is given in Table 2. Among the ovarian masses, 82.4% were benign and 17.6% were malignant. The distribution of ovarian masses by age is given in Table 3. Most of the benign ovarian tumors were found in the age group of 20–39 years (*n* = 53, 72.6%), the most common being mature cystic teratoma (61.6%), followed by serous cystadenoma (31.5%) and mucinous cystadenoma (6.8%).

There were 19 malignant ovarian tumors of which 13 (68.4%) were primary and 6 (31.6%) were metastatic tumors to the ovaries with primaries from gastrointestinal tract (*n* = 4), endometrium (*n* = 1) and lymphoma (*n* = 1). Malignant ovarian tumors were found commonly in patients aged 50 years and above (63.2%). We found 84.6% of malignant ovarian tumors were of epithelial origin of which serous cystadenocarcinoma (*n* = 7, 63.6%) was the most common.

Table 1: Characteristics of women operated for adnexal masses in a tertiary care hospital from January 15, 2017, to January 15, 2018 (*n*=127)

Characteristics	Benign (*n*=108)	Malignant (*n*=19)	Total (*n*=127)
Age categories (years)			
Below 20	4 (3.7)	2 (10.5)	6 (4.7)
20-29	34 (31.5)	0	34 (26.8)
30-39	49 (45.4)	2 (10.5)	51 (40.2)
40-49	12 (11.1)	3 (15.8)	15 (11.8)
50-59	4 (3.7)	5 (26.4)	9 (7.1)
60-69	4 (3.7)	4 (21.1)	8 (6.3)
≥70	1 (0.9)	3 (15.8)	4 (3.1)
BMI categories			
Underweight (<18.5)	5 (4.6)	2 (10.5)	7 (5.5)
Normal (18.5-24.9)	61 (56.5)	9 (47.3)	70 (55.1)
Overweight (25-29.9)	30 (27.8)	6 (31.6)	36 (28.3)
Obesity I (30-34.5)	9 (8.3)	1 (5.3)	10 (7.9)
Obesity II (≥35)	3 (2.8)	1 (5.3)	4 (3.1)
Marital status			
Married	93 (86.1)	17 (89.5)	110 (86.6)
Unmarried	15 (13.9)	2 (10.5)	17 (13.4)
Education			
Primary	20 (18.5)	1 (5.3)	21 (16.5)
Secondary	34 (31.5)	3 (15.8)	37 (29.1)
Tertiary	18 (16.7)	1 (5.3)	19 (15)
Monastic	2 (1.9)	0	2 (1.6)
Uneducated	34 (31.5)	14 (73.7)	48 (37.8)
Parity			
Nulliparous	34 (31.5)	3 (15.8)	37 (29.1)
Low (para 1-4)	64 (59.3)	9 (47.3)	73 (57.5)
High (para ≥4)	10 (9.3)	7 (36.8)	17 (13.4)
Sub-fertility			
No	46 (42.6)	3 (15.8)	49 (38.6)
Yes	6 (5.6)	1 (5.3)	7 (5.5)
Menopausal status			
Premenopausal	99 (91.7)	8 (42.1)	107 (84.3)
Postmenopausal	9 (8.3)	11 (57.9)	20 (15.7)

Data expressed as *n* (%). BMI=Body mass index

We studied the risk factors of 39 patients with epithelial ovarian tumors. Twenty-eight of them had benign lesions whereas 11 were malignant. Among the 11 patients with malignant epithelial ovarian tumors, seven of them (64%) presented in advanced stages (Stage III or IV). The statistical analysis of risk factors of adnexal masses and epithelial ovarian tumors is given in Table 4.

Benign lesions were significantly more common in patients below 50 years and malignant above 50 years. Mean age of women with malignant tumors was 60.63 years (95% confidence interval [CI] 50.1–71.2 years), whereas those with benign tumors was 40.8 years (95% CI 34.9–46.9 years), and the difference was significant.

Factors associated with epithelial ovarian cancer such as body mass index (BMI), oral contraceptive pill (OCP) use, and parity could not give statistically conclusive results due to very few numbers of women with primary epithelial ovarian cancers, except for menopausal status. Low RMI score was significantly associated with benign lesions and high RMI score with malignant lesions. However, there were five patients with low and intermediate RMI scores who had malignancy and four patients with high RMI score who had benign lesions.

