STUDY OF SURFACE EPITHELIAL OVARIAN MALIGNANCIES WITH REFERENCE TO THEIR HISTOLOGICAL GRADING AND ER & KI-67 IMMUNOREACTIVITY

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ABSTRACT

BACKGROUND

We wanted to evaluate the relation of histopathological grading of malignant surface epithelial ovarian neoplasms and evaluate ER and Ki -67 as prognostic markers to provide the clinician a better platform for therapeutic management.

METHODS

All patients attending OPD and diagnosed as ovarian neoplasms were included in the study & were further subjected to histopathological & IHC studies. ER scoring was done by ALLRED scoring system (proportion score + intensity score), score 0-2 was taken as negative and 3-8 was taken as positive. The Ki 67 labelling index was expressed as 1+ when 5-25% of cell stained, 2+ when 25-50% cells stained. 3+ when 50-75% cells stained, 4+ when 75-100% cell stained.

RESULTS

Total number of cases was 42. Maximum number of cases were between fifth and sixth decade of life. 31 cases (73.80%) were serous cystadenocarcinomas, 6 cases (14.29%) were mucinous cystadenocarcinomas and 4 cases (9.53%) were endometroid carcinoma. One case of clear cell carcinoma (2.38%) was also seen. Oestrogen receptor was positive in 26/31 cases (83.87%) in serous cystadenocarcinoma, 2/6 (33.33%) cases of mucinous cystadenocarcinoma and, 2/4 cases (50%) of endometroid carcinoma and the single case of clear cell carcinoma was negative for ER. The total number of cases showing ER positivity was 71.42%. 12 cases were Grade 1 carcinomas showing ER positivity 58.33% (7/11) cases and Ki67 percentage 36.88%, 22 cases Grade 2 carcinomas showing 100% ER positivity and Ki67 percentage 66.98%, 8 cases in Grade 3 carcinomas showing 62.50% ER positivity (5/8 cases) and Ki67 index 81.30%.

CONCLUSIONS

Serous cystadenocarcinoma was the most common of all malignant surface epithelial ovarian tumours. ER positivity was maximum in Grade 2 tumours showing that once a case is ER positive, recommendations are there for hormone therapy whatever be the degree of positivity. ER was maximally expressed in serous carcinomas followed by mucinous carcinoma followed by endometroid carcinomas. Ki67 labelling index increases with increasing grade of surface epithelial ovarian malignancies.

KEYWORDS

ER, Ki-67, Malignant Surface Epithelial Ovarian Tumours

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BACKGROUND

Worldwide, ovarian cancer is the sixth most common cause of cancer in women and seventh most common cause of cancer death.[1] The age adjusted incidence rates of ovarian cancer vary between 5.4 and 8/100,000 population in different parts of the country.[1]

Ovarian cancer is one of the most lethal malignancies in women worldwide due to a) diagnosis in late tumour stage and vague symptoms and, b) the rapid onset of resistance to standard chemotherapy.[2] There have been persistent efforts in the investigation of molecular markers in malignant surface epithelial tumours of ovary by IHC studies.[3] ERs are expressed in over half of ovarian malignancies and oestrogen is the primary culprit in the pathogenesis and progression of ovarian cancers.[4,5] It is associated more with malignant surface epithelial ovarian tumours than benign and borderline cases. Hormone receptor determination in malignant ovarian neoplasms can help in selection of patients for targeted therapy. Ki67 is a proliferation marker and is expressed more in higher grade ovarian malignancies than in lower grades followed by borderline and benign ones.[6]

This study was undertaken to analyse the IHC profile of ER and Ki67 in malignant surface epithelial ovarian tumours of ovary and to correlate with the histopathological grading of ER and Ki67 as prognostic markers. We wanted to evaluate the relation of histopathological grading of

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Malignant Surface Ovarian Tumours and the co-relation of ER and Ki67 as prognostic markers and provide the clinician a better platform for therapeutic management protocol from prognostic point of view.

METHODS

Type of Study and Study Area

Prospective study of "Study of Surface Epithelial Ovarian Malignancies with reference to their Histological Grading and ER and Ki67 immunoreactivity" was carried out over a period two years from 1st November 2016 to 30th September 2018 in the PG department of Pathology, Hi Tech Medical College and Hospital, Bhubaneswar.

