Study of Comparison of conventional ultrasound, RMI 4 score and CT imaging in diagnosis of Ovarian Cancer confirmed by surgical-pathological findings.

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Abstract

Background: Ovarian cancer; 5th commonest cancer among Nepalese women is the leading cause of gynecologic cancer related death. Proper diagnostic studies therefore assist Gyne-oncologist for appropriate surgery and chemotherapeutic planning, there by optimizing the patient prognosis. Objective of current study was to compare ultrasonography imaging, CT imaging, CA 125 value, RMI 4 score and surgical staging in diagnosis of ovarian cancer correlated with histo-pathological findings. **Materials and Methods:** The study was retrospective observational study, carried out between 14th April 2019 to 16th October 2021, in the department of surgical oncology (Gynecology oncology unit), B.P Koirala Memorial Cancer Hospital, Bharatpur. **Results:** 53 patient data were included in the observation. The efficacy of Ultrasound (sensitivity-90.90%, Specificity-60%) and CT (sensitivity-100%, specificity-65%) gave the best result in non-invasive investigations; whereas surgical staging (sensitivity- 96.96%, specificity- 90%) gave the better result when invasive modalities were considered. RMI 4 score had sensitivity 96.96% and specificity 60%. **Conclusion:** All modalities had good diagnostic performances and complemented each other in further defining the characterization of the ovarian mass, local spread and distant tumor dissemination.

Key words: Ovarian cancer, Ultrasound, CT, RMI 4, Surgical staging.

Introduction

Cancer is an important cause of morbidity and mortality worldwide, in every world region, and irrespective of the level of human development. In year 2020, there were approximately 3,14,000 new cases and 2,07,000 deaths from ovarian cancer (GLOBOCAN 2020).[1] Among Female, ovarian cancer (5th commonest cancer among Nepalese women[1]) is more lethal than endometrial and cervical cancer combined due to delayed diagnosis. Ovarian cancer is the leading cause of gynecologic cancer related death among women, with estimated 1,51,900 deaths worldwide.[2] Owing to the lack of symptoms and early peritoneal dissemination, over 75% of women with the disease have tumor spread beyond the pelvis at the time of diagnosis, and their treatment requires the appropriate use of surgery and chemotherapy.[3]

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CA 125 is an antigenic determinant on a high-molecular weight glycoprotein recognized by a monoclonal antibody (OC 125), which was raised using an ovarian cancer cell line as an immunogen. CA 125 levels were found to be elevated to more than 35 U/mL preoperatively in 80% to 85% of women with epithelial ovarian cancer compared with 1% of healthy controls.[4] CA-125 which has been found to be elevated in epithelial cancer is more often nonspecific, and through gynecological examination and ultrasound evaluation too have low sensitivity, CT and MRI imaging have become the popular method of detection and preoperative assessment of ovarian tumors.[5] Preoperative evaluation by CT scan with contrast enhancement, till today is one of the best method available to characterize the ovarian mass and to determine its extent of spread. Proper diagnostic studies therefore assist gyne-oncologist for appropriate surgery and chemotherapeutic planning; therefore avoiding unnecessary extensive surgeries and associated morbidities in advanced cases of ovarian cancer.

This study was done to compare ultrasonography imaging, RMI 4 score, CT imaging, surgical staging in diagnosis of ovarian cancer correlated with histo-pathological findings. In this article we tried to determine the optimal investigative modality for diagnosis of ovarian cancer in a low resource setting like ours and thereby aiding in better management and survival outcome of the patient.

Materials and Methods

Our study was a retrospective observational study carried out between 14th April 2019 to 16th October 2021, in the department of Surgical oncology (Gynecology oncology unit), B.P Koirala Memorial Cancer Hospital (BPKMCH), Bharatpur. Case notes were retrieved from medical record section of the hospital.

Criteria for sample selection:

Inclusion Criteria:

1. All cases of suspected ovarian tumours, who underwent CA 125 estimation, imaging (USG, CT scan) followed by Staging laparotomy and histo-pathological examination of the specimen during the course of study.