Table 2: Distribution of histologic types of adnexal masses in women operated in a tertiary care hospital between January 15, 2017, and January 15, 2018 (*n*=127)

Adnexal mass by origin	Age (years)							Total
	<20	20-29	30-39	40-49	50-59	60-69	≥70	
Ovarian	5 (4.46)	26 (24.1)	42 (41.6)	13 (12.0)	9 (8.3)	8 (7.4)	5 (4.6)	108 (85.03)
Pelvic endometriosis	0	5 (50)	5 (50)	0	0	0	0	10 (7.87)
Tubal	0	1 (20)	2 (40)	2 (40)	0	0	0	5 (3.93)
Uterine	0	0	1 (100)	0	0	0	0	1 (0.78)
Tubercular	0	1 (100)	0	0	0	0	0	1 (0.78)
Inflammatory	0	1 (100)	0	0	0	0	0	1 (0.78)
Hydatid	0	0	1 (100)	0	0	0	0	1 (0.78)
Total	5 (3.9)	34 (26.8)	51 (40.2)	15 (11.8)	9 (7.1)	8 (6.3)	5 (3.9)	127

Data expressed as *n* (%)

Table 3: Distribution of ovarian masses by age in women operated for adnexal masses in a tertiary care hospital between January 15, 2017, and January 15, 2018 (*n*=108)

Ovarian masses	Age (years)							Total
	<20	20-29	30-39	40-49	50-59	60-69	≥70	
Benign								
Epithelial								
Benign serous	0	5 (21.7)	9 (39.1)	3 (13)	3 (13)	3 (13)	0	23 (21.3)
Benign mucinous	1 (20)	1 (20)	1 (20)	0	0	1 (20)	1 (20)	5 (4.6)
Germ cell tumor								
Mature cystic teratoma	2 (4.4)	14 (31.1)	23 (51.1)	5 (11.1)	1 (2.2)	0	0	45 (41.7)
Malignant								
Epithelial								
Malignant serous	0	0	0	1 (14.3)	2 (28.6)	3 (42.9)	1 (14.3)	7 (6.5)
Malignant mucinous	0	0	0	1 (50)	0	0	1 (50)	2 (1.9)
Borderline mucinous	0	0	1 (100)	0	0	0	0	1 (0.9)
Brenner's	0	0	0	0	0	0	1 (100)	1 (0.9)
Germ cell tumor								
Embryonal carcinoma	1 (100)	0	0	0	0	0	0	1 (0.9)
Sex cord stromal tumor								
Granulosa cell tumor	0	0	0	0	1 (100)	0	0	1 (0.9)
Metastatic								
Metastatic	1 (16.7)	0	1 (16.7)	1 (16.7)	2 (33.3)	1 (16.7)	0	6 (5.6)
Functional								
Functional	1 (6.3)	6 (37.5)	7 (43.8)	2 (12.5)	0	0	0	16 (14.8)

Data expressed as *n* (%)

We calculated sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of the RMI score to predict malignancy using two different RMI score cutoffs: (a) consolidating intermediate and low RMI scores together (RMI <200) versus high RMI score (RMI >200) and (b) consolidating high and intermediate RMI scores together (RMI >25) versus low RMI score (RMI <25). The results of the two different diagnostic test agreement tests are given in Table 5.

We calculated Cohen's Kappa agreement of diagnostic tests between these two groups. Agreement between RMI score (low and intermediate together) with histopathological result of malignancy was "moderate" with Kappa statistic 0.414 (95% CI 0.095–0.733). Agreement between RMI score (high and intermediate together) with histopathological result of malignancy was "fair" with Kappa statistic 0.239 (95% CI 0.031–0.446).

A ROC curve was produced to show the relation between sensitivity and specificity of the RMI in distinguishing between benign and malignant masses and is given in Figure 1. Optimal results were found at RMI cut-off of 58.7 from ROC curve analysis, with sensitivity of 84.2%
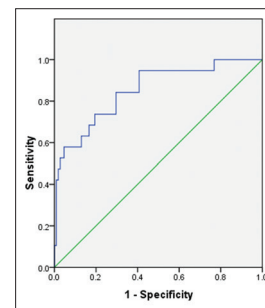
Figure 1: Receiver operating characteristic curve analysis of risk of malignancy index of women who were operated for adnexal masses in a tertiary care hospital between January 15th, 2017, and January 15th, 2018 (*n* = 127)

and specificity of 70.4% (area under the ROC curve 0.852 [95% CI = 0.755–0.946, *P* = 0.000]).

Discussion

Our study showed a prevalence of women requiring surgery for adnexal mass was 16% among 793 gynecology in-patients.

The prevalence of benign adnexal masses in our study is similar to a study conducted in India.[5] The most common benign ovarian mass was mature cystic teratoma, which

Table 4: Statistical analysis of risk factors of women with epithelial ovarian tumors in a tertiary care hospital between January 15, 2017, and January 15, 2018 (*n*=108)

Risk factors	Epithelial tumors		
	Benign (*n*=28)	Malignant (*n*=11)	*P*
Age (years)			
<50	20 (71.4)	3 (27.3)	0.011
≥50	8 (28.6)	8 (72.7)	
BMI (kg/m²)			
<25	16 (57.1)	7 (63.6)	0.791
≥25	12 (42.9)	4 (36.4)	
Parity			
Nulliparous	6 (21.4)	1 (9.1)	0.189
Para 1-4	15 (53.6)	5 (45.5)	
Para 5 or more	7 (17.9)	5 (45.5)	
OCP			
Not used	25 (89.3)	10 (90.9)	0.88
Used <5 years	3 (10.7)	1 (9.1)	
Menopause			
Premenopause	20 (71.4)	4 (36.4)	0.044
Postmenopause	8 (28.6)	7 (63.6)	
RMI			
Low	12 (42.9)	1 (9.1)	0.006
Intermediate	12 (42.9)	4 (36.4)	
High	4 (14.3)	6 (54.5)	

