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ORIGINAL RESEARCH

Evaluation of HER2/neu in Ovarian Cancer: A Systematic Analysis of Observational Study in a Tertiary Care Centre in Northern India

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ABSTRACT

Introduction: Ovarian cancer accounts for 6% of all cancers in the female and is the fifth most common form of cancer in women which is caused by amplification of HER2/neu gene and it is widely studied most of the cancer but in gynecologic neoplasms it not well established biomarkerhence the study is carried out to analyse incidence of ovarian carcinoma in the local population and analysed relationship of HER2/neu positive cases with the histological type of ovarian tumour.

Materials and Methods: The present study was an observational study. A total of 30 cases were studied and systematically evaluated the HER2/neu reactions by histopathological and immunohistochemical study done in Shri Ram Murti Smarak Institute of Medical Sciences, Bareilly, Uttar Pradesh.

Result: Majority of the cases of ovarian carcinomas fell in the age group of 30-50 years with premenopausal age group followed by menopausal age group. Surface epithelial tumours were the most frequently encountered carcinomas in the present study in 50% of the cases followed by granulosa cell tumour in 20% of the cases.

Conclusion: Present study emphasized the HER2/neu reactivity in ovarian carcinomas. 76.7% of the cases were negative for HER2/neu. Positivity was noted in 23.3% cases.

Keywords: Cancer ovary, Gynaecological Cancers, Her2neu.

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INTRODUCTION

Ovarian tumours include a complex wide spectrum of neoplasm involving a variety of histological diagnosis ranging from epithelial tissues, connective tissues, specialized hormone secreting to germinal and embroyonal cells.[1] It is one of the most treatable tumours because majorities are sensitive to anticancer therapies.[2]

There are numerous types of ovarian tumours, both benign and malignant. About 80% are benign, and these occur mostly in young women between the ages of 20 and 45 years while malignant tumours are more common in older women between the ages of 40 and 65 years.[3] Ovarian carcinoma accounts for the greatest number of deaths from malignancies of female genital tract.

Unlike most malignancies, the surface epithelium transforms into a malignant phenotype, it becomes more differentiated, and it can differentiate toward many of the different cell types found in the Mullerian tract, including those in the fallopian tube, uterus, cervix, and ovarian stroma.[4] It is widely thought that most ovarian cancers develop from the surface epithelium or postovulatory inclusion cysts that were subjected to prolonged exposure to hormones or other chemokines.[5] Ovarian tumours can occur at any age. Paediatric ovarian tumours are uncommon but important form of childhood tumours. Ovarian tumours occurring in adolescence are unique with regards to its rarity, notoriously lethal when malignant and controversial in management.[6]

The HER-2/neu proto-oncogene encodes a 185 kDa transmembrane receptor protein with intrinsic tyrosine kinase activity and encoded by ERBB2, a known proto-oncogene located at the long arm of human chromosome 17 (17q12). The precise mechanism by which HER-2 overexpression transforms cells remains unknown, but presumably involves activation of the signal transduction pathways through which the receptor operates. HER-2/neu can be activated by at least three different genetic mechanisms including point mutation, gene amplification, and overexpression.[7,8]

Overexpression is strongly associated with increased disease recurrence and a worse prognosis but studies of human cancers have demonstrated that HER2 gene amplification (on17q12 chromosome) and overexpression are observed in a variety of tumour types. Such tumour types include breast,[9] ovarian,[10] pancreatic[11] and lung cancer.[12,13] The data from studies of cell lines and animal xenograft models suggest that these findings are not

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Table 1: Scoring algorithm of IHC kit.

Score 0	No staining is observed or membrane staining is observed in less than 10% of the tumour cells indicating negative.
Score 1+	A faint/barely perceptible membrane staining is detected in more than 10% of the tumour cells. The cells are only stained in part of their membrane indicating negative.
Score 2+	A weak to moderate complete membrane staining is observed in more than 10% of the tumour cells indicating weakly positive.
Score 3+	A strong complete membrane staining is observed in more than 30%(formerly 10%) of the tumour cells indicating strongly positive.

incidental, i.e.HER2 amplification/overexpression is involved in malignant transformation rather than being a marker of cancer cells that has no role in their production. HER2 amplification/overexpression has been detected in varying proportions of a range of human cancers. The percentage of tumours in which the HER2 gene is amplified is usually lower than the percentage in which the protein is overexpressed. The incidence of HER2 gene amplification is 25–30% for breast and 15–30% for ovarian carcinomas, with the incidence of HER2 protein overexpression being slightly higher.[14]

Ovarian cancer is considered one of the hardest to diagnose diseases in gynaecological pathology, often being referred as the silent killer because of the lack of precursor lesions and a specific set of symptoms, the disease being diagnosed in most cases during a routine examination and even then in a late stage. The medical history is very important, and we must be careful not to exclude any risk factors. Family history is in most cases very meaningful, women being more exposed to ovarian cancer if a blood relative had ovarian or breast cancer.