Inclusion Criteria

All patients of all ages who were suspected clinically and radiologically as Malignant Ovarian Tumours and samples only with definite histopathological features of malignant surface epithelial tumours of ovary were considered.

Exclusion Criteria

Non-neoplastic and inflammatory lesions, Non-epithelial tumours and metastatic lesions were excluded. Other exclusion criteria were those who did not give consent to IHC, inadequate tissue samples and improperly preserved tissues.

Study Size

42 cases of malignant surface epithelial tumours of ovary were included in the study.

Statistical Analysis

The data were entered in Microsoft office excel work sheets. It was then subjected to statistical analysis by Chi Square test using Graph Pad Prism, version 5.01. p value <0.05 is considered statistically significant.

Criteria for Reporting

ER immune staining was quantified by using Allred scoring system. Sum of Proportional score and Intensity score ranging from 3-8 was taken as positive score.[7] The nuclear staining of Ki67 was graded by counting the labelling index as a percentage of positively stained tumour nuclei in 1000 tumour cells in hot spot area of the tumour.[8]

<1%- negative
1%- 30%-+
30%-50%-++
50%-75%-+++
>75%-++++

RESULTS

In the present study, total number of cases were 42. Maximum patients were seen in the age group of 50-59 years of age, representing 35.71% of total cases studied. Age specific analysis of serous carcinomas revealed maximum cases (14 cases, 93.3%) in 50-59 years age group. The most common symptoms were of ascites constituting 20/42(47.61%) of total cases.

The number of unilateral cases were 34(80.94%) out of which 20 cases were right sided (47.62%) and 14 cases were left sided (33.34%). 8 cases were bilateral (19.04%). Out of the total number of 42 cases received, there were 31 cases of serous carcinomas (73.80%), 6 cases of mucinous carcinomas (14.29%), 4 cases of endometroid carcinomas (9.53%) and 1 case of clear cell carcinoma (2.38%). No case of Malignant Brenner tumour was received during the study period. The result is significant at p value of <0.05. In the present study (According to the WHO classification) number of cases in high grade serous carcinomas were 26/31 (83.88%) and number of cases in low grade serous carcinomas were 5/31 (16.12%). The result is significant at p value of 0.001. Out of 31 cases of serous carcinomas, (according to the Universal Grading system for malignant tumours of ovary) 18 cases belonged to Grade 2 and Grade 3 and Grade 1 had 8 and 5 cases respectively. Out of 6 cases of mucinous carcinomas, Grade 2 had 4 cases and 2 cases belonged to Grade 1. All the cases of endometroid and clear cell carcinomas were in Grade 1. The result was found to statistically significant at a p value of <0.05.

ER Expression

In the present study, observation for ER in individual carcinomas showed 26/31 (83.87%) positivity in serous carcinoma, 2/6 (33.33%) positivity in mucinous carcinoma, 2/4 (50%) positivity in endometroid carcinoma. The single case of clear cell carcinoma was ER negative. The result was found to be statistically significant at a p value of <0.05.

Ki67 Labelling Index

In the present study, Ki67 Labelling Index studied in all cases of malignant surface epithelial ovarian tumours showed maximum value obtained in serous carcinomas (83.87%) followed by clear cell carcinomas (82%) followed by endometroid carcinoma (64%). Least value of Ki67 labelling index was obtained in case of mucinous carcinoma (35%). The Ki67 labelling index was higher in High grade serous carcinomas (70.79%) as compared to Low grade serous carcinomas (37.39%) suggesting that Ki67 is a proliferation marker. The expression of ER and Ki 67 labelling index was studied in the three grades of malignant surface epithelial ovarian tumours according to the Universal Grading system. The expression of ER was maximum in Grade 2 (100%) tumours followed by Grade 3 (62.50%). The Ki67 labelling index increased with increase in Grades of carcinoma (81.30%, 66.98% and 36.88%) showing that there is an association between increased KI67 Labelling index and tumour aggressiveness and prognosis.

DISCUSSION

The results and observations of the present study carried out in Hi-Tech Medical College & Hospital, Bhubaneswar from 1st November 2016 to 30th September 2018 in malignant surface epithelial ovarian tumours with special reference to ER and Ki67 Immuno expression were studied. Most studies reported the highest incidence of malignant surface epithelial tumour of ovary in the age group of 50-60 years

(Sylvia M T et al (2012)[3]; Pooja S Naik et al (2015)[6]; Marino M J et al (1993)[9]; Maheswari V at el, (1994)[10]); as seen in the present study which constitutes 15/42 that is 35.71% of cases.

