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Review article

Evaluation of Ovarian Neoplasms in Honduras: Characteristics and Diagnostic Concordance Between Ultrasound, Tumor Markers and Histopathology

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1. Introduction

Ovarian cancer is the second most common gynecologic malignancy among women in high income countries with an incidence of 9.4 per 100,000 and mortality rate of 5.1 per 100,000 (Jemal et al., 2011). In low income countries, ovarian cancer has an incidence of 5.0 per 100,000 and mortality rate of 3.1 per 100,000 (Jemal et al., 2011). From the latest 2018 GLOBOCAN data on Honduras, there were 166 estimated incident cases of ovarian cancer and 94 estimated number of deaths from ovarian cancer (Bray et al., 2018). According to GLOBOCAN, ovarian cancer represented 3% of all new cancer cases in Honduras.

In Honduras, the total health expenditure as percentage of gross domestic product (GDP) is 8.7%, lower than the average of 14.1% for other countries of Central America and South America (WHO, 2014). This corresponds to approximately $100 investment per person, compared to high income countries, which invest around $2880 per person. The Honduran health system is divided into public and private sectors, with over 60% of the population in the public sector and an estimated 17% of Hondurans with no regular access to health services (Luis Bermúdez-Madriz et al., 2011). For a country of over 9 million people, San Felipe Hospital (HSF) serves as the single public national cancer center in Honduras. It is located in the capital city Tegucigalpa, Francisco Morazán department, where there are 24 doctors per 10,000 people.

Although basic services including surgery, chemotherapy and radiotherapy are available at HSF, there is a waiting period before patients can be treated, similar to many of the hospitals in the country and region. In addition to the need for HSF to provide care to a large number of patients, there is a lack of surgical providers and pathology services. Specifically, there are two pathology services in Tegucigalpa, covering four hospitals including Hospital Escuéla—the largest hospital in the country. Intraoperative frozen section diagnosis does not exist in Honduras. Computed tomography has been out of function at HSF for several years. Ultrasound is available in the public sector but can have a waiting period of one to three months. Due to such limited resources, appropriate referrals of patients suspicious for malignant ovarian tumor is needed to allow patients to receive care at the cancer center while patients with likely benign tumors may receive care at local hospitals. Therefore, preoperative ultrasounds and tumor markers may serve as important decision-making tools in selecting patients for potential surgical management in Honduras.

The ultrasound findings of malignant ovarian neoplasms have been well documented since the 1980s (Valentin et al., 2011). There are several imaging algorithms based on certain morphological parameters that have helped with predicting the likelihood of ovarian malignancy. The International Ovarian Tumor Analysis (IOTA) Simple Rules Model is a pre-operative classification system that discriminates between benign and malignant adnexal masses based on the following ultrasound parameters: presence of solid components, presence of ascites, irregular internal septations, solid or cystic components of the lesion, Doppler color flow and acoustic shadowing (Timmerman et al., 2005) (Table 1). The IOTA Simple Rules Model was developed from a multicenter study that evaluated over 1200 adnexal masses, of which 76% could be classified as either benign or malignant with sensitivity of 93%, specificity of 90%, positive predictive value (PPV) of 80%, negative predictive value (NPV) of 97% (Timmerman et al., 2008). Based on a 2014 meta-analysis comparing 19 different imaging models for adnexal mass classification, the IOTA Simple Rules and Logistic Regression Model 2 continued to demonstrate the highest sensitivity of 92–93% and specificity of 81–83% (Kaijser et al., 2014).

The IOTA Simple Rules Risk Estimate Model expanded upon the Simple Rules Model by estimating the risk of malignancy in both development and validation studies (Timmerman et al., 2016). The designation B1 (unilocular cyst) was most predictive of benign tumor while B3 (acoustic shadows) was least predictive. M2 (ascites) was most

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Table 1
International Ovarian Tumor Analysis Criteria (IOTA) Simple Rules Model. Adapted from Timmerman et al. (2008).

