Original Article

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Pathology Section

Profile of HER2/neu Expression in Surface Epithelial Ovarian Tumours: A Clinicomorphological Study

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ABSTRACT

Introduction: Surface Epithelial Ovarian Tumours (SEOT) are most prevalent tumours and account for about two third of all ovarian cancers. Survival of ovarian carcinoma is poor despite optimal surgical and chemotherapeutic management. Evaluation of new diagnostic and prognostic Immunohistochemical (IHC) markers will be essential in this aspect.

Aim: To evaluate quantitatively the profile of Human Epidermal growth factor Receptor 2 (HER2)/neu IHC expression with standard scoring system in SEOTs and their association with various clinicpathologic variables (age, laterality, CA 125 levels, histological subtype and FIGO staging).

Materials and Methods: The present ambispective study was done in the Department of Pathology, SRM Medical College Hospital and Research Centre, Kattankulathur, Tamil Nadu, India, from August 2020 to August 2022 with a sample size of 166 cases. All the histopathological samples of SEOT during the study period from August 2020 to August 2022 (prospective) and all borderline, malignant and few benign cases from June 2016 to August 2020 (retrospective) were also included in the study. Cases for which slides and blocks were not available and patient treated with neoadjuvant chemotherapy or radiotherapy were excluded in the study. For prospective cases after getting clinical history and Cancer Antigen 125 (CA 125) level, specimens were fixed, processed and Haematoxylin and Eosin (H&E), IHC staining was done as per standard lab protocol, for retrospective cases clinical history, CA 125 levels, pathological diagnosis and tissue blocks were retrieved, IHC performed and finally both prospective and retrospective cases HER2/neu IHC expression association was studied related to clinicopathological parameters.

Results: Out of total sample, SEOT was the most common (n=184, 76.98%) tumour cases, followed by germ cell tumours (n=42, 17.57%) cases and least common was sex cord stromal tumour (n=13, 5.43%). HER2/neu had higher IHC expression in malignant tumours and showed statistically significant positive association with age (p-value=0.001), CA 125 level (p-value-0.001), and histological diagnosis (p-value <0.001), but there is no significant association with size of tumour (p-value=0.786), parity (p-value=0.717), laterality (p-value=0.514) and the International Federation of Gynaecology and Obstetrics (FIGO) grading (p-value=0.274).

Conclusion: Malignant tumours had high HER2/neu IHC expression, thus emphasising its carcinogenic role and helps in the diagnostic differentiation of benign and borderline tumours with malignant potential from actual malignant tumours and can be a therapeutic target in future.

Keywords: Cancer antigen 125, Human epidermal growth factor receptor 2, Immunohistochemical

INTRODUCTION

Ovarian cancer is the seventh most common cancer to cause death worldwide [1]. In India, ovarian tumour ranks third in female genital malignancy, World Health Organisation (WHO) 2020 classified ovarian cancer based on histomorphological features and origin of cell [2]. Surface Epithelial Ovarian Tumours (SEOT) are most prevalent tumours and accounts about two-third of all ovarian cancers [3]. SEOT show high proliferative activity and more than 80% of SEOT patients have increased serum Cancer Antigen 125 (CA 125) values at the time of diagnosis and on serial screening of CA 125 level which is correlating with disease status in most of the cases [4,5]. Despite advances in surgical procedures and chemotherapeutic drugs, chemotherapy related morbidity and mortality is still prevalent. Hence, appropriate diagnosis as benign, borderline and malignant tumours along with histological typing is important for selecting patients with a favourable or worse clinical outcome, it also helps for improving the individualised treatment planning of patients [6]. Evaluation of new diagnostic and prognostic markers will be essential in this aspect.

Human Epidermal growth factor Receptor 2 (HER2)/neu (c-erbB2) is a proto-oncogene and is mainly expressed in epithelial tissue and activated due to its amplification [7]. HER2/neu overexpressed in 15-30% of invasive breast cancers, and could be a possible therapeutic target in epithelial ovarian cancer too [8]. Nearly 20-30% patients with ovarian carcinoma will have HER2/neu overexpression. Berchuck et al., were the first to establish that overexpression of HER2 gene will have poor survival rate in high stages of epithelial surface ovarian cancer [9].