The advancements in science and modern diagnostic methods made possible the thorough investigation of this organ but there are still unsolved questions. The reason behind to chose this as a research work because of the alarming increase in the number of cases in the last 20 years, this type of tumour becoming the main cause of death from malignancy in gynaecology and there is relative paucity of literature in India on HER2/neu. It was therefore considered worthwhile to undertake this study with the idea that the following study can shed more light on incidence of ovarian carcinoma in the local population, relationship of HER2/neu positivity with the histological type of ovarian tumour.The present study was aimed to find out the relationship of HER2/neu positivity with the histological type of ovarian carcinoma with respect to age and menstrual status.

MATERIAL AND METHOD

The present study consist of 30 cases of ovarian carcinoma from the histopathology records in the Department of Pathology, Shri Ram Murti Smarak Institute of Medical Sciences, Bareilly(U.P) for the period of 4 years i.e. retrospective from 2010–12 may and prospective from June 2012–14.

Applicable samples from the surgically excised specimens were selected and fixed in 10% formalin for at least 12-24 hours and embedded in paraffin blocks. After that 4 μm thick sections from blocks were stained with hematoxylin and eosin (H&E) as per standard laboratory protocol.

After histopathological diagnosis of ovarian carcinoma, tumour is classified according to WHO classification and all the 30 cases are subjected to immunohistochemical study for HER2/neu from the representative areas of the tumour. The polymer based IHC kit of BioGenex RTU was used and scores were assigned according to the following algorithm (Table 1)A score of 2+ and 3+ Her2/neu were considered positive for immunostaining (Though score 2± needs to be confirmed by FISH, we considered positive due to unavailability of FISH).

Exclusion Criteria

Specimens diagnosed as non neoplastic ovarian lesions and cysts, simple ovarian cysts, tubo-ovarian mass and serous and mucinous cyst adenomas.

RESULTS

Present study included patients of varied age group from 2nd to 9th decade. In this study ovarian tumour incidence was seen more commonly in 4th to 5th decade of age group, 22 cases among 30 total studied cases accounting to 87.6 %. It was also seen that most of the females were premenopausal (11/30) followed by menopausal (9/30) (Table 2).

Among 30 cases of ovarian carcinomas 15 (50%) cases were surface epithelial carcinomas including eight cases of mucinous cyst adenocarcinomas and seven cases of serous cyst adenocarcinomas, 6 (20%) were sex cord stromal tumours, 5 (16.6%) were germ cell tumours among these one was immature teratoma grade 1, 2 were yolk sac tumours and 2 were Dysgerminoma. 4 cases of Krukenberg's tumour were noted and shown in Table 3.

In the present study HER2/neu positivity was found in 7/30 (23.3%) of cases. Out of seven positive cases, five cases of surface epithelial tumour, 1 case of granulosa cell tumour, and 1 case of metastatic ovarian carcinoma (Table 4).

Table 5 showed relation of HER2/neu positive case with histological diagnose and it was found that 37.5%

of mucinous cyst adenocarcinomas (3/8), 28.5% of serous cyst adenocarcinomas (2/7), 16.7% of granulosa cell tumour (1/6) and 25% of metastatic adenocarcinoma of ovary (1/4) have HER2/neu positive case.

In the present study 76.6% cases were found negative score 0 and 1+ while 13.3% were weakly positive and 10% cases were strongly positive. Mucinous cyst adenocarcinomas showed 2 cases scored 2+ positivity score while 1 case scored 3+ positivity score. Serous cyst adenocarcinomas showed 1 case of 2+ and 1 case scored 3+ positivity score. Granulosa cell tumour was strongly positive (score 3+) and metastatic adenocarcinoma was weakly positive (score 2+) (Table 6).