Classification	Malignant Characteristics
M1	Irregular solid tumor
M2	Presence of ascites
M3	At least 4 papillary structures
M4	Irregular multilocular solid tumor with largest diameter ≥100 mm
M5	High Doppler blood flow (color score 4)
	Benign Characteristics
B1	Unilocular
B2	Presence of solid components with largest component < 7 mm
B3	Presence of acoustic shadows
B4	Smooth multilocular tumor with largest diameter < 100 mm
B5	No Doppler blood flow (color score 1)

predictive of malignancy and M4 (irregular multilocular solid tumor with largest diameter ≥100 mm) was least predictive. Although histopathology is the gold standard for cancer diagnosis, there is a general consensus that sonographic evaluation of the morphology of an adnexal mass by a radiologist or experienced sonographer can properly estimate the risk of malignancy.

Cancer antigen 125 (CA 125) is a transmembrane glycoprotein originating from coelomic (pericardium, pleura, peritoneum) and mullerian (fallopian tubal, endometrial, endocervical) epithelia. CA 125 has been shown to aid in diagnosis of a malignant ovarian tumor if levels are severely elevated, especially in postmenopausal women. The overall sensitivity and specificity in detecting malignant ovarian masses has been studied and validated in multiple, large studies. In premenopausal women, the sensitivity was 70–79% and specificity was 69%. In postmenopausal women, the sensitivity was much higher at 93–94% and specificity was 58–59% (Dearking et al., 2007; Im et al., 2005). In women older than 50 years old with a CA 125 > 200 U/mL, one retrospective study showed a PPV of 70% and NPV of 85% (Im et al., 2005). In tumors classified as malignant based on ultrasound criteria, the elevation of CA 125 indicated a greater possibility of malignancy (Timmerman et al., 2008).

Given the limited resources in Honduras, the current method of selecting women for specialized surgery, including staging, is based on preoperative ultrasound and serum tumor markers, when available. At HSF, there has been no formal evaluation of the sensitivity and specificity of the sonographic diagnosis and histopathological correlation of malignant ovarian tumors. Due to our reliance on these preoperative assessment tools, we aim to evaluate the concordance of ultrasound and tumor markers with histopathology diagnosis in our context at HSF.

2. Methods

This is a retrospective cohort study evaluating patients between January 1, 2015 and December 31, 2016. The medical records of all patients with suspected malignant ovarian tumor during the study period were located in the national tumor registry. Institutional authorities, the Surgical Oncology Postgraduate Program and the Department of Oncology at HSF granted permission to conduct this study. All female patients above 18 years old who had undergone a single preoperative ultrasound evaluation and were subsequently surgically treated at HSF on suspicion of malignant ovarian tumor were included. Patients were included only if both ultrasound and pathology reports were complete and available. Patients with incomplete records were excluded.

A questionnaire comprised of nine questions was designed for research staff to extrapolate and record data from the medical records. Questions were divided into four sections comprised of ultrasound variables, laboratory and histopathology results, and concordance. The collected information was entered in an electronic database generated with the epidemiological statistical program Epi-Info 7.2.1.0. Once the quality control of the database and final editing were performed, the "Analysis" software module was used, which generated a statistical report composed of frequency tables and descriptive statistics with 95% confidence.

The kappa index (κ) is used to evaluate the concordance or reproducibility of measurement instruments whose result is categorical (2 or more categories). The kappa index (κ) represents the proportion of agreements observed beyond chance relative to the maximum possible agreement beyond chance. In the interpretation of the kappa index (κ), it must be taken into account that the index depends on the agreement observed, but also on the prevalence of the studied character and the symmetry of marginal totals (Clavijo Rodríguez et al., 2012).

$$\text{Kappa} \quad K = Po - Pe/1 - Pe$$

The kappa index is within a range of 0–1, with 0 corresponding to no agreement and 1 to perfect agreement.

3. Results

A total of 147 patients were surgically treated for suspected malignant ovarian tumor at HSF between January 1, 2015 and December 31, 2016. Thirty-four patients were excluded because of incomplete medical records.

A total of 111 patients (75.5%) were included in the study. Based on final histopathological results, 61 patients (55.0%) had a malignant tumor and 49 patients (44.1%) had a benign tumor. There was one borderline tumor (0.9%). According to the WHO classification, 49 (79.0%) were epithelial ovarian carcinomas, six (9.7%) were germ cell tumors and four (6.5%) were sex cord-stromal tumors. The remaining three (4.8%) malignant tumors were of non-gynecologic origin including sigmoid colon adenocarcinoma and metastatic tumors.