In India, currently only little reported details about expression of HER2/neu in ovarian cancer is available [9-12]. Hence, this study is done to identify the diagnostic and prognostic role of HER2/neu Immunohistochemical (IHC) marker. The aim of the present study was to evaluate the immunological expression of HER2/neu in SEOT and to compare HER2/neu values with clinicopathological parameters {age, laterality, CA 125 levels, histological subtype and The International Federation of Gynaecology and Obstetrics (FIGO) staging}.

MATERIALS AND METHODS

The present ambispective study was conducted in the Department of Pathology, SRM Medical College Hospital and Research Centre, Kattankulathur, Chengalpattu, Tamil Nadu, India, from August 2020 to August 2022 with a sample size of 166 cases. Ethical clearance was obtained from Institutional Ethical Committee (IEC NO:2418).

Inclusion criteria: Retrospective cases with borderline, malignant diagnosis and few of benign cases from June 2016 to August 2019 were included in the study.

Exclusion criteria: Cases for which slides and blocks were not available, blocks with insufficient tissue material for IHC and patients treated with neoadjuvant chemotherapy or radiotherapy were excluded from the study.

Study Procedure

All histopathological samples of SEOT cases received between August 2020 and August 2022 were studied. Analysis of all cases (both prospective and retrospective) was done between August 2020 to August 2022. Study included 166 cases of SEOT. Clinical details of the patient, morphological findings were recorded. CA 125 levels were available for 140 cases. For retrospective cases, tissue blocks and Haematoxylin and Eosin (H&E) stained slides were collected. In prospective cases, specimens were fixed, processed and H&E staining was done as per standard lab protocol. Tumours were classified according to WHO classification of SEOTs 2020 [13]. HER2/neu, rabbit monoclonal antibody (clone:EP3) IHC staining was performed in all benign, borderline and malignant SEOT as per the standard protocol followed in the present study histopathology lab and associated with clinicopathological parameters (age, laterality, CA 125 levels, histological subtype and FIGO staging [13]). CA 125 level <35 U/mL considered to be normal [14]. Scoring for HER2/neu was done as per the [Table/Fig-1] [15].

Staining pattern	Score	Results
No staining is observed, or membrane staining is observed in <10% of tumour cell	0	Negative
Faint/barely perceptible membrane staining is detected in >10% tumour cell. Incomplete membrane staining	1+	Negative
A weak to moderate complete membrane staining in >10% of tumour cell	2+	Positive
A strong complete membrane staining is observed in >10% of tumour cell	3+	Positive

[Table/Fig-1]: Interpretation of HER2/neu immunoreactivity.

STATISTICAL ANALYSIS

All data were analysed using Statistical Package for the Social Sciences (SPSS) software version 21.0. Numerical values like age were represented in mean and standard deviation. For test of significance, Chi-square test was used. Association between HER2/neu IHC expression and clinicopathological parameters were tested by Student's t-test for two categories and Analysis of Variance (ANOVA) test for more than two categories. The p-values <0.05 were considered statistically significant.

RESULTS

Distribution of ovarian tumours: A total of 239 cases of ovarian tumours received between the period of 2016 June to 2022 June. Out of which SEOT was the most common tumours occurring as 184 (76.98%) cases, followed by germ cell tumours of 42 (17.57%) cases and least was sex cord stromal tumours of 13 (5.43%) cases. Eighteen cases were not included in the study as per exclusion criteria and finally 166 cases were included in the study.

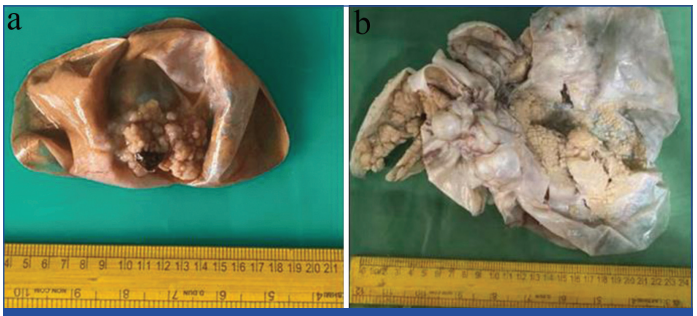
Distribution of cases according to age group: On analysing the distribution of age among the subjects, the most common age group was found between 41-50 years of age seen in 50 (30.12%) cases and least were less than 20 years of age group seen in 4 (2.41%) cases [Table/Fig-2].