Exclusion Criteria:

All cases of ovarian cancer who didn't fulfill the inclusion criteria and those cases who received neo-adjuvant chemotherapy.

Sample size calculation:

The minimum required sample size is determined by Buderer's formula;

$N = [Z^2_{1-\alpha/2} \times P \times (1-P)]/L^2$

Where;

- N = number of patients, $Z_{1-\alpha/2} = 1.96$ (standard normal deviate value that divides the central 95% of z distribution from 5% in the tails),
- P = the reported sensitivity (As per the study done by Jung et al. (2002)[6], the calculated sensitivity of the ultrasound for the detection of ovarian carcinoma is around 85% i.e., 0.85),
- L= absolute precision desired on either side (half width of the confidence interval of the confidence interval) of sensitivity (10% i.e., 0.1).

Accordingly, the minimum sample size was 49 and we had 53 cases taken into consideration. Points taken into considerations were:

- The score for CA-125 remained unchanged (corresponds to actual level of serum concentration in units/mL).
- Tumor size <7cm, were given S=1, and size > 7cm were given S=2.

Table 1: IOTA Group ultrasound 'rules' to classify masses as benign (B-rules) or malignant (M-rules)[7,8]

B-RULES	**M-RULES**
Unilocular cyst	Irregular solid tumor
Presence of solid components where the largest solid component <7mm	Presence of ascites
Presence of acoustic shadowing	At least four papillary structures
Smooth multilocular tumour with a largest diameter <10cm	Irregular multilocular solid tumour with largest diameter > 10cm

- The score for CA-125 remained unchanged (corresponds to actual level of serum concentration in units/mL).
- Tumor size <7cm, were given S=1, and size > 7cm were given S=2.

The RMI 4 at a cutoff level of 450 (RMI score more than 450 were considered to represent malignancy) yielded a sensitivity of 86.8%, a specificity of 91.0%, a positive predictive value of 63.5%, a negative predictive value of 97.5%, and an accuracy of 90.4%.[9]

The histo-pathological analysis of surgical resected specimens was considered as gold standard for comparison of diagnostic values of various investigative modalities. Then the filled questionnaire were converted to a spreadsheet which were restructured as per need for the data analysis in SPSS 25 software.

Table 2: CT imaging features suggestive of Benignity or Malignancy of Ovarian mass. [9]

SN	Imaging features	Diagnosis		
		Benign	Malignant	
PRIMARY FINDINGS				
1.	Lesion size	<4cm	>4cm	
2.	Presence of mass unilaterality/bilaterality	unilateral mass	bilateral mass	
3.	Mass component	entirely cystic	cystic-solid or soft-tissue mass with necrosis	
4.	Wall/septal thickness	smooth, thin (of thickness <3mm)	irregular, thick (>3mm)	
5.	Papillary projections	absent	present	
SECONDARY FINDINGS				
6.	Ascites	absent	present	
7.	Peritoneal metastases	absent	present	
8.	Pelvic organ invasion	absent	present	
9.	Lymphadenopathy	absent	present	

Interpretation:

- MALIGNANT: when at least 2 primary criteria or 1 primary and 1 secondary criterion were present.
- BENIGN: when 3 primary criteria out of 4 were present.

Results:

Total of 53 patients were included in the study. The youngest patient was 14 years and the most elderly patient was 82 years, mean age ± standard deviation was calculated which was 44.4 ± 14.34 years. Majority of patients

(29) included were above 40 years. 24 patients were in the age group less than 40 years. Table 4 and 5 show patient demographic details.