The most common malignant tumors were papillary serous cystadenocarcinoma seen in 30 patients (48.4%), followed by endometrioid adenocarcinoma in nine patients (14.5%) and dysgerminoma in six patients (9.7%). The most common benign tumors were cystadenomas in 15 patients (30.6%), mature teratomas in nine patients (18.3%) and endometriomas in six patients (12.2%) (Supplementary Table S1).

The most commonly performed type of ultrasound was the transabdominal method in 65 patients (68.5%) where abdominal and pelvic structures were evaluated. Pelvic ultrasound, which was performed with an abdominal probe, evaluated pelvic structures only and was performed in 24 patients (21.6%). Transvaginal ultrasound was performed in 22 patients (19.8%). Seventy-two (64.8%) of all ultrasound evaluations were performed by a radiologist. The remaining ultrasound evaluations were performed by a gynecologist in 32 patients (28.8%), a primary care physician in three patients (2.7%) and resident physicians in four patients (3.6%). Furthermore, of those with histologically confirmed malignant tumors (n = 61), 40 patients (65.6%) had an ultrasound performed by a radiologist (Supplementary Table S2).

We reviewed the ultrasound reports to determine how many of the studies were performed using the IOTA criteria (Table 2). The most commonly identified characteristic was irregular solid tumor as seen in 67 patients (60.3%). The second most commonly identified characteristic was irregular multilocular solid tumor larger than 100 mm in diameter in 64 patients (57.6%). In histopathological malignant patients only (n = 61), the most common IOTA criteria were irregular solid tumor in 41 patients (67.2%), followed by irregular multilocular solid tumor with largest diameter ≥100 mm in 33 patients (54.1%), the presence of ascites in 25 patients (40.9%), increased vascularity in 12 patients (19.6%) and papillary projections in four patients (6.5%).

Tumor markers CA 125, human chorionic gonadotropin (HCG) and alpha fetoprotein (AFP) were collected in 76 patients (68.4%) (see Supplementary Table S3). Most of these patients had all three tumor markers measured when possible. Elevated tumor markers were seen in 37 (48.7%) of these patients. Two patients had elevated AFP levels and

Table 2
Operational Characteristics of Ultrasound Findings in Surgically Treated Patients for Suspected Malignant Ovarian Tumor, San Felipe Hospital, 2015–2016.

Characteristics	N (%)
Characteristics of Ultrasound	
Type	
Transabdominal	65 (58.5)
Pelvic	24 (21.6)
Transvaginal	22 (19.8)
Operator	
Radiologist	72 (64.8)
Gynecologist	32 (28.8)
Family Doctor	3 (2.7)
Gynecology Resident	2 (1.8)
Radiology Resident	2 (1.8)
Institution	
Private	65 (58.5)
HSF	25 (22.5)
HEU	21 (18.9)
Ultrasonographic Findings	
Number of IOTA criteria Identified	N (%)
1	57 (51.0)
2	36 (32.0)
3	15 (13.5)
4	2 (1.8)
5	0 (0)
0	1 (0.9)
IOTA Criteria Identified	
Irregular solid tumor	67 (60.3)
Irregular multilocular solid tumor with largest diameter ≥ 100 mm	64 (57.6)
Ascites	29 (26.1)
Doppler positive	17 (15.3)
More than 4 papillary projections	5 (4.5)

*HSF: Hospital San Felipe *HEU: Hospita Escuela Universitario.
Transabdominal: Abdominal probe assessing abdomen and pelvis.
Pelvis: Abdominal probe assessing pelvis only.
Transvaginal: Vaginal probe assessing pelvis only.

one patient had an elevated HCG level. Of the remaining 34 patients who had elevated CA 125 (> 35 U/mL), 26 (76.4%) had a malignant tumor. Normal tumor markers were seen in 39 out of 76 patients (51.3%) who had tumor markers collected. In the 61 malignant ovarian masses, 26 (42.6%) presented with elevated CA 125 levels and 10 (16.4%) had normal CA 125 levels.

The kappa concordance index for ultrasound and histopathological diagnosis was 0.03, corresponding to slight agreement, with a standard error of kappa 0.04 and a 95% confidence interval between 0.11 and −0.05. Sensitivity was 97%, specificity 6%, PPV 56% and NPV 60%. The kappa concordance between ultrasound with tumor markers and histopathological diagnosis was 0.60, corresponding to moderate agreement, with standard error of kappa 0.11 and a 95% confidence interval between 0.82 and 0.37. Sensitivity was 80%, specificity 81%, PPV 82% and NPV 78% (Table 3).