Distribution based on laterality of SEOT: On evaluation of all cases of SEOT, unilateral right ovarian involvement was more common and seen in 78 (46.99%) cases followed by 73 (43.98%) cases of unilateral right ovarian involvement and least 15 (9.04%) cases had bilateral ovarian involvement.

Age group	Frequency (n)	Percentage (%)
≤20 years	4	2.41
21-30 years	31	18.67
31-40 years	47	28.31
41-50 years	50	30.12
51-60 years	25	15.06
>60 years	9	5.42
Total	166	100

[Table/Fig-2]: Distribution of cases according to age group.

Gross features: On gross examination of all cases, predominantly 96 (57.83%) cases had cystic lesion followed by 24 (14.46%) cases who had cystic lesion along with solid areas and least is 2 (1.20%) cases with predominantly solid lesion. The gross features of few cases of SEOTs are shown in [Table/Fig-3a,b].



[Table/Fig-3]: a) Gross picture of serous cystadenocarcinoma showing uniloculated cyst, with focal solid areas and papillary excrescences; b) Gross picture of mucinous cystadenocarcinoma showing grey brown, irregular, cyst with solid areas and papillary excrescences.

Histological type: On evaluating the total cases, most common histological type among SEOTs were of serous type seen in 84 (50.6%) cases followed by mucinous type noted in 61 (36.75%) cases, seromucinous type noted in 14 (8.43%) cases, least were 4 (2.41%) cases of endometrioid type and 3 (1.8%) cases of transitional type.

Histopathological diagnosis: On analysing the histopathological diagnosis, out of 166 cases, predominantly 132 (79.52%) cases were found to have benign tumours followed by 22 (13.25%) cases of malignant SEOTs and least is 12 (7.23%) cases of borderline tumour.

Evaluation of CA 125 level with histopathological diagnosis: On evaluating the mean serum CA 125 level with histopathological diagnosis, high serum CA 125 Level was noted among Malignant tumours with a mean of 693.19 U/mL and least in benign tumours with a mean CA 125 level of 31.87 U/mL and their association was statistically significant (p-value <0.05) [Table/Fig-4].

	Histopathological diagnosis	n	Mean	Standard deviation	p-value
Serum CA 125 level U/mL	Benign	132	31.87	222.53	**0.001**
	Borderline	12	78.16	47.56	
	Malignant	22	693.19	603.87	

[Table/Fig-4]: Association of serum CA 125 level with histopathological diagnosis. Bold p-values represent statistical significance

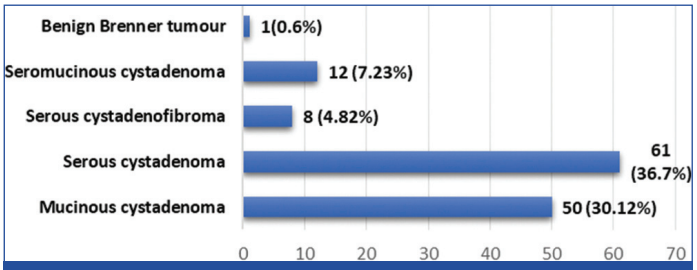
Comparison of serum CA 125 level with histological type: Comparing the serum CA 125 level with histological type distribution, Endometroid type had higher mean of CA 125 level with 660.13 U/mL and least in seromucinous type with 25.65 U/mL and their association is statistically significant (p-value <0.05) [Table/Fig-5].

Distribution of benign tumours: On analysing the total cases, the most common histological type of benign tumours were

61 (36.74%) cases of serous cystadenoma and least is 1 (0.6%) case of transitional histological types [Table/Fig-6].

	Histological type	n	Mean	Standard deviation	p-value
Serum CA 125 level U/mL	Serous	84	177.16	476.18	0.002
	Mucinous	61	26.40	42.09	
	Seromucinous	14	25.65	42.81	
	Endometroid	4	660.13	567.08	
	Transitional	3	301.00	406.18	

[Table/Fig-5]: Association of serum CA 125 Level of each histological type of SEOT.



[Table/Fig-6]: Frequency of histological subtypes of benign surface epithelial tumours.