Table 3: Laparotomy Findings (to differentiate between benign and malignant mass)

SN	Characters	Benign	Malignant
1.	Ascites	Absent	Present, often hemorrhagic
2.	Exophytic growth on surface	Absent	Present
3.	Adhesions	Absent	Present
4.	Peritoneal nodules	Absent	Present
5.	Metastatic deposits to other organs	Absent	Present
6.	Cut section	Cystic	Solid and hemorrhagic areas

Table 4: Age-wise Distribution of patients

SN	Age Group (years)	N
1.	10-19	4 (7.5%)
2.	20-29	6 (11.3%)
3.	30-39	14 (26.4%)
4.	40-49	6 (11.3%)
5.	50-59	13 (24.5%)
6.	60-69	6(11.3%)
7.	70-79	3(5.66%)
8.	80-89	1(1.88%)

Majority of patients were multi-parous (39 cases) and were in surprisingly in premenopausal age group (20 cases).

The commonest presenting complain being abdominal complaints including post meal distention of abdomen, loss of appetite and lower abdomen pain (Table 6).

CA 125 levels were low (<35U/ml) in 9 (16.9%) cases, mildly elevated (35-200U/ml) in 21 (39.6%) cases, significantly elevated (201-1000U/ml) in 20 (37.7%) cases and were very high (>1001 U/ml) in 3 (5.6%) cases.

The histo-pathological analysis of surgical resected specimens was considered as gold standard for comparison of diagnostic values of various investigative modalities (Table 7).

Diagnostic comparison was done (Table 8) for different modes of evaluation using sensitivity, specificity, Positive Predictive Value (PPV), Negative Predictive Value (NPV) and accuracy.

CT showed a 86.79% accuracy compared to 79.24% by USG in detection of ovarian cancer. In our study, both USG and CT showed remarkable accuracy for detection of ovarian cancer. CT had better specificity in diagnosing malignant ovarian mass and better accuracy in pre-operative staging of the disease compared to ultrasound imaging.

RMI 4 score showed better sensitivity and accuracy in diagnosing ovarian cancer compared to ultrasound imaging.

Discussion:

This retrospective study evaluated various modalities of investigations in ovarian masses mainly to determine malignant nature of ovarian cancer. The diagnostic abilities of each was analysed and correlated with one another, considering final histo-pathological report as gold standard. The results indicated that each parameters were unique in detection of ovarian malignancy and its spread.

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Table 5: Parity and Menopausal Status of Patients

S.N.	Parity	Number(%)	Premenopausal (%)	Menopausal <5 years, (%)	Mmenopausal 6-10 years (%)	Menopausal > 11 years (%)
1	NULLI	9 (16.9%)	8 (15%)	0	0	1 (1.8%)
2	PRIMI	5 (9.4%)	3 (5.6%)	1 (1.8%)	1 (1.8%)	0
3	MULTI	34 (64.1%)	18 (33.9%)	2 (3.7%)	7 (13.2%)	7 (13.2%)
4	GRAND-MULTI (> 5)	5 (9.4%)	2 (3.7%)	0	2 (3.7%)	1 (1.8%)

Table 6: Presenting Complaints of Patients

SN	Chief Complaints	N (%)
1	Abdominal Complaints (post meal distension, loss of appetite, lower abdominal pain)	37 (69.8%)
2	Post Menopausal Bleeding	2 (3.7%)
3	Menstrual Complaints	9 (16.9%)
4	Asymptomatic (Incidental Findings)	5 (9.4%)

Regarding the role of ultrasound in evaluation of adnexal lesion, our aim was not only to evaluate its role for routine screening for malignancy, but also to study indicators of malignancy such as thick walls, thick septae, intra-cystic projections, solid areas, bi-laterality, presence of ascites and intra-abdominal metastasis, so that we could estimate RMI 4 scores accurately. We also estimated CA-125 levels in all the cases, though we knew that this marker is primarily meant for tumors of epithelial origin which constitutes the majority of ovarian tumors (up to 80%). However CA-125 is not very specific for ovarian cancer and it is well-known that false positive results may result from several benign conditions such as pelvic inflammation, endometriosis, adenomyosis, uterine fibroids and even normal menstruation.[10]

Comparison of studies on USG for detection of ovarian malignancy:

Our results of USG compared to other studies in literature showed a comparable sensitivity of 90.9% especially when compared to the results of international ovarian tumor association and United Kingdom Collaborative Trial of Ovarian Cancer Screening (UKCTOS) [11] and study by Moideen N et al.[12] in detection of ovarian malignancy. Our study showed a very low specificity of 60% in detection of ovarian carcinoma when compared to other studies in literature [11,13,14,15,16,17] but comparable with the study done by Moideen N et al. [12] This may be because of the inter-observer variation in results of ultrasonography and also the failure of USG in assessment of the involvement of retroperitoneal area.