4. Discussion

In low resource countries such as Honduras where there is a single national cancer center, appropriate referrals need to be made to maximize resources and avoid futile treatment. Without intraoperative frozen section support and advanced imaging modalities, the current method of selecting women for specialized cancer surgery in Honduras is based on preoperative ultrasound features and serum tumor markers.

In our study, when ultrasound and tumor marker results were evaluated concurrently, there was improved concordance with histopathology: sensitivity of 80%, improved specificity of 81%, PPV of 82% and NPV of 78%. This supports that ultrasound and CA 125 provided a more comprehensive preoperative evaluation of adnexal masses at our institution than ultrasound alone. In our study, CA 125 was elevated in 26 (42.6%) of all patients with histopathologically confirmed ovarian cancer. Conversely, in patients who had ovarian cancer and had tumor markers collected (n = 39), 26 (66.7%) had elevated CA 125. Our finding is consistent with Hartman et al on the ability of using CA 125 and ultrasound criteria to predict malignancy in women with adnexal tumors (Hartman et al., 2012). They observed that 69.0% of women with malignant tumors had elevated CA 125 levels.

When using ultrasound only, the sensitivity in detecting ovarian cancers was 97% and the specificity was 6%. This was largely due to the high false negative rate of 46 out of 49 histopathologically benign tumors that were initially suspected to be malignant based on ultrasound features. This discrepancy can be attributed to the predominantly transabdominal method of ultrasound used to assess adnexal masses in our study. Specifically, 80.2% of all patients were evaluated with only an abdominal probe to assess the suspicious ovarian tumor. This is in stark contrast to the standard of transvaginal ultrasound to evaluate adnexal masses, which was performed in only 19.8% of our patients. There was no comparison between transvaginal and transabdominal ultrasound with respect to diagnostic concordance in evaluating adnexal masses.

In Clavijo Rodriguez et al, 92 adnexal masses were evaluated by transvaginal ultrasound, which showed 96% sensitivity in detecting malignancy as confirmed by histopathology (Clavijo Rodríguez et al., 2012). Similar to our study, Hartman et al evaluated 110 adnexal masses to assess the capability of IOTA ultrasound criteria and CA 125 in differentiating benign and malignant tumors (Hartman et al., 2012). They used both transabdominal and transvaginal ultrasound for all patients. The ultrasound criteria had sensitivity of 90%, specificity of 87%, PPV of 69% and NPV of 97%. Interestingly, in tumors classified as malignant on ultrasound, CA 125 levels contributed significantly to the detection of histopathological malignant tumors (p = 0.025).

Endovaginal transducers have higher resolution and are positioned closer to the pelvic organs compared to abdominal transducers. The closer proximity and better resolution of transvaginal ultrasound allow for optimal visualization of most adnexal masses (Abuhamad et al., 2014). Transabdominal ultrasound is useful for larger or more cephalad

Table 3
Diagnostic Concordance between Ultrasound, Tumor Markers and Histopathology in Surgically Treated Patients for Suspected Malignant Ovarian Tumor, San Felipe Hospital, 2015–2016.

Diagnostic Concordance							
	Histopathology Result		Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Kappa CI
Ultrasound	Malignant (N = 61)	Benign (N = 49)	97%	6%	56%	60%	0.03 (0.11 to −0.05)
Malignant	59	46					
Benign	2	3					
Ultrasound and Tumor Markers	Malignant (N = 39)	Benign (N = 36)	80%	81%	82%	78%	0.60 (0.82–0.37)
Malignant	32	7					
Benign	8	29					

PPV: positive predictive value; NPV: negative predictive value.
All above cases had abnormal ultrasounds and where indicated, tumor markers were collected.

or lateral masses, and can assess neighboring structures for possible intra-abdominal dissemination of disease (Brown et al., 2010). The use of transabdominal ultrasound can serve as a complement particularly in low resource countries or communities where computed tomographic imaging is not readily available.

For Timmerman et al, the IOTA criteria could be applied to about 76% (937/1233) of masses with a sensitivity of 93%, specificity of 90%, PPV of 80% and NPV of 97%. The remaining 24% of masses could not be classified as either benign or malignant. When prospectively tested, Timmerman et al demonstrated similar sensitivity, specificity, PPV and NPV, and again that only 76% of masses could be classified as either benign or malignant.