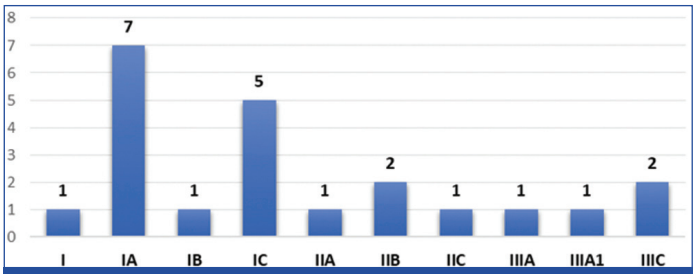
Distribution of borderline tumours: On evaluation of borderline SEOTs, the most common histological type were 6 (50%) cases of mucinous borderline tumour followed by 4 (33.33%) cases of serous borderline tumour and least were 2 (16.7%) cases of seromucinous borderline tumours.

Distribution of malignant tumours: On analysis of malignant SEOTs, the most common histological subtype were 9 (40.9%) cases of serous cystadenocarcinoma followed by 6 (27.28%) cases of mucinous cystadenocarcinoma and least was 4 (18.14%) cases of endometrioid carcinoma [Table/Fig-7].

Malignant tumours	Frequency	Percent
Serous cystadenocarcinoma	9	40.91
Mucinous cystadenocarcinoma	6	27.28
Endometrioid carcinoma	4	18.14
Malignant Brenner tumour	2	9.09
Mixed (Endometroid and Serous)	1	4.55
Total	22	100

[Table/Fig-7]: Frequency of subtypes of malignant surface epithelial tumours.

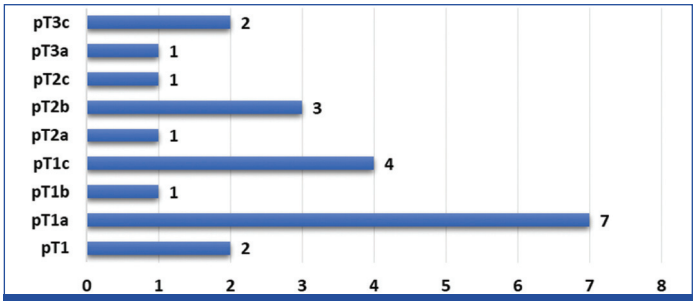
FIGO staging for malignant tumours: On evaluating the FIGO staging in 22 malignant cases, predominantly 7 (4.22%) cases had IA stage followed by 5 (3.01%) cases with IC stage, 2 (1.20%) cases had IIB and IIIC (1.20%) stage [Table/Fig-8].



[Table/Fig-8]: FIGO stage for malignant tumours.

Distribution of pathological tumour stage: On analysing the pathological tumour stage among 22 malignant cases, predominantly 7 (4.22%) cases had pT1a followed by 4 (2.41%) cases with pT1c stage [Table/Fig-9].

Frequency of nodal involvement in malignant SEOTs: Out of 22 malignant cases among the subjects, only 1 (4%) case had

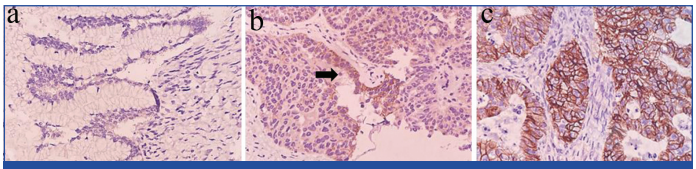


[Table/Fig-9]: Distribution of pathological tumour stage.

nodal involvement N1b and 18 (82%) cases had no nodal involvement (N0) followed by 3 (14%) cases in which the nodal involvement could not be assessed (Nx).

Distribution of metastasis in malignant SEOTs: On analysis of metastatic status of 22 malignant SEOTs, in 19 (11.45%) cases the metastatic status could not be assessed (Mx) and in 3 (1.81%) cases there was no evidence of metastasis (M0).

Distribution of HER2/neu grades among study population: On evaluating the total 166 cases predominantly 146 (87.95%) cases had 0 HER2/neu grading followed by 14 (8.43%) cases had 1+HER2/neu grading, both showed HER 2/neu negative expression. HER2/neu positive expression of 2+ grading of 3 (1.81%) cases and 3+ grading of 3 (1.81%) cases were noted. HER2/neu showed membranous positivity and the IHC expression of HER2/neu showed in [Table/Fig-10a-c].



[Table/Fig-10]: a) Microscopic picture of HER2/neu expression in benign serous cystadenoma. HER2/neu membrane positivity is 1+(Negative) (IHC;10X); b) Microscopic picture of HER2/neu expression in borderline serous cystadenoma. HER2/neu membrane positivity is 2+(Positive) (IHC;10X); c) Microscopic picture of HER2/neu expression in mucinous cystadenocarcinoma. HER2/neu membrane positivity is 3+diffuse membranous positivity (IHC;40X).