In our study, the most common presenting symptoms was ascites which was similar to studies done by Sylvia M et al[3] and Ruchika Garg et al.[11] Ruchika Garg et al (2014),[11] Thangraj Priya et al (2016),[12] Rinku Bhagora et al (2017),[13] J Pratt et al (2005)[14] and Santosh Kumar Mandol et al (2011)[15] reported that unilateral involvement of ovary is more common than the bilateral cases. In our study, we also found the similar result with unilateral involvement of ovary in 24 cases (80.96%) than bilateral involvement in 8 cases (19.04%). When compared to the work of Sylvia M T et al,[3] Pooja S Naik et al,[6] Bhagyalakshmi et a[7] with the present study, the incidence of serous carcinomas was 53.3%, 79.46%, 52% and 73.80% respectively. The incidence of mucinous carcinomas of the ovary was much lower in all the studies mentioned which constituted 14.28% of cases in the present study. Thangaraj Priya et al,[12] also showed that papillary serous cystadenocarcinomas were the most common type among all malignant serous epithelial tumours of ovary. This could be due to the fact that malignant serous epithelial tumours of ovary display tumour heterogeneity.

The number of high-grade serous carcinoma (26/31, 83.87%) was much higher than the number of cases of Low grade serous carcinomas (5/31, 16.13%) in our study showing the serous carcinomas present at a much advanced stages of the tumour. According to Luminija Nicoleta et al.[16] the number of cases in high grade serous carcinoma was 10/14(71.43%), while the number of cases in low grade serous carcinoma was 4/14(28.57%). Maximum number of cases were diagnosed as Grade 2, in our study (52.38%) as seen in studies done by Bhagyalakshmi et al (2016)[7] -64%. The least number of cases were in Grade 3 (19.05%) in our study which was comparable to 12% of cases obtained by Bhagyalakshmi et al[7] (2016).

In our present study the total ER percentage positivity was 71.42% which was same as obtained by Cardilo et al[17] in 1998 and close to Pooja S Naik et al [6] in 2015. The present study shows that ER had highest expression in serous carcinomas (83.87%) which was comparable to studies done by Rinku Bhagora et al 2017 (85%),[13] Pooja S Naik et al 2015 (100%)[6] and Mahak Wadhwa et al (70.5%).[18] The second largest expression of ER was seen in endometroid carcinomas (50%) which was followed by mucinous carcinomas (33.33%) in the present study. The difference in ER expression in serous and mucinous carcinomas may be attributed to the fact that STAT-3 is overexpressed in serous carcinomas while mucinous carcinomas is associated with other pathways. Since oestrogen receptors act through the STAT-3 pathway, ER expression is expected to be higher in serous carcinomas.[19] In the present study maximum expression of ER was seen in grade 2(100%) carcinomas which was same as Pooja S Naik et al (2015).[6] The expression seen in Grade 1 and Grade 3 was 58.33% and 62.5% respectively which was comparable to that of Pooja S Naik et al (50% in each grade 1 & 3).

In the present study, the Ki-67 labelling index show increasing values with increasing grades of tumour, Grade-1 has value 36.88%, Grade 2 66.98% and Grade 3. 81.30% which almost coincided with that of Pooja S Naik et al.[6] The expression of Ki-67 more in higher grades could be explained by the fact that it is a monoclonal antibody expressed by proliferating cells.[20]

Author	No. of Cases	Method	ER Positive (%)
Kommoss et al 1992[21]	87	IHC	38
Cardilo et al 1998[17]	28	IHC	71.42
Arias-Pulido et al 2009[22]	89	IHC	56.2
Ayadi et al 2010[23]	57	IHC	35.1
Sylvia et al 2012[3]	33	IHC	33
Pooja S Naik et al 2015[6]	16	IHC	81.25
Present Study	42	IHC	71.42

Table 1. Comparative Studies Done on Expression of Oestrogen Receptors in Malignant Surface Epithelial Ovarian Tumours