In our study, the IOTA criteria were not fully applied or described in the radiological reports. In the ultrasound reports of 57 patients (51%), only one of the criteria was described. The ultrasound reports of two patients (1.8%) described four of the criteria and no studies described all five criteria. In looking at the relationship between the ultrasound findings and ovarian cancers, Rivas-Corchado et al reported the presence of at least two or more high risk ultrasound markers in 80.6% of malignant ovarian tumors (Rivas-Corchado et al., 2011).

Our study is limited by its retrospective nature and extrapolation of data only from medical records. The raw data is limited in that the ages of patient were recorded as only above the age of 18. Therefore, we cannot determine if image and tumor marker assessment were more or less accurate with increasing age of the patient. We also cannot evaluate the correlation of age and CA 125 in this study population, although it is known that the predictive value of CA 125 is more helpful and specific in postmenopausal women.

The correlation between imaging and tumor markers with malignancy and extraovarian disease at time of surgery was not available. Intraoperative findings were available in operative records, which were sometimes missing from the patient records. We included patients whose record had both ultrasound and pathology reports. Intraoperative findings are not always included in the information sent to pathology.

Given the limited infrastructure in the Honduran health system, there are only two public pathology services in Tegucigalpa. The current waiting time for a pathology report in HSF is between four and six weeks. Therefore, we did not have the capacity nor resources for a re-review of final pathology in our study to confirm accurate benign versus malignant tumor.

Another limitation is the unknown skills of the sonographers at outside facilities which performed the majority of the imaging studies. Although we were able to provide the professional role of the sonographers, most of whom were radiologists (64.8%), we do not have information of their level of training, such as number of ultrasounds previously performed. However, discrepancy between sonographers is not unique to HSF nor to Honduras but may be applied to many other studies evaluating diagnostic accuracy of ultrasound.

This study evaluated patients who were surgically treated at HSF even if preoperative ultrasound was performed at outside centers. The information of patients who had ultrasounds and ultimately were not referred to the cancer center is not available to us. There is currently no control if all referred patients ultimately received treatment at HSF or private centers. We acknowledge that there is a selection bias but the observed diagnostic concordance of ultrasound and tumor markers with histopathology pertain primarily to HSF. Patients who were not referred to HSF are usually patients with low suspicion of malignancy.

We demonstrated the potential of quality improvement at our institution in the use of ultrasound to evaluate adnexal masses. Ultrasound is arguably the most cost effective imaging modality and therefore is available in most towns of Honduras. In order to have useful patient referrals to HSF, ultrasound assessments must be standardized and accurate. From our data, we revealed an area of quality improvement at HSF and in Honduras through effective training in performing transvaginal ultrasounds, including using IOTA parameters to adequately classify the adnexal masses as benign or malignant. If ultrasound evaluations using these criteria deem an adnexal mass as more likely benign, the patient can then be referred to an outside, non-cancer center for treatment. This would save the patient the additional costs of travel and save the HSF referral for another patient.

On the contrary, if an adnexal mass is highly suspicious for malignancy based on these improved ultrasound studies, the patient would then be referred to HSF where tumor markers can be collected. Tumor markers are primarily but not routinely analyzed at major hospitals in the larger cities. The use of tumor markers will contribute more information to the preoperative assessment of suspicious adnexal masses for potential surgical intervention at our institution. Having baseline tumor marker results will also serve a prognostic utility for the surveillance of ovarian cancer.

Our study has demonstrated an innovative approach to caring for women with potential ovarian cancer in a low resource country. We evaluated how accurate preoperative ultrasound and serum tumor markers may correlate with malignant pathology in the absence of frozen section support. Furthermore, we have shown that preoperative ultrasound and tumor markers are decision-making tools in referring patients to a cancer center for specialized surgery, all within the context of resource and financial limitations at an institutional and regional level.

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Author contribution

Ashley Moon, Andrea Bourdeth and Linus Chuang wrote and edited the manuscript. Andrea Bourdeth, Roberto Jerez and Jackeline Alger designed the study, acquired, analyzed and interpreted the data. All the authors reviewed and approved the final version of the manuscript.

Declaration of Competing Interest

None of the authors have financial or personal disclosures

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.gore.2019.100501.

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