Association of age group with the HER2/neu grading: Comparing the age group with HER2/neu grading distribution, 41-50 years had higher proportion of 0 grading with 30.82%, 21-30 years had higher proportion of 1+ grading with 35.71%, and ≤20 years had higher proportion of 2+ grading with 33.33%. The association between them are statistically significant (p-value <0.05) [Table/Fig-11].

Age group (Years)	HER2/neu grading				p-value (Fisher-exact test)
	0	1+	2+	3+	
≤20	3 (2.05%)	0	1 (33.33%)	0	0.001
21-30	26 (17.8%)	5 (35.71%)	0	0	
31-40	42 (28.76%)	4 (28.57%)	0	1 (33.33%)	
41-50	45 (30.82%)	3 (21.42%)	1 (33.33%)	1 (33.33%)	
51-60	21 (14.38%)	2 (14.28%)	1 (33.33%)	1 (33.33%)	
>60	9 (6.16%)	0	0	0	
Total	146 (87.9%)	14 (8.43%)	3 (1.8%)	3 (1.8%)	

[Table/Fig-11]: Association of age group with the HER2/neu grading.

Association of CA 125 level with HER2/neu grading: Comparing the CA 125 level with HER2/neu grading distribution, 2+ grading had higher mean of CA 125 level with 472.19 followed by 3+ grading with 327.12 and least in 0 grading with 96.52 and the association between them are statistically significant.

Association of HER 2/neu grading with the histopathological diagnosis: Comparing the histopathological diagnosis with HER2/neu

positivity distribution, malignant had higher proportion of HER2/neu positivity with 18.18% followed by borderline with 16.66% and least in benign with 0% and the association between them are statistically significant (p-value <0.05). Evaluation of HER2/neu IHC expression among malignant SEOTs: Among 22 malignant tumours, 4 (18%) cases showed positive expression with HER2/neu IHC expression while 18 cases (82%) showed negative expression [Table/Fig-12].

Histopathological diagnosis	HER2/neu positivity		p-value
	Yes	No	
Benign SEOTs	0	132 (100%)	**0.001**
Borderline SEOTs	2 (16.7%)	10 (83.3%)	
Malignant SEOTs	4 (18.2%)	18 (81.8%)	
FIGO grading			
Grade I	2 (14.3%)	12 (85.7%)	0.274
Grade II	2 (50%)	2 (50%)	
Grade III	0	4 (100%)	

[Table/Fig-12]: Association of HER2/neu IHC expression with the histopathological diagnosis and with FIGO staging.

Association of histopathological type with HER2/neu positivity: Comparing the histological type with HER2/neu positivity distribution, mucinous had higher proportion of HER2/neu positivity with 4.91% followed by serous with 3.57% and least in seromucinous with 0%. The association between them is not statistically significant (p-value >0.05).

Association of FIGO staging with IHC markers in malignant SEOTs: Comparing the FIGO stage with HER2/neu positivity distribution in 22 malignant cases, stage II had higher proportion of HER2/neu positivity with 50% followed by stage I with 14.28% and least in stage III with 0% and the association between them is not statistically significant (p-value >0.05) [Table/Fig-12].

Association of size, laterality and parity of tumours with HER2/neu IHC expression: On comparing the parity, laterality, size of tumours with HER2/neu IHC expression there was no significant association with p-values 0.717, 0.514 and 0.786, respectively.

DISCUSSION

On comparing with other ovarian tumours SEOTs have high likelihood of changing into malignant ovarian tumours and therefore prompt diagnosis and timely intervention is important for successful patient treatment and management. Hence, the current study was done with a motive to identify the individuality of IHC marker to assist in the proper subtyping and grading of SEOT.

Frequency of SEOT in the study population: In the present study, 184 cases out of 239 were SEOTs, followed by 42 cases of germ cell tumours and 13 cases were sex cord stromal tumours. Hence, this study clearly states that SEOT is the most common (76.98%) ovarian tumours. Similar results were obtained by Buchynska LG et al., at National Institute of Cancer at Uttar Pradesh, and Mondal SK et al., at Kolkata, India [16,17].