Comparative Studies	Serous Carcinoma	Mucinous Carcinoma	Endometroid Carcinoma
Pooja S Naik et al 2015[6]	100%	50%	80%
Rinku Bhagora et al 2017[14]	85%	60%	100%
Mahak Wadhwa et al 2017	70.5%	13.5%	-
Present Study (p=0.001)	83.87%	33.33%	50%

Table 2. Comparative Studies Done On Expression of Oestrogen Receptor in Different Types of Malignant SEOT

Comparative Studies	Grade-1		Grade-2		Grade-3	
	ER%	Ki-67%	ER%	Ki-67%	ER%	Ki-67%
Pooja S Naik et al 2015[6]	50	40	100	63.3	50	78.6
Present Study	63.6	36.88	100	66.98	62.5	81.30

Table 3. Comparative Studies Done on Expression of Oestrogen Receptor & Ki -67 Labelling Index in Different Grades of Malignant SEOT

Low Grade Serous Cystadenocarcinoma (Ki-67%)	High Grade Serous Cystadenocarcinoma (Ki-67%)
21% (Luminista Nicoleta Giurge et al)[16]	75% (Luminista Nicoleta Giurge et al)[16]
37.96% (Asha Mahadevappa et al)[24]	65.34% (Asha Mahadevappa et al)[24]
37.39% (Present Study)	70.79% (Present Study)

Table 4. Comparative Studies Done on Ki-67 Labelling Index in High- and Low-Grade Serous Carcinomas

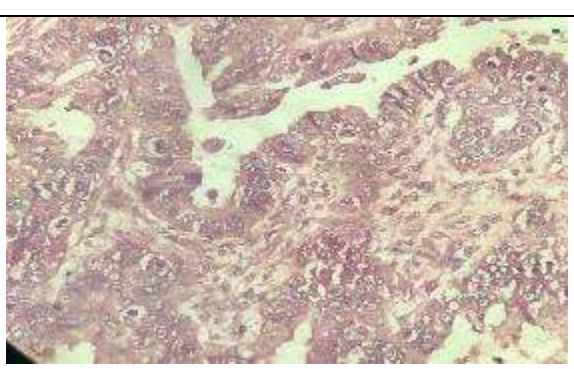

Figure 1. Grade 3 Serous Carcinoma 400x

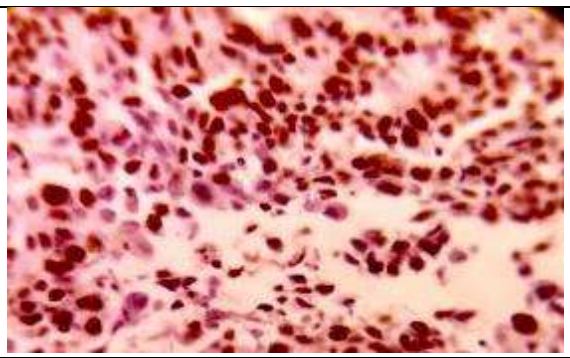

Figure 2. Grade 3 Serous Carcinoma 400X ER, Allred Score 8

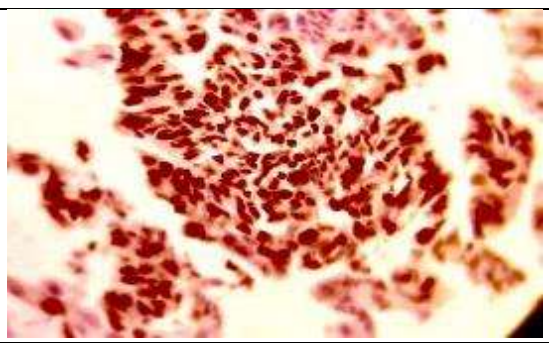

Figure 3. Grade 3 Serous Carcinoma 400X, Ki 67% 4+

CONCLUSIONS

Oestrogen has a major role in ovarian cancer pathogenesis and progression. Anti-oestrogen therapy may benefit patients who are refractory to or develop early resistance to chemotherapy. It is also indicated in recurrent cases of ovarian carcinomas. For ER positive tumours indications are there for anti-oestrogen therapy, whatever may be the degree of positivity. This study is an institution based one with a sample size of 42 cases. The result may not actually reflect the original age distribution and histological pattern of ovarian malignancies in the entire Indian population. Ki-67 is strictly associated with cell proliferation and is an excellent marker to determine the growth fraction of a given cell population.

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