Data expressed as *n* (%). BMI=Body mass index, RMI=Risk of malignancy index, OCP=Oral contraceptive pill

Table 5: Diagnostic test evaluation of different cut-offs of risk of malignancy index score to predict malignancy of women who were operated for adnexal masses in a tertiary care hospital between January 15, 2017, and January 15, 2018 (*n*=127)

Parameter	High versus (intermediate + low) RMI score >200	Low versus (intermediate + high) RMI score >25
Sensitivity	54.6 (23.4-83.3)	90.91 (58.7-99.8)
Specificity	85.7 (67.3-95.9)	42.9 (24.5-62.8)
Positive predictive value	60 (34.3-81.2)	38.5 (30.1-47.5)
Negative predictive value	82.8 (71.2-90.3)	92.31 (63.8-98.8)
Accuracy	76.9 (60.7-88.9)	56.4 (39.6-72.2)

Data in parenthesis are 95% CI. CI=Confidence interval, RMI=Risk of malignancy index

is different from some studies which found benign serous cystadenoma as the most common.[6] Our study shows that adnexal masses occur with maximum frequency in the reproductive age group of 20–49 years, as seen in multiple other studies.[7,8]

In our study, 15% of women presenting with adnexal mass had an ovarian malignancy. Epithelial ovarian cancers accounted for a majority of them, the rest being metastatic from other primaries. This was thrice the incidence of 4.9% reported from a study in India[7] but less than the 19.3% prevalence reported by another study from Northern India.[5] Another study from south India reported an incidence of 9.5%.[9] The seemingly high rate of ovarian malignancy seen in our study could have been due to referral bias since our hospital is the only center with gynecologic-oncology services in the country.

Metastatic tumors to ovary constituted 32% in our study which was significantly higher than the 5%–8% reported in the literature.[10] Among metastatic tumors to the ovaries, 66.7% were of gastrointestinal origin, showing high rate of gastrointestinal cancers in our country with late diagnosis.

Women above 50 years were shown to have significantly increased risk of ovarian malignancy. We recommend screening women above 50 years for ovarian malignancy when they present to the clinic with suggestive symptoms because there is a lifetime risk of 1%–1.5% of having ovarian cancer.[1,11]

Our analysis failed to show an association between BMI and malignancy. This could have been due to the lower BMI cutoff of 25 that we used to stratify our patients. Since only around 10% of the women in our study had used OCPs, and all of them had used for <5 years, we could not derive any statistically significant protective effect. Nulliparity was not a statistically significant risk factor for ovarian malignancy in our study due to the small number of nulliparous women with malignancy.

There was a significant association among women of menopausal group and malignancy similar to results from India[5] and Serbia.[12] We should accord more priority to exclude malignancy in the postmenopausal women since the average age of diagnosis of ovarian malignancy is in the sixth decade and around 30% of malignant ovarian tumors are found in the postmenopausal women.[11] In our study, we found a higher proportion of 47%.

In our study, we have used RMI for preoperative evaluation to differentiate benign and malignant adnexal masses. The accuracy of RMI to differentiate between the two was statistically significant overall as well as specifically for epithelial ovarian cancers. However, few cases were wrongly classified which resulted in overall low sensitivity. Preliminary findings given our limited sample size suggest our current method of calculating RMI scores for preoperative prediction of epithelial ovarian malignancy is of only moderate efficacy. This could have been due to use of only gray-scale ultrasound. Combining gray-scale ultrasound with color Doppler study and incorporating International Ovarian Tumor Analysis (IOTA) rules to describe sonographic features of adnexal masses have shown a high sensitivity and specificity for prediction of malignancy in adnexal masses.[13]

The main limitations of the study were its hospital-based nature which predisposes to referral bias and increased prevalence of malignancies compared to the general population and that color Doppler study was not done for any patient in our study due to resource constraints.

Conclusions

Adnexal masses are an important cause of morbidity and mortality. The most commonly encountered adnexal masses were benign and arose from the ovary. Germ cell tumors were the most common benign ovarian tumor, serous cystadenocarcinoma being the most common malignant ovarian tumor.

Benign adnexal masses were most common in younger women. However, patients with malignancy were older and mostly postmenopausal. Fifteen percent of all adnexal masses were malignant and most of them presented in the advanced stages.

Age >50 years, postmenopausal status, and high RMI were significantly associated with malignant epithelial ovarian tumors whereas BMI and parity were not. Use of OCP also did not significantly protect against malignancy.

RMI and histopathology findings are in positive correlation. Therefore, it can be concluded that RMI can be used for evaluation of adnexal mass preoperatively. The low sensitivity of our preoperative evaluation through RMI can be improved with the use of new scoring models for describing ultrasonographic features of adnexal masses, such as IOTA rules, and by incorporating color Doppler study with gray-scale ultrasound.

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Conflicts of interest
There are no conflicts of interest.

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