Age of occurrence: It can be detected that benign SEOT tumours presented more in younger females while malignant SEOT present during fifth and sixth decades. The distribution of various tumour types according to age was similar to previous studies [1,2,18]. This can be explained by the proposal that occasionally over a period of time, few of the benign SEOT can progress to malignant counterpart by marked increase in grades of the epithelial abnormality [1]. Majority of the subjects (50 out of 166) were in 41-50 years age group similar to the study observation of Thakkar N and Shah S in which majority of patients were found to be in the age group of 40-59 years [19]. However, discordant with the study observation of Pathak P et al., in which major cases were between 20-30 years [9].

Analysis of tumour laterality in SEOTs: Unilateral ovarian involvement is more common than bilateral ovarian involvement in this study. Results are similar to the study observation by Mondal SK et al., whereas Koonings PP et al., and Kar T et al., found a greater number of bilateral tumours 22% and 26.8%, respectively [17,20,21], but there is no statistically significant association between laterality and IHC expression of HER2/neu in the current study.

Distribution of serum CA 125 level in SEOTs: In the present study. the mean serum CA 125 level among the malignant tumours was higher 693.19 U/mL and the association between distribution of serum CA 125 level and histopathological diagnosis were statistically significant which is similar to a previous study [22]. Serum CA 125 level has been contemplated to be as an independent prognostic marker, which can reflect the tumour burden and also the advanced stage of illness [23].

Distribution of benign, borderline and malignant neoplasms: On analysing the histological diagnosis in the current study, 132 (79.52%) were benign followed by 22 (13.25%) were malignant and 12 (7.23%) were borderline tumours. There are several studies showing similar distribution of SEOTs specifically conducted in South Asia [15].

Distribution of different histopathological types of SEOTs: In the present study, among 166 cases predominantly 84 were of serous (50.6%) type and least 4 (2.41%) cases were of endometrioid type. The above mentioned findings help us to interpret that serous histological type of SEOT was the most common histological type. This can be the main reason for many studies who have encompassed only serous type of SEOTs in their research studies [1]. Similar distribution noted in several studies of Asian countries [15].

Distribution of FIGO staging: On evaluating the distribution of FIGO staging among the malignant SEOT of our study, 7 (4.22%) had IA stage followed by 5 (3.01%) had IC stage. This observation is discordant with the study performed by Kurta ML et al., in which stage III tumours is more common [24]. But the present study observation is correlating with study done by Mclaughlin JR [25].

Association of HER2/neu IHC expression with clinicopathological parameters: The recent concept of classifying ovarian carcinomas as five broad histological types is: High-grade Serous Carcinoma (HGSC), clear-cell carcinoma, endometrioid carcinoma, mucinous carcinoma, and Low-grade Serous Carcinoma (LGSC), as they differ in their biology, clinical presentation, and chemotherapeutic response. Hence, IHC is useful as robust companion tool for subclassifying ovarian carcinomas [26].

HER2/neu IHC expression among study population: Positive expression rate in this study were 18% which is comparable to the rate of HER2/neu positivity in SEOTs reported in the literature, which ranges from 7-50% [27,28]. Comparing the age group with HER2/neu grading distribution, 20 years had higher proportion of 2+ grading and the difference between HER2/neu expression and distribution of age had statistically significant positive association. In studies who have analysed the same parameters no significant association was documented. Comparing the CA 125 Level with HER2/neu grading distribution, 2+ grading had higher mean of CA 125 Level with 472.19 U/mL and HER2/neu expression had statistically significant positive association with pre-treatment CA

125 levels similar to study done by Arif S et al., [30]. Comparing the histopathological diagnosis with HER2/neu grading distribution, malignant had higher proportion of 2+HER2/neu grading thus highlighting the fact that mutation of HER2/neu gene plays a vital role in pathogenesis of tumours as they are the part of signalling pathways occurring intracellularly resulting in cell proliferation and differentiation [9]. The difference in HER2/neu grading distribution between different histopathological diagnosis had statistically significant positive association. HER2/neu was negative in all benign cases, higher in grade 2 and 3 malignant tumours in concordance to previous studies [2]. Comparing the histological type with HER2/neu positivity distribution, mucinous had higher proportion of HER2/neu positivity with 4.91% followed by serous with 3.57%. This study findings showed concordance with reports of other studies in literature [9].