Table 2: Age wise and phase of cycle distribution of ovarian carcinomas

Age group	*Number of cases*	*Percentage (%)*
10 – 20	2	6.7
21 – 30	2	6.7
31 – 40	9	30
41 – 50	13	43.3
51 – 60	3	10
61 – 70	1	3.3
Phase of cycle		
Menstrual	2	
Childbearing	6	
Premenopausal	11	
Menopausal	9	
Postmenopausal	1	
Geriatric	1	

Table 3: Histological diagnosis of ovarian neoplasm

Histological diagnosis	*No. of cases*	*Percentage*
Surface epithelial tumours	15	50.0
Germ cell tumours	5	16.7
Sex cord tumours	6	20
Metastatic	4	13.3

Table 4: Showing HER2/neu expression of the tumour

HER2/neu expression	*Number*	*Percentage%*
Positive	7	23.3
Negative	23	76.7

DISCUSSION

Ovarian neoplasms are one of the most fascinating tumours in women in terms of their histogenesis, clinical behaviour and malignant potentiality. Many of the ovarian neoplasms cannot be detected early in their development, they account for a disproportionate number of fatal cancers being responsible for almost half of the deaths from cancer of the female genital tract.[15]

This study was undertaken to analyse the incidence of ovarian carcinoma and its correlation with histological type of carcinomas. In the present study the overall incidence of malignant ovarian carcinomas was 12%, similar to the study conducted by Yasmin *et al*.[16] where the incidence of malignant ovarian carcinomas was 10.3%. In this study maximum number of cases of ovarian carcinoma were noted in 4th to 5th decade age group, while in the other studies by Jagadeeshwari *et al*[17] and Verma *et al*.[18], malignant tumours occurred in the age range 31 to 40 years with 28 (29.47%) and 36 (27.07%) cases respectively.

In the present study most of the females were premenopausal 36.7% (11/30) followed by menopausal age group 30% (9/30). The youngest case in present series was 16 years old boy who had juvenile granulosa cell tumour & oldest one was an 83 years old patient.

Surface epithelial tumours account for 50 to 55% of all the ovarian carcinomas. In the present study 50% of surface epithelial tumours were the causes of ovarian carcinoma which is similar to the study done by Jha *et al*.[19], germ cell tumours accounted for approximately 30% of all ovarian carcinomas and 16.7% found in present

Table 5: Relationship of HER2/neu positivity with histological diagnosis

Type		*Total no. of cases*	*HER2/neu +ve cases*	*%*
Surface epithelial tumours	Mucinous adenocarcinomas	8	3	37.5
	Serous cyst adenocarcinomas	7	2	28.5
Germ cell tumours	Yolk sac tumour	2	0	0
	Dysgerminoma	2	0	0
	Immature teratoma grade 1	1	0	0
Sex cord stromal cell tumour	Granulosa cell tumour	6	1	16.7
Metastatic	Krukenberg's tumour	4	1	25

Table 6: Showing grading of HER2/neu expression in ovarian carcinomas

Her2/neu grading	*No. of cases*	*Percentage*
Negative (0)	16	53.3
Negative (1+)	7	23.3
Weakly positive (2+)	4	13.3
Strongly positive (3+)	3	10

study which correlated with Patel *et al*[20], (15.6%).20% and 13% found for sex cord stromal tumours and metastatic ovarian carcinoma, *respectively* similar to the finding of Tushar K *et al*[21].

Present study included 23.3%, HER2/neu positive cases similarly Holmes *et al*[22], found 22%, Steffensen *et al*[23], found 24% HER2 positive case.

In the present study surface epithelial tumours showed 3+ staining in 33.3% (1/3) of the cases, 2+ in 66.7% cases. Menezer *et al*[24] studied 20 non-epithelial ovarian malignancies (12 granulosa cell tumours and 8 germ cell tumours). Immunohistochemical staining for HER-2/neu was not present in any of these tumours. Higgins *et al* analysed 31 adult granulosa cell tumours, Her-2/neu expression was not seen in any of these cases. These studies are in accordance with the present study where HER-2/neu expression was not seen in germ cell tumours but granulosa cell tumour showed 16.6% (1/6) positivity.

CONCLUSION

To conclude the results of incidence of ovarian carcinoma was 10.3% in the present study and maximum number of cases was noted in 4th to 5th decade with most females being premenopausal (11/30). Results indicated that 76.7% cases of ovarian carcinoma were negative for HER-2/neu and 23.3% cases were positive. The present study also have maximum number of cases of surface epithelial tumours were positive for HER-2/neu (16.7%). Germ cell tumours were negative. 6.7% were graded as 1+ and 3.3% as 2+, while 10% case were graded as 3+. Granulosa cell tumour was weakly positive for HER-2/neu (2+).

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