Comparison of studies on CT for detection of ovarian malignancy:

The results of CT in our study compared to other studies[13,14,15,18,19] in literature showed a higher sensitivity, comparable to the study by Mubarak et al. [12,20]

Table 7: Histopathological Findings of Patients

S.N.	Nature of the Disease	WHO group	Histology	n
1.	Benign	Epithelial	SEROUS CYSTADENOMA	7
			MUCINOUS CYSTADENOMA	3
			MUCINOUS CYSTADENOMA WITH i. BRENNER ii. TERATOMA	 2 3
		Sex cord stromal tumour	FIBROTHECOMA	3
1.	Border line	Epithelial	BODERLINE MUCINOUS	2
			BODERLINE SEROUS	0
3.	Malignant	Epithelial	SEROUS CYSTADENOCARCINOMA	16
			MUCINOUS CYSTADENOCARCINOMA	8
			CLEAR CELL CARCINOMA	0
			ENDOMETRIOID ADENOCARCINOMA	0
			ADENOFIBROMA	0
		Germ Cell	YOLK SAC TUMOUR	3
			OVARIAN DYSGERMINOMA	4
			IMMATURE TERATOMA	2
			MALIGNANT MIXED MULLLERIAN TUMOUR	0
		Metastatic	KRUKENBERG TUMOUR	0
			FALLOPIAN TUBE CARCINOMA	0

Table 8: Diagnostic Value of the Single parameter VS Two parameters

Parameters	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
CA 125 (>35U/ml)	93.93	35	70.45	77.77	71.69
USG	90.90	60	78.94	80	79.24
CT	100	65	82.5	100	86.79
SURGICAL STAGING	96.96	90	94.11	94.73	94.33
RMI 4	96.96	60	80	92.30	83.01

Although our study showed a very low specificity of 65% because of the high number of false positives which may be due to non-specific inflammatory changes within the tumor, reactive lymphadenitis appearing as enlarged lymph nodes on CT, which were reported as possible malignancy. And also lack of extensive retroperitoneal and para-aortic lymph node dissection also would have contributed to the low specificity.

Based on our findings where we had a significant better result in staging laparotomy (Sensitivity 96.96%, specificity 90%) in detection of ovarian carcinoma, which lead us to conclude that patients with negative findings on imaging should continue to undergo staging laparotomy as this procedure result in the upstaging of a significant percentage of patients. We believe that comprehensive surgical staging remains a critical aspect in the evaluation of patients with apparent early-stage ovarian cancer, as this procedure aids in identifying patients who may benefit from adjuvant chemotherapy.

Conclusion

The results of the present study indicate remarkable diagnostic abilities of two different imaging (USG & CT) modalities in detection of ovarian cancer. Addition of the third parameter (CA-125) further improves the

precision. RMI 4 score estimation is better than ultrasound imaging alone. All the three modalities, though not inferior by themselves, are complimentary to each other in their diagnostic performance. Ultrasonography should provide adequate information for characterization of ovarian mass and assessment of extra-pelvic dissemination. CT imaging further augments ultrasound findings because of its ability to image the deeper areas and the minimal extra ovarian spread and proves to be important adjunct to assess and treat when surgical staging is not feasible (by neo-adjuvant chemotherapy). However, in cases where CT imaging is not feasible, a combination of CA 125 and USG (RMI 4 score estimation) can be considered satisfactory in preoperative evaluation of ovarian carcinoma.

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