HER2/neu expression was analysed in all histological types of malignant SEOTs and many of the studies showed that HER2/neu do not show significant expression in non mucinous histological subtype of malignant SEOT. Trastuzumab therapy, an option of choice for mucinous carcinoma with HER2/neu expression. In several studies, overexpression of HER2/neu shows chemotherapy resistance and poor patient survival [9], but the difference in HER2/neu grading distribution between different histological type and FIGO staging was not statistically significant similar to previous studies [29].

HER2/neu an epidermal growth factor receptor family member, overexpressed in 20-30% of ovarian cancer [7]. Berchuck et al., first recognised that, HER2/neu overexpression is related to poor survival of patients with late stages of malignant SEOTs which states that patients with HER2/neu overexpression had worse prognosis than patients with normal HER2/neu expression. In addition, patients with high HER2/neu expression did not show complete response to therapy [9].

The most of the findings of this study matching well with proportions and features of many other similar studies. However, the significant positive association between age and HER2/neu IHC expression identified in the present study only, not documented in the literature so far. Currently, very few reported data about HER2/neu protein expression in SEOTs available in India [9-12]. Hence, this proposed study is performed to evaluate HER2/neu status in patients with SEOTs [9].

Limitation(s)

Limitation of the study was lesser number of borderline and malignant SEOTs in the study population, analysis of larger samples of these types would have been adding more value to the results.

CONCLUSION(S)

The proposed study emphasised the high and consistent IHC expression of HER2/neu in malignant SEOTs and also confirmed its statistically significant positive association with age, CA 125 level and histological diagnosis, but there is no significant association with, size, laterality, histological type and FIGO grading of SEOTs. HER2/neu also had higher IHC expression in malignant tumours, thus emphasising its carcinogenic role and helps in the diagnostic differentiation of benign and borderline tumours with malignant potential from actual malignant tumours. It also paves a better way for understanding the biological nature of SEOTs, to modify treatment modalities and can be a therapeutic target in future.

REFERENCES

[1] Naik PS, Deshmukh S, Khandeparkar SG, Joshi A, Babanagare S, Potdar J, et al. Epithelial ovarian tumors: Clinicopathological correlation and immunohistochemical study. Journal of Mid-life Health. 2015;6(4):178.
[2] Sylvia MT, Kumar S, Dasari P. The expression of immunohistochemical markers estrogen receptor, progesterone receptor, Her-2-neu, p53 and Ki-67 in epithelial ovarian tumors and its correlation with clinicopathologic variables. Indian Journal of Pathology and Microbiology. 2012;55(1):33.
[3] Piek JM, van Diest PJ, Verheijen RH. Ovarian carcinogenesis: An alternative hypothesis. Adv Exp Med Biol. 2008;622:79-87.
[4] Hall PA, Levison DA. Review: Assessment of cell proliferation in histological material. J Clin Pathol. 1990;43:184-92.
[5] Lavin PT, Kanapp RC, Malkasian G, Whitney CW, Berek JC, Bast RC. CA125 for the monitoring of ovarian carcinoma during primary therapy. Obstet Gynecol. 1987;69:223-27.
[6] Elattar A, Bryant A, Winter-Roach BA, Hatem M, Naik R. Optimal primary surgical treatment for advanced epithelial ovarian cancer. Cochrane Database of Systematic Reviews. 2011;(8):CD007565.
[7] Iqbal N, Iqbal N. Human epidermal growth factor receptor 2 (HER2) in cancers: Overexpression and therapeutic implications. Molecular Biology International. 2014;2014:852748.
[8] Ajani MA, Salami A, Awolude OA, Oluwasola AO, Akang EE. The expression status of human epidermal growth factor receptor 2 in epithelial ovarian cancer in Ibadan, Nigeria. Southern African Journal of Gynaecological Oncology. 2016;8(1):05-09.
[9] Pathak P, Bamanikar S, Shetty A, Kumar H, Buch A. Histopathological analysis of ovarian tumours and overexpression of HER2/neu in ovarian carcinomas. Indian Journal of Pathology and Oncology. 2019;6(3):440-44.
[10] Yadav V, Deshmukh AV, Kumar V, Gangane NM. Expression of HER2/neu receptor in epithelial ovarian cancers: An immunohistochemical pilot study in central India. Indian Journal of Gynecologic Oncology. 2021;19(4):01-06.
[11] Gupta S, Mehra M, Khattri J, Madhvi M. A study of her-2/neu oncogene expression in benign and malignant ovarian tumors. Int J Med Res Rev. 2020;8(2):169-75.
[12] Grover A, Mohanty M, Dash K. HER-2 neu expression in surface epithelial ovarian tumors and its relationship with clinic-pathological parameters: A pilot study. International Journal of Reproduction, Contraception, Obstetrics and Gynecology. 2021;10(4):1363-68.
[13] International Agency for Research on Cancer, World Health Organization. WHO classification of female genital tumours: Who classification of tumours. 5th ed. Who Classification of Tumours Editorial Board, editor. IARC; 2020.
[14] Gupta D, Lis CG. Role of CA125 in predicting ovarian cancer survival-a review of the epidemiological literature. Journal of Ovarian Research. 2009;2(1):01-20.
[15] Verma R, Gupta P, Tiwari N, Lal N, Gupta HP, Srivastava AN. Histological grade, CA-125 Levels and IHC expression of ER/PR. HER-2/NEU, p53 and Ki-67 markers in epithelial ovarian neoplasms: A correlative study. International Journal of Advanced Research. 2017;5(6):235-54.
[16] Buchynska LG, Iurchenko NP, Grinkevych VM, Nesina IP, Chekhun SV, Svintsitsky VS. Expression of the estrogen and progesterone receptors as prognostic factor in serous ovarian cancers. Experimental Oncology. 2009.
[17] Mondal SK, Banyopadhyay R, Nag DR, Roychowdhury S, Mondal PK, Sinha SK. Histologic pattern, bilaterality and clinical evaluation of 957 ovarian neoplasms: A 10-year study in a tertiary hospital of eastern India. Journal of Cancer research and Therapeutics. 2011;7(4):433.
[18] Maheshwari V, Tyagi SP, Saxena K, Tyagi N, Sharma R, Aziz M, et al. Surface epithelial tumours of the ovary. Indian J Pathol Microbiol. 1994;37(1):75-85.
[19] Thakkar N, Shah S. Histopathological study of ovarian lesions. 2015;4(10):1745-49.
[20] Koonings PP, Campbell K, Mishell DR. Relative frequency of primary ovarian neoplasms: A 10 year review. Obstet. 1989;74:921-26.
[21] Kar T, Kar A, Mohapatra PC. Intraoperative cytology of ovarian tumours. J Obstet Gynecol India. 2005;55(4):345-49.
[22] Garg S, Marwah N, Chauhan G, Gupta S, Goyal R, Dahiya P, et al. Estrogen and progesterone receptor expression and its correlation with various clinicopathological parameters in ovarian tumors. Middle East Journal of Cancer. 2014;5(2):97-103.
[23] Laishram S, Gupta V, Bhake A, Wankhede A, Agrawal D. To assess the utility of proliferative marker Ki-67 in surface epithelial ovarian tumor. J Datta Meghe Inst Med Sci Univ. 2019;14:06-10.
[24] Kurta ML, Moysich KB, Weissfeld JL, Youk AO, Bunker CH, Edwards RP, et al. Use of fertility drugs and risk of ovarian cancer: Results from a us-based case-control study fertility drugs and ovarian cancer. Cancer Epidemiology, Biomarkers & Prevention. 2012;21(8):1282-92.
[25] Mclaughlin JR. Hereditary Ovarian Cancer Clinical Study Group. Reproductive risk factors for ovarian cancer in carriers of BRCA1 or BRCA2 mutations: A case-control study. Lancet Oncol. 2007;8:26-34.
[26] Amanullah NA, Poothiode U, Vilasiniamma L. Expression of p53 in epithelial ovarian tumors. Indian Journal of Pathology and Microbiology. 2020;63(2):235.
[27] Grabowski JP, Harter P, Heitz F, Pujade-Lauraine E, Reuss A, Kristensen G, et al. Operability and chemotherapy responsiveness in advanced low-grade serous ovarian cancer. An analysis of the AGO study group metadatabase. Gynecologic Oncology. 2016;140(3):457-62.

[28] Verri E, Guglielmini P, Puntoni M, Perdelli L, Papadia A, Lorenzi P, et al. HER2/neu oncoprotein overexpression in epithelial ovarian cancer: evaluation of its prevalence and prognostic significance. Oncology. 2005;68:154-61.

[29] Arif S, Samad FA, Syed AS, Khan A, Riaz A, Zahid R. HER2/neu: A prognostic marker for ovarian carcinoma. Middle East Journal of Cancer. 2022;13(3):449-57.

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